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Low doses of ionizing radiation: biological effects and regulatory control

Contributed papers

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FOREWORD

The International Atomic Energy Agency and the World Health Organization, in co-operation with the United Nations Scientific Committee on the Effects of Atomic Radiation, are organizing an international conference on Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control, to be held in Seville, Spain, from 17 to 21 November 1997. The Government of Spain is hosting this Conference and is facilitating its organization through a group of Spanish institutions (CSN, ENRESA, ENUSA, UNESA and CIEMAT) led by the Nuclear Safety Council.

This TECDOC contains concise papers submitted on issues falling within the thematic scope of the Conference which were accepted by the Conference Programme Committee for consideration at the Conference. The papers are in one of the two working languages of the Conference, English or Spanish.

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OXIDATIVE STRESS AND LOW DOSE IRRADIATION

Emerit I, Alaoui-Youssefi A, Cernjavski L, Gentilini M.
Institute of Health & Development, University Pierre & Marie Curie, Paris, France.
Nikiforov N, Zybina N, Katashkova G,
All Russia-Centre of Emergency & Radiation Medicine, St. Petersburg, Russ. Federation.
Tsyb AF, Riabchenko NI, Liasko, LI, Souchkevitch GN*, Kaplan MA,
Medical Radiological Research Centre of RAMS, Obninsk, Russian Federation.
Piatak OA, Ovsiannikova M, Alekhina SM, Drobiskaya OW, Khalyavka IG, Lyshenko LA
Research Centre of Radiation Medicine, UAMS, Kiev, Ukraine.
Antipkine U, Omelchenko L, Arabskaya L, Ossinskaya K, Ivanov K, Pochinok T,
Institute of Pediatrics, Obstetrics and Gynecology, UAMS, Kiev, Ukraine.
Shefel UV, Lukina EA, Levina AA, Khoroshko ND, Dzerzhitsky VE,
Gomel State Medical Institute, Gomel, Belarus
Oganessian N, Pogosian A, Abramian A, Arutyunian R, Sarkisian T, Esayan A, Asrian K,
Research Centre of Radiation Medicine & Burns, RCRMB, Yerevan, Armenia.
Neriishi K
Radiation Effects Research Foundation, Hiroshima, Japan.

* Present address: World Health Organization, Environmental Health, Geneva, Switzerland

Abstract: **Studies of this working group indicate a shift of the prooxidant - antioxidant balance to the prooxidant side for a large proportion of workers engaged in the clean-up of the Chernobyl Nuclear Power Plant in 1986-87. Similar findings were obtained in children exposed to radiation after the explosion or still living within contaminated regions. Increased superoxide and hydrogen peroxide production by phagocytes were correlated with an increase in lipid peroxidation products and a decrease in the enzymatic and non enzymatic antioxidant defenses of the organism. The clastogenic factor test, which detects the presence of lipid peroxidation products and cytokines due to their chromosome damaging effects, yielded positive results for 41% of 89 workers from Armenia and 52% of 200 workers from St. Petersburg. Clastogenic plasma activity was increased even in those workers, who had received radiation doses between 5 and 10 cGy only. The number of CF-positive workers increased in the subgroups with increasing radiation dose. In children, the data varied according to sites and suggested correlations with the radioactive contamination of the soil. Treatments with antioxidant vitamins, flavonoids and terpenes improved the health status of this high risk population. However, the type of antioxidant, the treatment schedule and the dosage have to be standardized in order to obtain comparable results.**

The possibility that low doses of ionizing radiation may be responsible for health effects other than those wellknown for high doses has been much debated during recent times. It is our aim to draw attention to the role of oxidative stress at the origin of pathological manifestations after low dose irradiation. Oxidative stress is defined as an imbalance between the degree of oxyradical formation and the antioxidant defenses of the organism. If the equilibrium is shifted to the prooxidant side, oxidative damage will occur in macromolecules such as carbohydrates, collagen, DNA, lipids and proteins. Chronic oxidative stress is thought to be involved in a great number of pathologies, including aging, atherosclerosis, cancer, inflammatory diseases or ischemia- reperfusion injury of different organ systems. During these last years, various drugs or health foods with antioxidant properties were evaluated in clinical trials with the hope to treat or prevent these oxyradical-related diseases.

In 1994, The World Health Organization convened the International Consultation in St. Petersburg in order to develop a project for the study of the health status of the Chernobyl Accident Recovery Workers (liquidators). It was recommended, inter alia, to investigate biomarkers of oxidative stress in this category of the affected population. The above cited laboratories and institutes decided to select the most appropriate biomarkers for clinical trials

and to establish protocols for optimal treatment schedules in a joint venture. Nikiforov and coworkers (St. Petersburg) studied more than 100 liquidators (mean age 35 years), who participated in the clean-up operations during the period 1986-1987. Significant differences were observed for superoxide and hydrogen peroxide production by macrophages from bronchopulmonary lavage fluids in liquidators with pulmonary symptoms. These cells also showed lower activities of superoxide dismutase (SOD) and catalase ($p < 0.05$ and 0.01 respectively) and contained higher levels of thiobarbituric acid reactive substances (TBARS). Similar findings were also obtained with peripheral blood leukocytes, while TBARS in plasma did not significantly differ from control values. Increased production of reactive oxygen species was also noted in workers with cardiovascular symptoms, associated with an increase in conjugated dienes and TBARS in the plasma. The level of reduced glutathione (GSH) was diminished in erythrocytes, while the activities of GSH peroxidase and reductase were higher than in controls ($p < 0.05$). SOD levels remained unchanged. Treatment with vitamin E during a short period of 10 days reduced lipid peroxidation, but the differences were not significant.

Tsyb and coworkers, Obninsk, noted increases in conjugated dienes, trienes and diene ketones in a large number of liquidators (mean exposure dose 10.7 cSv), 5-6 years after the accident. The total antioxidant capacity of the plasma was reduced correspondingly. The changes were most important in workers, who were in Chernobyl in 1986. In this group, catalase levels were significantly decreased also. Clinical use of antioxidant preparations containing beta-carotene, vitamins E and C, selenium and other oligoelements reduced lipid peroxidation markers by 17-24 % [1].

Piatak and coworkers, Kiev, reported similar findings in a group of 57 workers, who had received total radiation doses of more than 1 Gy. Conjugated dienes and lipid hydroperoxides (but not malondialdehyde) were increased compared to controls, in particular in those with symptoms of acute radiation sickness. Among the antioxidant enzymes, catalase activity was low, while the modifications of glutathione peroxidase, glutathione reductase and SOD were not significant. For 557 persons, working at present in the Chernobyl nuclear power plant, the values were even higher than those measured in the liquidators with acute radiation sickness of the first study group.This suggests hazardous effects of long term exposure to even relatively low doses. Those workers whose official radiation dose had reached 0.5 Gy, were treated with antioxidant vitamins or hydrolysates of oysters. This led to a 48 % increase in the antioxidant capacity of the plasma, but the markers of lipid peroxidation were not normalized.

In agreement with the findings in Russian and Ukrainian liquidators, results of investigations conducted by Oganessian and coworkers in Yerevan indicated significantly increased levels of lipid peroxidation products. In their institute, beneficial effects were observed with various plant extracts whose free radical scavenging properties are probably due to their content in flavonoids and terpenes.

Shefel and coworkers noted decreased antioxidant defenses in 68% of 73 soldiers from Gomel, who had been working in Chernobyl between 1986 and 1988. Impaired iron metabolism, evidenced principally by increases in serum ferritin ($p < 0.05$) , was observed in 48 % of them. According to official dosimetry, the radiation dose received by these persons was less than 20 cGy.

In children living in controlled territories, important decreases in the antioxidant activity of the plasma were observed by Antipkine and coworkers, Kiev. The indices of lipid peroxidation such as conjugated dienes, hydroperoxides, malondialdehyde were significantly higher than in children from "clean " cities. The same was true for children evacuated from Pripyat after the accident, who live now in " clean" cities.

For comparison of subgroups of patients varying in radiation exposure, the biochemical analysis of lipid peroxidation products appeared to be less sensitive than the clastogenic factor test (CF-test), which detects lipid peroxidation products, together with other oxidants (in particular tumor necrosis factor) due to their clastogenic properties. The test is based on cytogenetic methods and comparable to chromosome mutation assays for exogenous clastogens. The chromosome damaging effects induced by plasma ultrafiltrates (cut off 30000 DA) in blood

cultures of healthy donors are compared to the background level of chromosomal aberrations in a simultaneous untreated culture, set up with the blood of the same donor. The results are expressed as adjusted clastogenic scores (ACS) i.e. the increase in chromosomal aberrations per 100 mitoses after deduction of the background level. On the basis of more than 100 CF-tests with normal plasma ultrafiltrates, persons whose plasma induces ACS of +8 and higher are positive for CF. In Table Ia, the data of liquidators are given in comparison to healthy persons from Armenia, while Table Ib shows the proportions of individuals positive for CF as a function of the radiation dose received. The differences between plasma samples from liquidators exposed to less than 25 cGy and those exposed to higher doses are statistically significant ($p < 0.05$).

Table I. STUDIES IN CHERNOBYL-EXPOSED WORKERS (LIQUIDATORS).

a) Results of CF- Tests°

ACS	Liquidators*	Healthy**
0	11 %	52 %
<6	37 %	43 %
6	10 %	5 %
8	13 %	0 %
>8	29 %	0 %
Mean	6.2 +/- 4.8	0.8+/- 1.0

b) CF positivity as a function of radiation dose

cGy	CF+	CF++	n***
0 - 5	27 %	0	22
5 - 10	43 %	7 %	30
10 - 15	26 %	5 %	19
15 - 20	58 %	13 %	24
20 - 25	71 %	35 %	52
25 - 60	79 %	36 %	14

* Center of Radiation Medicine, Yerevan, n= 89
** Blood donors from Yerevan, n= 96
*** Liquidators from ARCEM, St. Petersburg, n=161

ACS = adjusted clastogenic score
CF + : ACS 8 -11
CF++ : ACS 12 or higher

With the authorization of the Armenian Ministry of Health, thirty liquidators were treated with an extract of Gingko biloba leaves. After the two months treatment, the plasma was no longer clastogenic, and the workers reported improvement of their general health condition. The benefit persisted for at least 6 months after arrest of the treatment, for many liquidators even up to one year [2].

When plasma ultrafiltrates from children were studied, the differences were highly significant in comparison to children from "clean" cities. Interestingly, the plasma from children, who had emigrated to Israel, still exerted clastogenic effects even 4 years after having left the contaminated areas. The percentage of children positive for CF and the mean values of ACS were higher for those living in Gomel, Narodici or Bazar, which are high exposure sites (IAEA measurements) compared to those coming from Kiev (Table II) [3].

Table II. CF- TESTS IN CHERNOBYL-EXPOSED CHILDREN.

City	n	ACS	CF+
Gomel, emigrated to Israel*	95	7.74 +/- 1.2	48 %
Narodici- Bazar	27	12.2 +/- 2.6	100 %
Kiev	50	5.0 +/- 4.4	30 %
Kiev, emigrated to Israel*	67	6.0 +/- 1.2	31 %
Chernigov region			
- M. Kotsubinsky village	58	6.1 +/- 4.3	41 %
- Goncharovsk	47	3.0 +/- 4.3	15 %
Sumy region (Choten)	15	2.8 +/- 4.1	13 %
"Clean" cities Russia	24	1.9 +/- 1.1	8 %
Israeli school children	47	1.0 +/- 0.7	2 %

CF are not specific for irradiated persons, but are produced in a variety of pathological conditions including chronic inflammatory diseases with autoimmune reactions, HIV-infected persons, the congenital breakage syndromes and others. The consistent protective effect of SOD suggests a key role for the superoxide anion radical on the pathway to the clastogenic effects in all these conditions [4]. CF can be considered as biomarkers of oxidative stress, and their formation in irradiated persons may be similar to their formation in chronic inflammatory diseases. Indeed, according to observations of Neriishi in A- bomb survivors, inflammatory reactions such as leukocytosis, accelerated erythrocyte sedimentation rate, increased levels of acute phase proteins and increased levels of fibrinogen are common even many years after radiation exposure [5].

Also cells irradiated in vitro release CF. Significant clastogenic activity was detectable after exposure to radiation doses of 50 cGy (Table III).While serum irradiated in absence of cells was not clastogenic, irradiation of blood cells in PBS yielded clastogenic supernatants. If the irradiated cells were washed and resuspended in fresh culture medium, they continued to release CF. The formation as well as the chromosome damaging effects of CF were preventable by SOD.

Table III. Release of clastogenic factors by cells irradiated in vitro.

		Whole blood °	Culture supernatants of irradiated cells°°	
cGy	n	ACS +/- SD	n	ACS +/- SD
0	15	0.73 +/- 2.79	26	1.23 +/- 2.12
50	15	4.73 +/- 3.51*	12	1.67 +/- 3.39
100	11	6.36 +/- 4.08	7	6.00 +/- 3.06**
250	6	7.83 +/- 6.46	8	5.25 +/- 2.82
500	8	8.13 +/- 5.08	15	7.73 +/- 4.54
1000	12	10.75 +/- 4.43	19	6.53 +/- 4.10

Analysis of variance: $p<0.001$ * $p<0.001$ ** $p = 0.01$ compared to 0 cGy

° After irradiation , the plasma was ultrafiltrated and 250 µl aliquots were added to blood cultures from non irradiated donors. °° After irradiation in PBS, the cells were washed and grown in fresh medium. CF reached detectable levels in the supernatants after 10-12 h.

In conclusion, all results taken together are in agreement with the notion that even low doses of irradiation lead to an oxidaive stress status, which can be influenced by antioxidants. It appears of interest to organize large scale intervention trials for Chernobyl victims using biomarkers of oxidative stress for evaluation of the efficacy of the respective antioxidant or free radical scavenger.

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ESTUDIO DEL α-TOCOFEROL COMO PROTECTOR DE LOS DAÑOS INDUCIDOS EN LA PIEL POR LAS RADIACIONES IONIZANTES

LUCERO, M.J.[a], SÁNCHEZ, J.A.[b], VIGO, J.[a], LEÓN, M.J.[a], MARTÍN, F[c].

a Departamento de Farmacia y Tecnología Farmacéutica. Facultad de Farmacia. Universidad de Sevilla. 41012 Sevilla. España.

b Servicio de Radioterapia. Hospital Universitario "Virgen Macarena". Sevilla. España.

c Servicio de Medicina Preventiva. Hospital Universitario "Virgen de Valme". Sevilla. España.

Resumen

Se ha llevado a cabo un estudio en animales de experimentación para determinar el carácter protector del α-tocoferol frente a las lesiones causadas por los radicales libres producidos por las radiaciones ionizantes. Para ello se han utilizado dos concentraciones diferentes de fármaco incluidas en un mismo excipiente. Para producir los radicales libres se ha utilizado un acelerador lineal de electrones con 6 MeV y una dosis de 2800 cGy. Las lesiones se han sometido a estudios tanto clínicos como anatomopatológicos. La conclusión de este estudio ha sido que el α-tocoferol aplicado sobre la piel antes e inmediatamente después de la exposición a las radiaciones ionizantes es capaz de protegerla, originando una epidermis perfectamente diferenciada y de mayor grosor a la considerada normal.

1. Introducción

En los últimos años, el conocimiento teórico y el derivado de la experimentación científica se han ido acumulando en líneas bastantes coherentes, relacionando la existencia de los radicales libres (característico del carácter aerófilo del metabolismo celular) con patologías asociadas con envejecimiento anormalmente acelerado tanto celular como tisular.

De los muchos elementos protectores con los que cuenta el organismo humano es quizás la vitamina E (en su forma α-tocoferol) la más efectiva contra el fenómeno antes mencionado. Esto es debido al hecho de su carácter antioxidante *yscavenging*, ya que impide los cambios morfológicos celulares fundamentalmente ocasionados por el efecto peroxidativo de los radicales libres sobre los ácidos grasos poliinsaturados, constituyentes de las membranas sobre todo de las mitocondriales. Este efecto degradativo no es previsible y podría estar causado por deficiencias energéticas, acumulación de lipopigmentos procedentes de la degeneración de las membranas, etc., con la consiguiente disminución de la funcionalidad de los órganos y tejidos.

El objetivo central de este estudio es investigar sobre la capacidad protectora del α-tocoferol, administrado por vía tópica, contra los agentes nocivos que producen radicales libres, en concreto las radiaciones ionizantes. Posteriormente se determinará la viabilidad de estos medicamentos para su inclusión en la terapéutica específica.

2. Materiales y métodos

2.1. Medicamentos

Se han elaborado medicamentos con α-tocoferol como sustancia activa para su administración por vía tópica. Para ello se ha seleccionado, de entre muchos, un excipiente

base constituido por una emulsión de fase externa acuosa. Se han probado dos tratamientos constituidos por dos concentraciones diferentes de fármaco, éstas son 1.5 y 2.5 % p/p.

2.3. Ensayo con radiaciones ionizantes

Se han tratado 30 ratas hembras de raza Wistar de 6 meses de edad (tiempo necesario para que a este tipo de animales se les considere maduros). Se ha procedido a la irradiación con un Acelerador lineal de electrones, de 6 MeV de energía para conseguir la mínima penetración y así proveer de mayor dosis en la piel con respecto a la dosis profunda. Se ha utilizado un localizador circular de 3 cm de diámetro, diseñado especialmente para este ensayo. Se ha considerado idónea para la irradiación la pata trasera del animal ya que se pretende no incidir sobre órganos nobles. En cuanto a las dosis de radiación, se ha procedido ha elaborar un modelo experimental para determinar la más adecuada para la lesión perseguida. Las dosis ensayadas han sido: 600, 900, 1000, 1200, 1500, 1800, 2800 y 4000 cGy. De ellas se ha seleccionado para nuestro estudio la de 2800 cGy por proporcionar una lesión clínicamente valorable pero no masivamente destructiva. Se han establecido tres grupos diferentes: **Control** (animales que han seguido el mismo protocolo de administración sin la presencia de fármaco), tratamiento con α-tocoferol al 1.5 % p/p (**TRAT 1**) y tratamiento con este fármaco al 2.5 % p/p (**TRAT 2**).

Las extremidades posteriores de todos los animales intervinientes en el estudio han sido rasuradas 24 horas antes de administrarse el tratamiento. Pasado este tiempo se han anestesiado con clorhidrato de ketamina.A continuación se les ha administrado 0.2 g de los distintos medicamentos según se ha indicado en los grupos establecidos y durante 10 días consecutivos.

Cuando el tratamiento se ha completado, las 30 ratas han recibido la radiación ionizante con la dosis seleccionada de los estudios preliminares de 2800 cGy. Inmediatamente después se les ha vuelto ha administrar los respectivos medicamentos, repitiéndose una vez más a las 24 horas de la irradiación.

Se ha valorado no sólo las lesiones macroscópicas más evidentes observadas en los distintos grupos de animales, sino también las modificaciones microscópicas detectadas como consecuencia de la irradiación:

* Alteraciones macroscópicas: acorde con las especificaciones de la OMS, convenientemente modificadas para este estudio, se han valorado desde eritema o hiperpigmentación hasta amplia ulceración o exudación con tendencia al sangrado (Tabla I).

* Parámetros anatomopatológicos: espesor epidérmico, metaplasia escamosa anexial, impresión global, atrofia folicular, y densidad de fibroblastos. En todos los casos las alteraciones se han cuantificado de 1 a 10 según el nivel patológico observado.

3. Resultados

3.1. Alteraciones macroscópicas

Se estima como dosis ideal para la irradiación de animales de experimentación la de 2800 cGy por producir lesiones clínicamente evidentes pero no masivamente destructivas. Se ha evidenciado la siguiente secuencia lesiva: hiperemia en las primeras 24-48 horas, marcado eritema e incremento en la vascularización al final de la primera semana, continuando con eritema y un marcado retraso en la curación de las biopsias a las dos semanas. A los 16 días, se observa epitelitis exudativa y ulceración parcial de la piel. La curación y reepitelización de las lesiones aparece alrededor de las tercera semana. A las 6 semanas se completan las últimas consecuencias de los efectos agudos, entre ellos alopecia y moderada atrofia de la piel.

Tras llevar a cabo el tratamiento propuesto por nosotros y la subsiguiente irradiación con 2800 cGy, se han valorado las alteraciones macroscópicas y se han expuestos en la Tabla I, donde se puede contemplar como el TRAT 1 muestra menor toxicidad que el correspondiente al TRAT 2 y al Control.

Tabla I. Toxicidad macroscópica máxima mostrada por cada uno de los animales irradiados con 2800 cGy en los grupos establecidos.

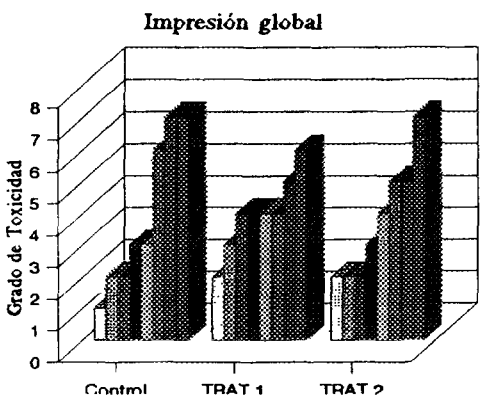
ALTERACIONES	VALOR	CONTROL	TRAT 1	TRAT 2
Eritema o hiperpigmentación	10	2	2	4
Mínima exudación-ulceración	20	1	3	3
Moderada exudación-ulceración	30	4	1	1
Exudación-ulceración	40	--	2	1
Amplia ulceración-exudación con tendencia al sangrado	50	3	2	1

3.2. Estudio anatomopatológico

El primer parámetro bajo estudio ha sido *espesor de la epidermis* (**EE**). Considerándose la piel de un animal sano como normal, se comparan con ella los distintos grupos de animales establecidos y que han sido sometidos a irradiación. Se observa epidermis atrófica en el Control, mientras en los TRAT 1 y TRAT 2 la epidermis está perfectamente diferenciada en sus distintas capas destacando un evidente incremento de espesor en relación al Control y a los animales sanos.

Metaplasia escamosa anexial (**MEA**) es detectada en la mayoría de los animales tratados (TRAT 1 y TRAT 2), pero no en el Control.

La *impresión global* (**IG**) mostrada por la piel de todos los animales se recoge en la Figura. En ella se puede observar que los TRAT 2 y Control presentan mayor toxicidad que el TRAT 1.



El estudio de la *atrofia folicular* (**AF**) muestra un mayor grado de toxicidad en el TRAT 1 que el TRAT 2 e incluso mayor que el Control.

Finalmente, en cuanto a la *densidad de fibroblastos* (**DF**) no se observan divergencias en la cantidad comparando los tres grupos establecidos.

4. Discusión

En 1896, Ostwald indicó que "la propia naturaleza de los radicales orgánicos es tal que excluye la posibilidad de obtenerlos aislados". Por esta razón nuestro Grupo de investigación ha diseñado un tratamiento con α-tocoferol para ser administrado antes e inmediatamente después de la irradiación con el fin de asegurar una cantidad suficiente de fármaco cuando estas especies reactivas se produzcan. Además, el α-tocoferol es una sustancia liposoluble que se acumularía en el estrato córneo de la epidermis.

Ante la disparidad de criterios entre los distintos investigadores con respecto a la concentración de α-tocoferol, excipientes utilizados, vías de administración y objetivos

perseguidos, se han establecido por nuestro Grupo de investigación, dosis de 1.5 y 2.5 % p/p intentando asegurar la eficacia terapéutica sin provocar efectos secundarios por dosis masivas.

Las alteraciones macroscópicas no muestran una clara diferencia entre los animales tratados y los controles. Esto podría ser debido al hecho de que la valoración de la lesión se ha realizado observando la totalidad del área irradiada, en donde existen dos zonas claramente diferenciadas:

* Zona 1: El área sobre el que el haz de electrones incide perpendicularmente sobre la superficie. Aquí la dosimetría del haz de radiación así como su distribución es la determinada por los estudios teóricos. Es en este área donde se administra sin lugar a dudas una dosis de 2800 cGy.

* Zona 2 (también denominada zona *fall off*): El área que se encuentra encerrada en los bordes del campo de la irradiación. A causa de la forma de la zona irradiada (elíptica en sección transversal), este área está en cierto modo eliminado del localizador de irradiación. La incidencia del haz de electrones en esta zona es oblícua, causando una completa sobredosis descontrolada desde el punto de vista dosimétrico ya que fuera se anula el pequeño efecto *build-up* del haz de electrones.

Cuando se describen macroscópicamente las lesiones en la zona irradiada, la descripción incluye las lesiones del área designada como zona 2 que son siempre de mayor envergadura que las de la zona 1. Por el contrario, el análisis histológico se ha realizado sobre biopsias tomadas siempre de la zona 1, en concreto de la zona central en donde incide el haz de electrones ya que así se asegura que la dosis recibida por todos los animales es la misma. El grado de *fall off* es diferente para cada animal y es siempre incontrolable ya que depende de la morfología anatómica del miembro irradiado.

Como consecuencia de estos factores es necesario completar los estudios macroscópicos con los histológicos. Con respecto al primer parámetro anatomopatológico estudiado, EE, los resultados obtenidos llevan a pensar que el α-tocoferol, bajo las condiciones de esta investigación, no sólo protege la piel de las radiaciones ionizantes sino también parece tener efecto regenerador, dando lugar a una epidermis de gran espesor y perfectamente diferenciada.

MEA se ha detectado sólo en los animales sometidos a tratamiento con α-tocoferol. Estos animales desarrollan un tejido diferente al que normalmente se produce en los folículos pilosos sin que conlleve su atrofia. Basados en las investigaciones de algunos autores sobre la importancia de la penetración percutánea por vía transfolicular en los animales, la MEA observada indicaría que el α-tocoferol, aplicado sobre la piel, desarrolla un tejido en los folículos, formado por distintas capas que dan lugar a un aumento en el espesor de la piel; este proceso observado es semejante en los animales irradiados y tratados con las distintas concentraciones de fármaco.

Los restantes parámetros estudiados (IG, AF y DF) no muestran diferencias entre los distintos grupos de animales establecidos.

Podemos afirmar que en las condiciones de nuestro estudio, el α-tocoferol aplicado por vía tópica en un excipiente emulsificado tiene un efecto protector de la piel contra las radiaciones ionizantes, favoreciendo la formación de una epidermis perfectamente diferenciada y de mayor espèsor a la observada en individuos sanos.

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Epidemiological analysis of common influence of low doses of ionising radiation, heavy metals and pesticides

Viacheslav M.Shestopalov, Marina V. Naboka
Scientific-Engineering Center of Radioecological Studies of Ukrainian National Academy of Science.
Kyiv. Ukraine

ABSTRACT

Comparison of ecological danger of substances of a chemical and radiating nature on the territory of Chernobyl's exhaust of Kyiv area is conducted. Epidemiological analysis, is conducted in accordance with "Methodical recommendations for radioechological assessment of territories by mapping". Influence on children's morbidity of 27 factors contamination of an environment (radiocesium, heavy metals, pesticides and fertiliser) was investigated. Analysis has shown, that the influence from all investigated ecological factors reaches 30-40 %, differing in different zones of supervision. The influence of radioactive factors in the Northern part of Kyiv test site, is 6 times greater than the risk caused by heavy metals and agrochemical pollution. A greater influence of heavy metals was found in the center of the Kyiv test site. The result of our research on the territory of Chernobyl's exhaust shows that there exist factors of different nature which influence on human health is significant and create combinations dangerous for health.

INTRODUCTION

These methods don't compare the contribution of different factors into the entire situation. As a combined index of different ecological factor's influence, a risk index is considered. It is often used for assessment of undesirable consequences. We use the term "ecological risk" for stressing that our research deals with ecological factors. Combination of small dozes of individually unharmed substance can give unexpected biological effects (the consequence of Persian Gulf War 1991).

The British Defence Ministry informed about the beginning of research of "Persian Gulf War Syndrome", which is evident in veterans being sick and their children's abnormalities.

So, we need a method of the assessment of different factor's influence.

METHOD

Our research was based on the unified official data collection of morbidity and pollution for the Kyiv site (1991-1995) [1]. The results of complex exploration held by the group of scientists were published in 1995 by the Ukrainian Ministry of Health, as an official document under the title "Methodical recommendations for radiohygienik assessment of territory by mapping". In this work the ecological risk was considered as a complex index of all the pathological ecological factor's influence. We define ecological risk as a probabilistic parameter characterising the number of undesirable deviations of human health from the average level for the territory under consideration, caused by environmental factors. It is expressed by morbidity rate over a year per 10000 residents.

The input of radioactive factors in it characterises the radioecological risk. We use mathematical modelling to calculate risks. We define a "state" as the numerical characteristics of the biological bodies peculiar to anthropogenosis and bioceogenosis over a given area (in our case it is the local population morbidity).

DATA AND DISCUSSION

We used our analytic approach elaborated during the last 5 years for the assessment of correlation between children's morbidity (up to the age of 14) and environmental factors (both radioactive and non radioactive).

Risk environmental variables used in our researches are as follows:

1. Pollution of soil with cesium-134 + 137.
2. Pollution of milk (from individual farms) cesium-134 + 137.
3. Pollution of soil by stroncium - 90.
4. Annual cumulative individual equivalent effective radiation dose.
5. Cumulative pesticide load.
6. Chloro-organic pesticide load and others.
7. Nitrogen, phosphoric and potassium fertiliser load.
8. Loading in soil of heavy metals and microelements etc.

Twenty seven factors were used in our models.

The "ecological risk contribution" into entire risk is about 30-40%. The influence of radioactive factors in the Northern part of Kyiv test site is 6 times greater than the risk caused by heavy metals and agrochemical pollution. A greater influence of heavy metals was found in the center of the Kyiv test site. (Fig. 1)

One of the main result of research is the fact that the influence of pesticides, heavy metals and radiation on human health are values of the same order. The reliability of the model is high enough (0.90) to make authentic conclusions, although the reliability of individual risks for different factors varied.

The special distribution of the risk shows that zones of high chemical radioactive risks coincide in some cases.

From the mathematical models analysis of the radioecological risk we found that the greatest level of children's morbidity caused by radiation is in the Polesskii region.

It is more than two times greater than the average risk for the Kyiv test site (14400 cases per 10 000 respondents). Almost the same situation we found for the Ivankovskii, Boguslavskii, Stavyschenskii, Taraschanskii, Belotserkovskii, Kagarlytskii regions.

The zones of the ecological danger caused by lead pollution are located in the Tetiivskii and Boguslavskii regions. The risk from lead ranges from 1.5 to 3 averages. In 9 regions (Kyivo-Svyatoshinskii, Vasylkovskii, Obuhovskii, Baryshevskii, Pereyaslov-Hmelnitskii, Taraschanskii, Mironovskii, Rakitnyanskii, Kagarlytskii) the risk from lead exceeds the average.

Note that in Boguslavskii, Rakitnyanskii, Taraschanskii, Kagarlytskii regions the population is subjected to the influence of radioactive and lead contamination, so under the combined influence of unfavourable factors.

Figure 2 presents total children's morbidity for those appealing for the medical first-time aid at Kyiv administrative regions in 1989-93 years.

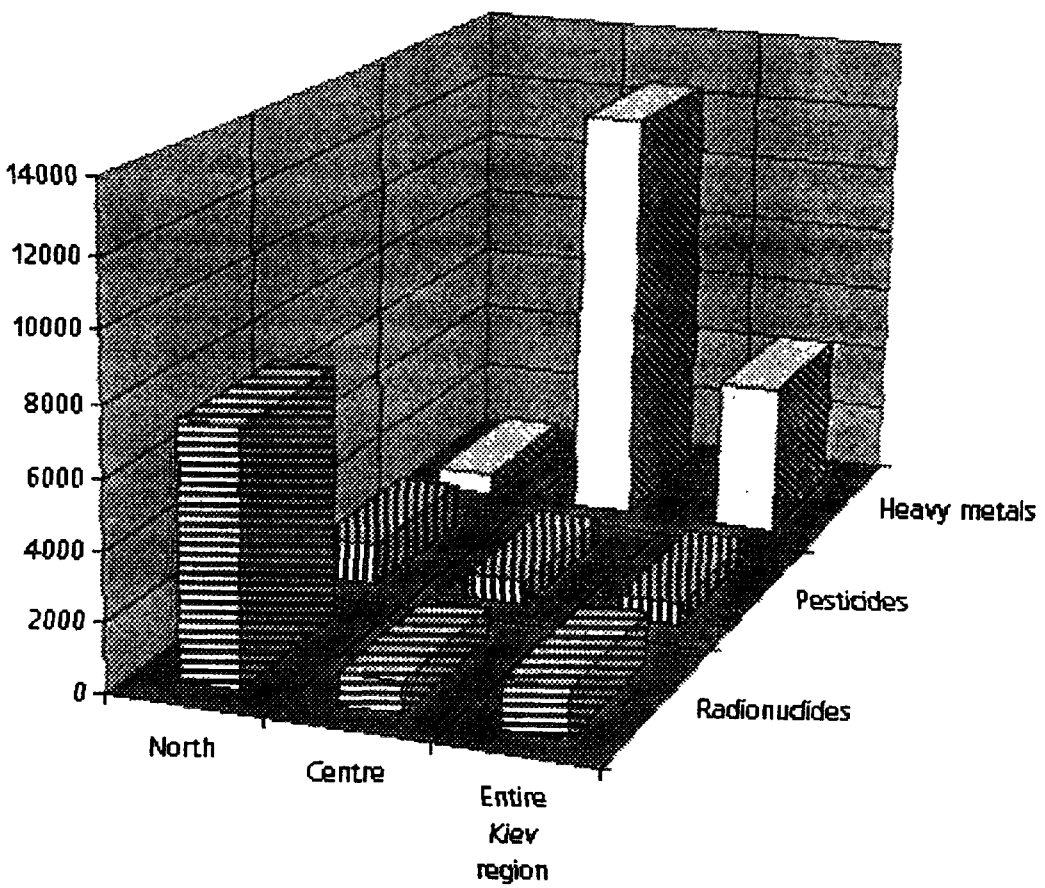

Figure 1

Risk graph of children illness related of the complex of factors

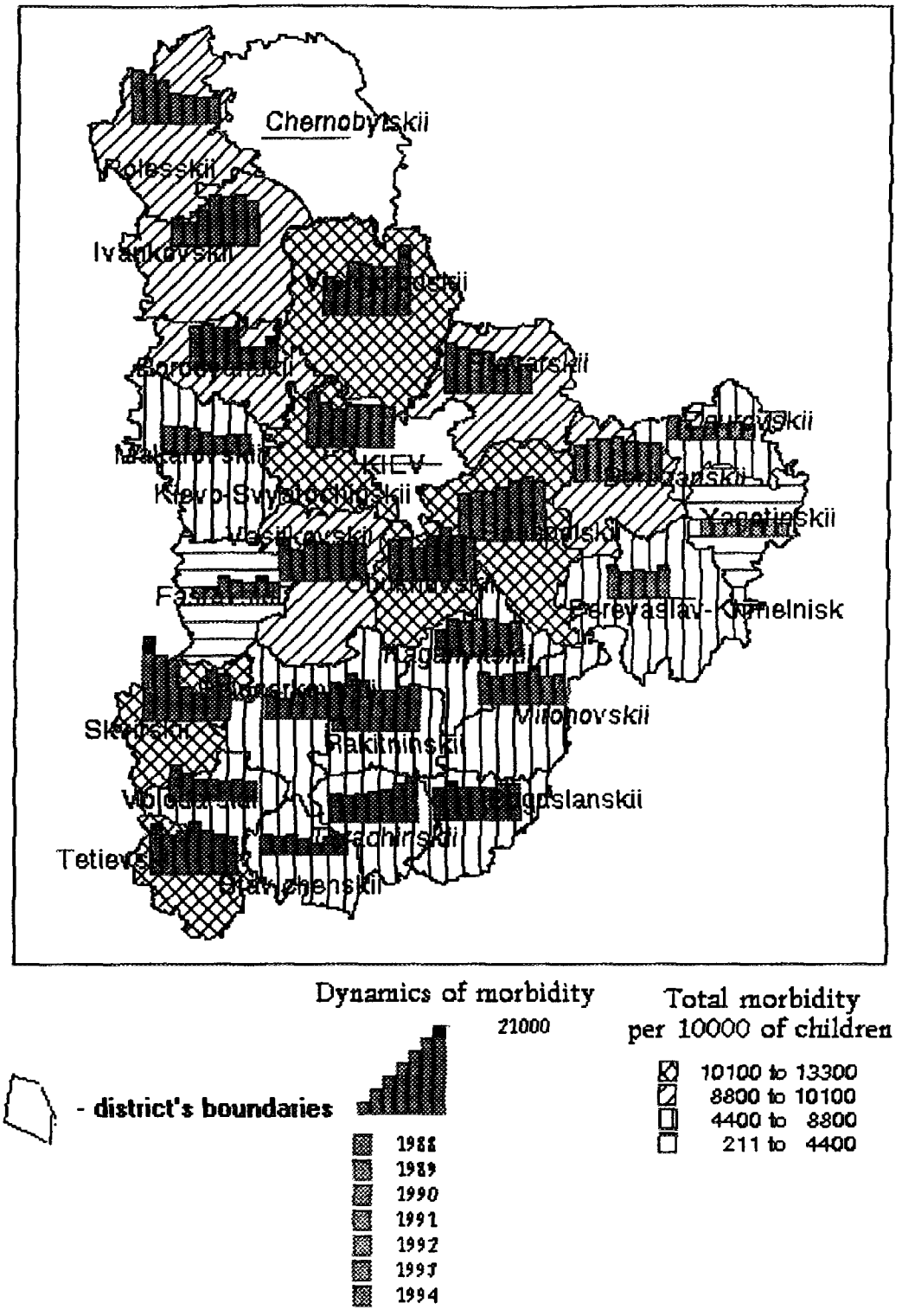

Figure 2

The distribution of the total morbidity and it's dynamics

The map shows a high morbidity rate (from 10000 to 13000 cases per 10000 residents) for the east-southern part (Boguslavskii, Taraschanskii regions) and for the northern part (Ivankovskii, Vyshgorodskii regions) of the Kyiv site. These zones of the extreme morbidity rate are located in the "west and south trace" of the Chernobyl fallout.

CONCLUSION

At the same time the Boguslavskii and Taraschanskii regions are zones of high contamination of the soil with lead. They are under combined unfavourable influence of both chemical and radioactive factors. The results of our research shows that there exist the factors of different nature the influence of which on human health is significant. Apparently the growth of the morbidity [2-3] rate in the area contaminated by Chernobyl can be explained by the combined influence of chemical factors and low dozes of radiation.

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EXPOSURE TO IONIZING RADIATION OF PATIENTS AT THE NUCLEAR MEDICINE DEPARTMENT FROM 1975 TO 1976 AND FROM 1985 TO 1996

J. Chaś[1], M. Marciniak[1], E. Dziuk[2], and M.K. Janiak[1]

1. Department of Radiobiology & Radiation Protection, Military Institute of Hygiene and Epidemiology, Warsaw, Poland;
2. Department of Nuclear Medicine, Central Clinical Hospital of the Military University Medical School, Warsaw, Poland.

Abstract

In order to evaluate the risks from ionizing radiation for both patients diagnosed at the Department of Nuclear Medicine, Central Clinical Hospital of the Military University Medical School in Warsaw, the collective committed effective dose equivalents and the mean personal effective dose equivalents were calculated for the subsequent years of the period from 1985 to 1996 and compared to the respective values obtained for the years 1975 and 1976. The results indicate that although the number of patients and the total radioactivities used in the radioisotope diagnostic assays at the DNM increased more than 2.5-fold in the 1980s and 1990s in comparison to 1975 and 1976, the collective committed effective dose equivalents during the last two decades were relatively lower than in the mid 1970s. When averaged over the tested periods, exposure of the patients to ionizing radiation in terms of both the collective committed effective dose equivalent and the mean personal effective dose equivalent was lower during the nineties (29.8 man-Sv and 9.0 mSv, respectively) than during the second half of the 1980s (40.2 man-Sv and 15.4 mSv, respectively). In fact, mean values of the effective dose equivalents per patient systematically decreased beginning from 1987 to the level of less than 10 mSv during the 1990s.

Introduction

The constantly increasing numbers of patients diagnosed *in vivo* with use of a variety of radionuclides make it necessary to control and verify the absorbed doses of ionizing radiation and to estimate the risk for the population at large.

The number of patients diagnosed at the Department of Nuclear Medicine (DNM), Central Clinical Hospital of the Military University Medical School in Warsaw increased almost 2.5-fold during the period from 1975 to 1996. At the same time, the annual activities of the radiopharmaceuticals used more than tripled. Similar increases were noted in other countries. For example, in the former German Democratic Republic the number of patients at nuclear medicine departments rose by 12% from 1978 to 1981,[1] whereas in the United States the frequency of the radioisotope *in vivo* tests doubled during the period from 1972 to 1982.[2] The present work was undertaken to compare the exposure to ionizing radiation in terms of the collective effective dose equivalent and mean personal effective dose equivalent in patients diagnosed at the DNM in a given year during the periods from 1975 to 1976 and from 1985 to 1996. The respective dose equivalents were calculated based on the activities of different radionuclides in different organs and tissues and the number of patients diagnosed in each particular year.

Material and Methods

Calculations of both the collective and mean effective dose equivalents were obtained for 2,901 patients diagnosed at the DNM in 1975 and 1976, and for 35,487 patients diagnosed during the period from 1985 to 1996 (Fig.1). In most cases the diagnostic tests consisted of a scintigraphy and/or radioimmunoassays which were used to examine a whole spectrum of organs and tissues. The radionuclides used included I-131, Tc-99m, In.113m, Tl-201, Cr-51 and Hg-203. To calculate the doses we used the values of the committed effective dose equivalents $H_T(\tau)$ obtained by a patient after administration of a given radionuclide per unit radioactivity, as calculated by others.[1-8] By multiplying the $H_T(\tau)$ value by the activity of the administered radionuclide and the number of patients in a given

year, the collective committed effective dose equivalents were obtained for all the patients diagnosed per year with a particular test. The quotient of the collective committed effective dose equivalents and the number of tests performed in a given year gave the total collective committed effective dose equivalent per year. The mean effective dose equivalent per patient was obtained by dividing the collective effective dose equivalent in a given year by the number of patients diagnosed in that year. Contribution of I-131 to the total collective effective dose equivalent was defined as the quotient of the collective effective dose equivalent from this radionuclide calculated for the thyroid gland and the total collective effective dose equivalent.

Results and Discussion

As shown in Fig. 2, total activities of the radionuclides used annually from 1985 to 1996 generally paralleled the number of patients tested and averaged 1.01 TBq for the period from 1985 to 1989, and 1.30 TBq for the period from 1990 to 1996. In fact, the highest total activity (1.62 TBq) was noted in 1993, when the number of patients was also the greatest (3599 patients, as shown in Fig. 1). In contrast, although the numbers of patients diagnosed in 1975 or 1976 equalled to more than one-third of the mean number of patients from the period 1985-1996, total activities of the radioisotopes utilised during 1975 and 1976 equalled to only 0.05 and 0.06 TBq, respectively,. These results reflect the quantitative and qualitative changes in both the radionuclides used and the types of tests employed during the 1970s and 1980s. Indeed, in 1975 and 1976 the I-131-labeled sodium iodide, the Hg-203-labeled neohydrine and the In-113m-labeled compounds were the predominant radiopharmaceuticals used in the radioisotope diagnostics. However, labeling of the diagnostic compounds with In-113m and Hg-203 was abandoned in 1985 and 1986 when, for the first time most of the *in vivo* tests were done using agents labeled with technetium Tc-99m and other short-lived radionuclides (e.g. Tl-201).[9-13] Moreover, the traditionally I-131-tagged compounds such as NaJ, albumins, albumin microspheres and hipuran began to be less and less frequently labeled with this radionuclide. In fact, in Poland in 1989 approx. 42,000 diagnostic tests of the thyroid gland were done using the I-131-labeled compounds and approx. 10,000 tests using the Tc-99m-labeled compounds, while in 1992 the number of tests in which I-131 and Tc-99m were used as the radionuclide tags equalled to approx. 33,000 and 35,000, respectively.[9] On the other hand, in 1985 and 1986 new radioisotope diagnostic tests, such as heart imaging, lung and bone scintigraphy, salivary gland imaging, and lung ventilation assays were introduced. These novel diagnostic methods obviously contributed to the increased total radioactivity of the radionuclides utilised annually per patient from 1986 onwards.

The total collective committed effective dose equivalents for all the patients tested in a given year are shown in Fig. 3. The highest value of 47 man-Sv was noted in the year 1986 after which, despite the constantly increasing number of the patients, the values of the collective dose equivalents tended to decline until the year 1992 (20 man-Sv), but rose again in 1993 to the level of 1989 (approx. 40 man-Sv). This sudden increase in 1993, paralleled, however, the elevated at that time total radioactivities used at the DNM (Fig. 2). In general, however, the total collective committed effective dose equivalents averaged over the the period from 1990 to 1996 were markedly lower than those averaged over the second half of the eighties (29.8 versus 40.2 man-Sv, respectively). When compared to the total radioactivities used in 1975 and 1976, the collective effective dose equivalents were in these two years relatively much higher than in the particular years of the 1980s and 1990s. These differences may result, at least in part, from the markedly lower utilisation of I-131 in the diagnostic tests during the 1990s than during the 1970s. In fact, contribution of I-131 to the total collective effective dose equivalent in 1993 (i.e., when the value of the collective dose was the highest during the 1990s) equalled to 12%, as compared to 79% and 77% in 1975 and 1976, respectively (data not shown).

As shown in Fig. 4, the mean effective dose equivalents per patient (per year?) were the highest during the period from 1985 to 1987 (mean value 17.3 mSv), after which these values decreased to a steady level of approx. 9.8 mSv during the years 1993-1996. Interestingly, the lowest mean effective dose equivalents per patient were noted in the years 1991 and 1992 (7.2 and 6.7 mSv, respectively). In contrast, in 1975 and 1976, these dose equivalents equalled to 13.4 and 11.4 mSv, respectively, which are relatively very high levels compared to the low total radioactivities used in those years. Nevertheless, these latter values are still below the level reported for the total population of the Polish nuclear medicine departments' patients in 1981.[14] However, the values of the mean effective dose

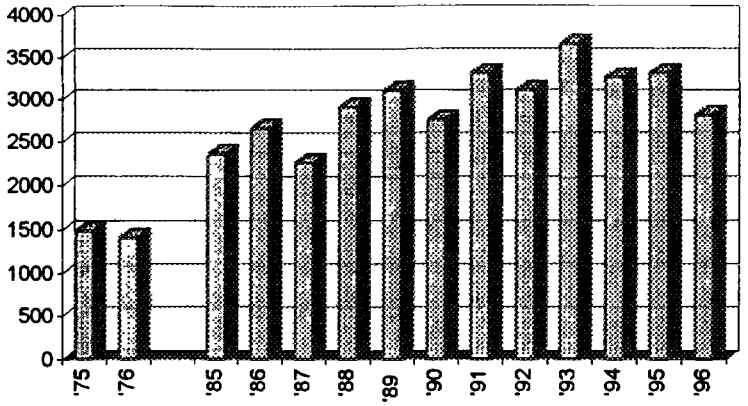

Fig.1. Numbers of patients diagnosed at the DNM per year in 1975 and 1976 and from 1985 to 1996.

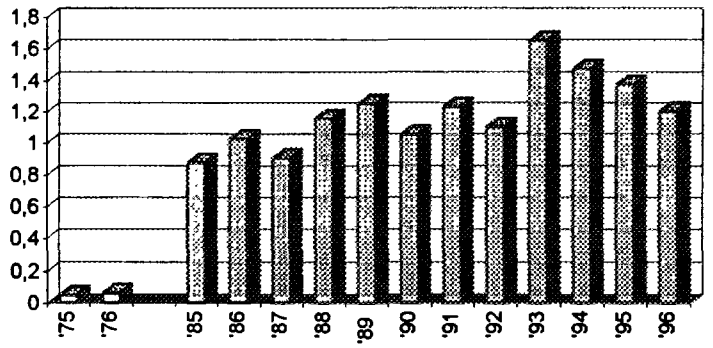

Fig.2. Total activities [TBq] of radionuclides used at the DNM per year in 1975 and 1976 and from 1985 to 1996.

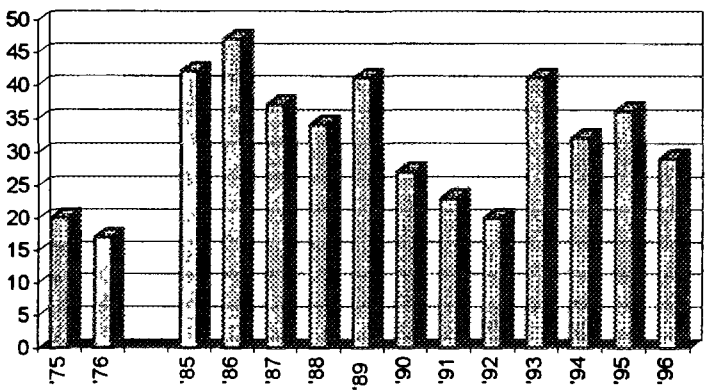

Fig.3. Total collective committed effective dose equivalents [man-Sv] for patients diagnosed at the DNM in 1975 and 1976 and from 1985 to 1996

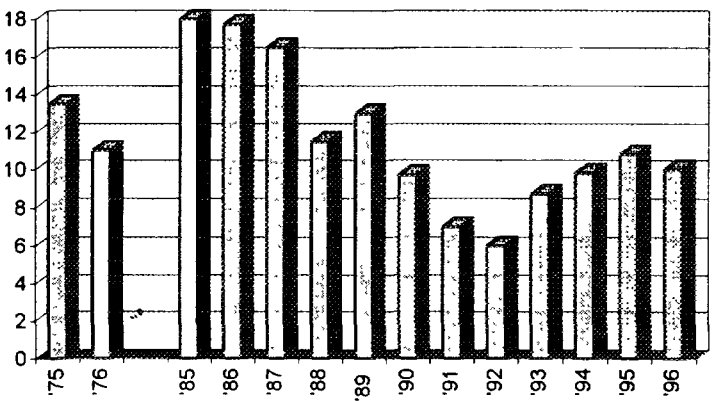

Fig.4. Mean personal effective dose equivalents [mSv] for patients diagnosed at the DNM in 1975 and 1976 and from 1985 to 1996

equivalents calculated for each patient diagnosed at the DNM during the 1990s, although generally not exceeding 10 mSv, were still somewhat higher than the respective doses reported for the 1980s from other European countries.[7,8,13,15] The reason for this discrepancy is unclear, but it is possible that different types and doses of radionuclides, and/or different diagnostic procedures used in these other countries are responsible.

In conclusion, the present results indicate that although the total radioactivities used in the diagnostic assays at the DNM substantially increased in the second half of the 1980s and during the 1990s in comparison to 1975 and 1976, the total collective committed effective dose equivalents during the last two decades were relatively much lower than in the mid 1970s. In general, when averaged over the tested period, exposure of the patients to ionizing radiation in terms of both the collective committed effective dose equivalent and the mean personal effective dose equivalent was lower during the 1990s than during the second half of the 1980s. In fact, mean values of the effective dose equivalent per patient systematically decreased beginning from 1987 to the level of less than 10 mSv during the 1990s. These results are in accord with the general trend in the industrialised countries to lower the risks from ionizing radiation for both the patients and their environment during medical diagnostic procedures.

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RISK FROM IONIZING RADIATION TO THE CLINICAL STAFF AND INCIDENTAL PUBLIC IN THE COURSE OF THERAPY WITH I-131

J. Chaś,[1] A. Kowalczyk,[2] M. Siekierzyński,[2] E. Dziuk,[2] M.K. Janiak[1]

1. Department of Radiobiology & Radiation Protection, Military Institute of Hygiene & Epidemiology, Warsaw, Poland
2. Department of Nuclear Medicine, Central Clinical Hospital of the Military University Medical School, Warsaw, Poland

Abstract

The aim of the study was to assess the risk to the personnel and neighbouring patients exposed to ionizing radiation during their stay at the Isotopic Therapy Clinic in Warsaw where therapeutic applications of I-131 are routinely performed. To this end, thermoluminescent dosimeters were deposited in various places throughout the Clinical ward and the absorbed doses were read after 125 days of the exposition. Additionally, exposure dose rates were determined at the skin surface over the thyroid gland and at 0.5 and 1.0 m away from 71 patients treated with I-131 for hyperthyroidism or thyroid cancer (as a supplementary therapy after thyroidectomy) and the potential dose equivalents were calculated. From these values "restriction times', i.e., the amounts of time needed for the potential dose equivalents to decline below the limit recommended for occupational or public exposures to ionizing radiation, were derived. The results indicate that a) the probability to exceed the recommended annual dose limit by the personnel (50 mSv y^{-1}) and neighbouring patients not subjected to radiotherapy (1 mSv y^{-1}) during their exposition at the Isotopic Therapy Clinic to the I-131-treated patients is practically equal to zero, b) no restrictions in terms of limiting the duration of contact with the I-131-treated patients are necessary during the occupational exposures of the personnel of the Clinic, and c) the treated patients may incur some risk to the general public only when injected with high doses of I-131 and/or only within about 3 days upon the application of the radionuclide.

Introduction

Disorders treated with I-131 include hyperthyroidism and thyroid cancer [1]. I-131 is also commonly used for diagnostic purposes and both therapeutic and diagnostic applications of this beta/gamma emitter may incur a risk to other patients and personnel of the clinical units and nuclear medicine departments [2]. Indeed, exposure to radiation occurs through a direct contact with the I-131-injected patient and/or with the patient's blood, sweat, urine and feces [3]. It is therefore important to establish and implement safe procedures of therapeutic and diagnostic applications of I-131 aimed at minimizing the potential radiological risk involved. In Poland, no such procedures have been legislated thus far.

In the present study we assessed the risk to the personnel and incidental public exposed to the ionizing radiation during their stay at the Isotopic Therapy Clinic, Central Clinical Hospital of the Military University Medical School in Warsaw, where therapeutic applications of I-131 are performed on a routine basis. To this end, thermoluminescent dosimeters were fixed in various places throughout the Clinical ward and the absorbed doses were read after 125 days of the exposition. Additionally, exposure dose rates were determined at the skin surface over the thyroid gland and at 0.5 and 1.0 m away from the skin in 71 patients treated with I-131 for hyperthyroidism or during supplementary therapy of the thyroid cancer and the potential dose equivalent rates were calculated. From these values 'restriction times', i.e., the amounts of time needed for the potential dose equivalents to decline below the limits recommended for both occupational and public exposures to ionizing radiation, were derived.

Material and Methods

In order to assess the exposure to ionizing radiation of the personnel during the daily work at the Isotopic Therapy Clinic, the TL-100 thermoluminescent dosimeters were deposited in different places of the Clinical ward and the absorbed doses were read and calculated after 125 days of the exposition. During that period, approx. 65.2 GBq (1760 mCi) of I-131 were applied to about 170 patients treated for

hyperthyroidism or as a supplementary therapy after thyroidectomy due to thyroid cancer. Briefly, three dosimeters were placed in a cartridge and the cartridges were fixed 1.5 m above the floor in 11 places throughout the ward, choosing those where contacts with the treated patients were most frequent. One cartridge was placed in a room devoid of any radioactive sources as an indicator of the natural background radiation. After the expositions, all cartridges were dismounted and the dosimeters read using the reader designed at the Institute of Nuclear Physics, in Cracow, Poland. The readings were used to calculate the dose equivalents per 125 days from which total annual dose equivalents and dose equivalents absorbed annually at 40 hours of work per week were derived.

In addition, exposure rates from the I-131-treated patients were measured at the skin surface over the thyroid gland and at 0.5 and 1.0 m. distance and the respective dose equivalent rates were calculated. Briefly, the treated patients were divided into three groups: i) those with immunogenic hyperthyroidism (46 patients), ii) those with autonomous hyperthyroidism (16 patients), and iii) those after the radical thyroidectomy due to thyroid cancer (9 patients). The exposure rates were measured with the seated patients at 1, 24, 48, and 72 h (in the third group also at 96, 120, 144, and 168 h) after the application of the radionuclide; the measurements were carried out with the VAJ-15A radiometer (VEB VakutronikWIB, Germany) and the results were expressed in mR h^{-1}. From these results, the respective dose equivalent rates expressed in μSv h^{-1} were calculated using the conversion factor: 1 mR h^{-1} = 10 μS h^{-1} [4]; the final results were divided by the total radioactivity injected to the patient and expressed in μSv h^{-1} MBq^{-1}. As shown in Table 1, in all the three groups of patients the decline of the dose equivalent rates, expressed as the decline rate per hour λ, at different points of the measurement of the exposure rates correlated well with the dose equivalent rates per unit injected radioactivity (P_0).

With use of the appropriate equations, dose equivalents H(t) were calculated for the three groups of patients at different distances from the skin and at different times after administration of the radionuclide. With the H(t) values set at the annual dose limits for the occupational and public exposures (1 and 5 mSv y^{-1}, respectively), 'restriction' times t were calculated, indicating when after the administration of I-131 the respective dose equivalents at a given distance from a given patient would fall beneath 1 or 5 mSv per year.

Table I. Correlation (R) of the P_0 and λ values calculated for patients with immunogenic hyperthyroidism (immuno), autonomous hyperthyroidism (auto) and thyroid tumor (tu) after measurements of the exposure dose rates made at the skin surface (skin), and 0.5 and 1.0 m from the skin surface of the patients treated with I-131.

Group of patients	Measured at	P_0 [μSv h^{-1} MBq^{-1}]	λ [h^{-1}]	R
immuno	skin	5.539 ± 0.113	0.0063 ± 0.0004	0.986
	0.5 m	0.194 ± 0.004	0.0047 ± 0.0005	0.964
	1 m	0.068 ± 0.001	0.0055 ± 0.0004	0.980
auto	skin	3.459 ± 0.026	0.0043 ± 0.0002	0.996
	0.5 m	0.199 ± 0.008	0.0101 ± 0.0013	0.945
	1 m	0.067 ± 0.002	0.0116 ± 0.0010	0.973
tu	skin	1.422 ± 0.080	0.0106 ± 0.0005	0.993
	0.5 m	0.146 ± 0.015	0.0174 ± 0.0019	0.961
	1 m	0.040 ± 0.006	0.0153 ± 0.0019	0.949

Results and Discussion

Mean dose equivalents over the 125-day period of the exposition of the thermoluminescent dosimeters located at 11 different places of the Clinical ward after subtraction of the background radiation are presented in Table 2. Based on these data, the respective mean total annual dose equivalents and mean dose equivalents absorbed annually at the 40 hours' working week were calculated and are also shown in Table 2. These data indicate the potential risk for the nurses, doctors and other personnel of the Clinic during their routine work. Unlike the values of the total annual dose equivalents which are unrealistic (they assume permanent residing at the ward through a whole year), the potential exposure involved is reflected by the

mean dose equivalents absorbed annually at 40 hours of work per week. Obviously, despite the fact that the highest values of these latter doses may be absorbed in the vicinity of the patients' beds in sick rooms 2 and 4 (assuming the constant contact with these beds for 40 h per week per year), in no cases the accepted annual dose limit for occupational exposure (50 mSv) was likely to be exceeded. In fact, even in cases of the unusually long permanent contact with a treated patient (e.g. for 4 h, starting 12 h after the administration of 600 MBq I-131), maximum dose equivalent received by the member of the personnel would amount to 0.44 mSv (not shown) which is close to the sensitivity level of the films used in individual dosimeters worn by a staff occupationally exposed to ionizing radiation. Importantly, the safest place was the nurse's station, where only the background level of radiation could be detected (Table 2).

Table II. Readings of the dosimeters located at different places of the Clinical ward and the calculated thereof dose equivalents per year.

Dosi-meter No.	Location	Equivalent dose read after 125 d [mSv y^{-1}]	Equivalent dose per year [mSv/rok]	Equivalent dose per year at 40 h working week [mSv]
1	nurse's station	background level	background level	background level
2	treatment room	4.13 ± 0.57	12.06 ± 1.66	2.87 ± 0.4
3	door, room 1	1.96 ± 0.45	5.72 ± 1.32	1.36 ± 0.31
4	door, room 2	2.27 ± 0.47	6.63 ± 1.36	1.58 ± 0.32
5	bed 1, room 2	28.08 ± 1.96	81.99 ± 5.71	19.52 ± 1.36
6	door, room 4	4.33 ± 0.50	12.64 ± 1.45	3.01 ± 0.35
7	bed 1, room 4	17.62 ± 0.88	51.45 ± 2.57	12.25 ± 0.61
8	bed 2, room 4	8.2 ± 0.90	23.94 ± 2.62	5.7 ± 0.62
9	bed 3, room 4	15.93 ± 0.93	46.52 ± 2.71	11.08 ± 0.64
10	bed 4, room 4	15.11 ± 1.06	44.12 ± 3.09	10.51 ± 0.74
11	bed 5, room 4	6.64 ± 0.70	19.39 ± 2.04	4.62 ± 0.49

One criterium for the assessment of the risk to personnel, neighbouring patients and the relatives who come into a contact with a patient treated with I-131 is a 'restriction time', i.e., the period of time to pass after the administration of the radionuclide in order for the potential dose equivalent absorbed at a given distance from the patient to fall beneath the annual dose limit recommended for the public and occupational exposures [5-7], i.e., below 1 or 5 mSv per year, respectively. In the present study, we estimated the restriction times for all three groups of the treated patients based on the H(t) values set at 1 or 5 mSv. Fig. 1 shows such restriction times at H(t) = 1 mSv and at 40 h of work per week calculated using the respective dose equivalent rates at various distances from the patient's skin for patients with autonomous hyperthyroidism (hy) and after thyroidectomy (tu) treated with different radioactivities of I-131. As indicated, no restriction times for the incidental public (i.e., relatives, neighbouring patients, etc) are necessary at small to medium activities of I-131 and for expositions at a distance ≥ 1 m, assuming that the patient remains in hospital for at least 3 days. Likewise, the calculated restriction times for the personnel of the Clinic (H(t) = 5 mSV) are close to zero at small and medium radioactivities and at the distance ≥ 1 m, i.e., for the most typical occupational exposures in the course of therapy with I-131 (Fig. 2).

In conclusion, the present results indicate that a) the probability to exceed the recommended annual dose limits by the personnel (50 mSv y^{-1}) and neighbouring patients not subjected to radiotherapy (1 mSv y^{-1}) during their exposition at the Isotopic Therapy Clinic to the I-131-treated patients is practically equal to zero, b) no restrictions in terms of limiting the duration of contact with the I-131-treated patients are necessary for the exposures of the personnel of the Clinic, and c) the treated patient may incur some risk to the general public only when injected with high doses of I-131 and/or only within about 3 days upon the injection of the radionuclide.

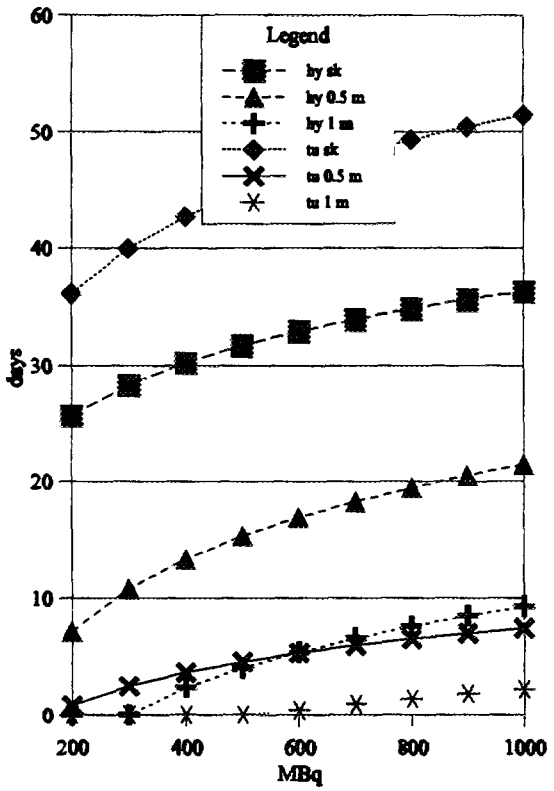

Fig. 1. Restriction times [in days] for the incidental public at 40 h of work per week for patients treated for immunogenic hyperthyroidism (hy) or thyroid tumor (tu) with various radioactivities [in MBq] of I-131. The times were calculated after measurements of the exposure dose rates at the skin level (sk) and 0.5 m and 1.0 m away from the skin of the patients.

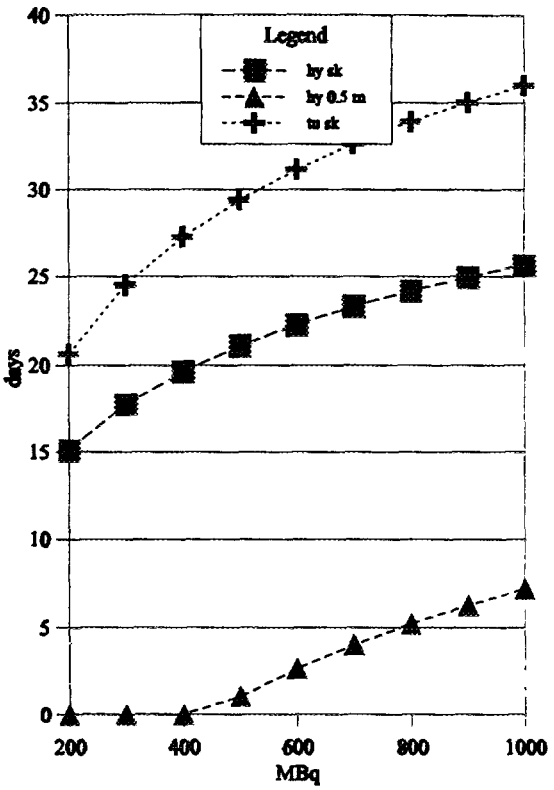

Fig. 2. Restriction times [in days] for the staff at 40 h of work per week for patients treated for immunogenic hyperthyroidism (hy) or thyroid tumor (tu) with various radioactivities [in MBq] of I-131. The times were calculated after measurements of the exposure dose rates at the skin level (sk) and 0.5 m and 1.0 m away from the skin of the patients.

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THE BRITTLE BASIS OF LINEARITY

Eike Roth, RWE Energie AG, Kraftwerk Mülheim-Kärlich,
POB 14 32, 56210 Mülheim-Kärlich, Germany

ABSTRACT

The LNT-theory of cancer generation by ionizing radiation is commonly vindicated by 3 arguments: The stochastic character of irradiation hits to cells, the monoclonality of cancer generation, and the error proneness of DNA-repair. It is shown that this conclusion is logically inadmissible. Equally, the rescuing attempts tried by some LNT-supporters are not successful. It contradicts the laws of thinking to exclude threshold and hormesis in this way.

INTRODUCTION

The Linear No-Threshold (LNT)-theory of cancer generation by ionizing radiation is commonly vindicated by the stochastic character of cells being hit by irradiation and by the monoclonality of cancer generation, i. e. the development of a malignant tumor out of a single transformed cell (e. g. [1] and [2]). These two features are said to enforce linearity in the low-dose region, where only part of the cells in a tissue are being hit by irradiation (this part being admittedly strictly proportional to dose). The frequently observed stimulation of biological defense mechanisms by low doses of irradiation („adaptive response", e. g. [3]) is said to potentially influence the slope of the dose-effect curve, but not its threshold-free linearity „unless a totally error-free repair system (of DNA-damages) is assumed", which is not likely to occur in biology.

On the basis of these 3 presumptions (later on referred to as „vindications") the „official radiation-protection establishment" feels that a threshold in the dose-effect curve or even an hormetical (benefitial) effect below this threshold can be excluded by logical laws of thinking. The fundamental shortcomings of this deduction shall be shown in the following:

1. INTERACTION WITH OTHER CAUSES OF CANCER

Cancer develops as a consequence of multiple DNA-damages in a cell. These damages can originate from different sources: reproduction failures, attacks of oxygenic radicals (which on their part can result from natural metabolism, chemical noxes, ionizing radiation and others), chemical attacks of so called carcinogenes, direct energy transfer of ionizing radiation, thermal instability, and so on. Life has developed defense mechanisms against all these attacks, repair mechanisms to restore the undamaged situation if an attack is nevertheless „successful", and incapability of dividing, apoptosis and immune-system reactions to eliminate cells with unrepaired or ill-repaired damages. Whatever the root causes, the biological defense system normally prevents serious consequences, and - measured to the number of attacks - cancer is a very rare consequence.

In this article all irradiation induced cancers shall be denominated „radiation cancers" and all others shall be denominated „spontaneous cancers" In the low-dose region the number of spontaneous cancers is much higher than the number of irradiation induced cancers

The 3 vindications of the LNT-theory quoted above might be justified if radiation was the only source of cancer But with the mere occurrence of spontaneous cancers they necessarily lose their validity, if there is any possibility of irradiation to interact with the number of spontaneous cancers Of course, irradiation cannot be expected to influence the intensity of spontaneous carcinogenic causes, but there is definitely a possibility for irradiation to influence the probability of spontaneous attacks leading to macroscopic cancers In principle, ionizing radiation can exercise an influence on the efficiency of all biological defense mechanisms against spontaneous cancers, and for many of them we have strong experimental indications that such influences actually exist („adaptive response")

Certainly, those indications cannot be considered as a proof But if we accept at least on principle the possibility of adaptive response, the cited vindications for linearity inevitably lose their validity And if the adaptive response indeed reduces the number of spontaneous cancers, threshold and even hormesis below the threshold only are a question of whether this reduction outweighs the number of irradiation induced cancers or not Evidently, threshold (and hormesis) can exist with stochastic irradiation hits and monoclonality of cancer generation and completely without error-free repair mechanisms

2 INTERACTION OF IRRADIATION HITS

But even independent of the existence of a second source of cancer, ever when we have irradiation hits to cells, and these hits are stochastic in nature and independent of each other in the low-dose region, the effects of these hits need not to be independent likewise For example, the stimulation of adaptive response could well be transferred from one cell being hit by radiation on to neighbouring cells by some transmitters, and the thus stimulated regions may overlap to a different extent depending on dose or dose rate This generally could lead to non-linearity, albeit a steadily growing form of the dose-effect relationship is still possible And if the amplification of the response effect by transfer of information to neighbouring cells is large enough to reduce the number of spontaneous cancers more than the irradiation itself produces cancers in the low-dose, low-overlapping region, even a negative slope and a threshold are possible (which would be a combination of no 1 and no 2)

A special form of overlapping response is the stimulation of the immune-response system of the whole body It presumably eliminates privilegedly cells in the higher stages of cancerous transformation or fully transformed cells It can introduce non-linearity and has at least in principle the potential to reduce the spontaneous cancer rate to overcompensate the rate of radiation induced cancers

3 RESCUING ATTEMPTS

To preserve the LNT-theory some of its supporters stress the crucial part double strand breaks probably play in carcinogenesis because of their substantially higher failure rate in cellular repair-processes and the much higher percentage of double strand breaks in radiation damages compared to damages from other sources But this influences only the strength of the cancer-generating part of radiation effects and does not jeopardize the cancer-reducing part via

adaptive response affecting the occurrence of spontaneous cancers Threshold and hormesis are still possible on the same conditions as discussed above

Other LNT-advocates hypothesize that a higher repair-rate due to adaptive response might also bring about a higher rate of misrepairs But firstly, if the misrepair-rate rose proportional to the repair-rate, we would not see anything of the adaptive response, contradicting our experimental evidence And secondly, if any effect of a higher rate of misrepairs occurs at all it would be very surprisingly, if it lead to a linear dose-effect relationship Hence, the theorized possibility of an increased misrepair-rate is as well not a good argument against the chance of threshold and hormesis

Again others argue with mathematical models They give some formula describing the cancer generation by radiation with no sink-term, administer some customary mathematical approximations, which in fact linearize the curve in proximity of the zero point, and pass the result off for proof of the LNT-theory in low-dose regions (for details see [4]). In all these cases linearity is a consequence of the selected model and performed reductions, not a description of reality, its epistemological worth is zero

Several other rescuing attempts have been tried, all with the same negative result

SUMMARY

Generally speaking, possible dose-depending interactions of the effects of primarily independent irradiation hits to cells can produce non-linearity and possible interactions between irradiation and spontaneous cancer generation can result in a threshold and hormesis Neither the 3 vindications cited in the introduction nor the desperate rescuing attempts can prove linearity Linearity is a convenient bookkeeping procedure, but it is not well-grounded by scientific evidence and it is not supported by logical laws of thinking on the basis of the official arguments in favour of it Of course, if the arguments for a theory fail, this theory need not to be wrong itself But it may be a good reason to look at that theory in another way

SUPPLEMENTARY REMARKS

1 If there was no interaction of any sort between irradiation and spontaneous cancers, an hormetic effect of irradiation (with respect to cancer frequency) would naturally be impossible and a threshold would only be possible in case of absolutely error-free repair mechanisms The latter not being a realistic assumption in biological systems, the interaction of irradiation and spontaneously generated cancers is a prerequisite for threshold and hormesis But actually, such an interaction is not only supported by numerous experiments showing an adaptive response after low-dose irradiation, it is also more or less generally believed to be a realistic phenomenon in radiation effects on men The multiplicative model of cancer generation by ionizing radiation itself is nothing less than a special form of such an interaction There is no clear understanding of the processes to lead to this multiplicative impact, but it is rather difficult (albeit possible) to think of processes, which would result in a linear dose-effect relationship the whole way down to zero dose But whatsoever the detailed processes, the multiplicative model in any way assumes an interaction between irradiation and spontaneously generated cancers and therefore it smoothes the way for hormetic effects in the low-dose region

2. All life on earth has developed in a substantially irradiating environment. In fact, the irradiation level has been significantly higher when life started to develop from primitive forms. Experience shows that life developed strategies to adjust to all routinely affecting interferences in an optimized way. There is no reason to assume that radiation would be the singular exception of this general rule. In the contrary, it rather seems prudent to assume that human beings as the probably most advanced result of evolution are well-adapted to cope with the upper limit of frequently occuring natural radiation exposures. A threshold in radiation effects does not seem to be in contradiction to our general knowledge of life on our planet earth.

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MONITORING AND CONTROL OF OCCUPATIONAL RADIATION EXPOSURE IN SWITZERLAND

XA9745546

M. MOSER
Federal Office of Public Health,
Bern, Switzerland

Abstract
Occupational exposure is the most prominent example for the prolonged exposure to low level ionizing radiation characterized by low doses and dose rates. In this paper the occupational exposure in Switzerland is presented and the regulatory control of this exposure in the framework of the new *radiation protection regulations is discussed.*

1. OCCUPATIONAL EXPOSURE IN SWITZERLAND

According to the statistics for 1996 [1] there were about 62000 radiation workers in Switzerland. Dose distributions in the different employment categories are shown in Table I. Almost the whole collective dose comes from the four distinguished fields: nuclear power plants, medicine, industry and research. These main fields have very different exposure characteristics and therefore different possibilities for exposure optimization.

More than half (53%) of the total collective dose is received by workers of the five Swiss nuclear power plants. The dose is divided between employees (30% of the workers, 37% of the collective dose) and contract workers. There are only about 1% women. The major part of the exposure comes from external photon radiation. Exposure from neutron radiation and internal contamination are negligible.

About half of all radiation workers are employed in medicine, about an equal number in hospitals and in the private medical practices. In 1996 they accumulated 13% of the total collective dose, 77% of it in hospitals. This is the only field with predominantly female radiation workers (64%). They received 48% of the collective dose in medicine.

19 % of the total collective dose is received by workers of universities and research institutes, mainly of the two research centers: the Paul Scherrer Institute and the European Organization for Nuclear Research. The exposure in these institutes is characterized by very different and inhomogeneous radiation fields mainly from accelerators. About 22% of the accumulated dose comes from neutron radiation. Radiation workers are both employees and temporary researchers, 17% are women.

Industry contributes 12% to the total collective dose. About 75% of it comes from tritium incorporation in the luminizing industry, received almost exclusively by women.

In the category „others", dentists, veterinary practices and public services are put together. This group is characterized by a relatively large number of radiation workers, but very small radiation doses (3% contribution to the total collective dose).

TABLE I. EFFECTIVE DOSES FOR EXTERNAL AND INTERNAL RADIATION 1996: NUMBER OF PERSONS AND COLLECTIVE DOSE [a]

Dose bracket [b] (mSv)	Nuclear power plants	Universities Research	Medicine	Industry Trade [c]	Others	Total
0 - 1	3020	9520	30034	3015	13917	59506
1 - 2	493	191	105	70	19	878
2 - 3	312	83	33	64	4	496
3- 4	206	46	22	45	1	320
4 - 5	116	25	13	25	1	180
5 - 6	102	14	14	21		151
6 - 7	60	10	4	8	1	83
7 - 8	45	2	9	10		66
8 - 9	26	2	1	10	2	41
9 - 10	17	1	2	4		24
10 - 11	14	2		5		21
11 - 12	7		1	5		13
12 -13	3		1	1		5
13 - 14	2		2			4
14 - 15	1			1		2
15 - 16	3					3
16 - 17				1		1
17 - 18				1		1
18 - 19				1		1
19 - 20						
20 - 50				1		1
> 50						
Total	4427	9896	30241	3288	13945	61797
Collective dose [Person-Sv]	5.43	1.89	1.32	1.22	0.29	10.15
Rad. workers with Dose = 0	1402	6824	27120	2745	12853	50944
Number of women	62	1648	19310	970	9759	31749
Women collective dose [Person-Sv]	0.01	0.10	0.64	0.92	0.16	1.83

[a] 54604 persons were monitored for external radiation only, 787 only for internal radiation and 6406 for both

[b] Doses which lie exactly on bracket boundaries are allocated to the lower brackets.

[c] In the category „Industry" the number of radiation workers with a dose=0 and the data for women were estimated for the 787 persons being monitored only for incorporation (as these data are not available from the Registry).

2. REGULATORY CONTROL OF THE OCCUPATIONAL EXPOSURE

The regulatory control of the occupational exposure is defined in the Radiation Protection Ordinance of 22 June 1994, in effect since 1. January 1995. The Ordinance is based on the ICRP-Publication 60 [2]. With the Ordinance the new dose quantities Hp(10) and Hp(0.07) are introduced

together with the new dose limits: 20 mSv per year, whereby the dose may amount to 50 mSv per year with the approval of the regulation authority, provided that the cumulative dose of the past five years remains below 100 mSv. A limit of 5 mSv per year is to be complied with for adolescents in the age group 16-18 years. For women exposed to radiation in the course of their work, the dose equivalent at the abdomen is limited to 2 mSv from knowledge of a pregnancy until its end. The allowed effective dose as a consequence of incorporation is 1 mSv for the same time interval. The occupational lifetime dose is no longer subject to a limit. The newly introduced concept of effective dose now permits the addition of the doses due to external and internal irradiation.

The monitoring of external exposure for radiation workers is performed by 10 approved dosimetry services, mainly using thermoluminescent dosimeters. Only one service uses film dosimeters. Some dosimetry services also provide individual monitoring for internal exposure, otherwise this is done locally by the companies which use unsealed sources.

Three national authorities share the supervision in the field of radiation protection. The Nuclear Safety Inspectorate provides the supervision for the radiation workers in the nuclear installations, the National Accidental Insurance Organization oversees the radiation workers in industry and the Federal Office of Public Health (FOPH) is responsible for all other radiation workers, mainly in the fields of medicine and research.

Since 1990 the FOPH operates the National Dose Registry [3]. It contains personal, employment and dosimetric data for all radiation workers in the country. The data are transferred monthly from the dosimetry services to the Registry. The external exposure part of the above mentioned statistics is done using the data in the Registry. Incorporation data are not yet included in the Registry. For these statistics the data from the dosimetry services were used.

In addition to the dose limits an intervention level of 2 mSv per month has been introduced in the supervision field of the FOPH. Each case exceeding this level has been examined and documented. An analysis of these cases in the last 15 years is underway.

3. DISCUSSION

The occupational radiation doses in Switzerland are generally very low. The annual average dose ranges from 1.23 mSv for workers in the nuclear power installations to 0.02 mSv for category „others". The majority of radiation workers are monitored but not really exposed. In 1996 only about 18% of all radiation workers have had a measurable dose with annual mean values of: 1.8 mSv for nuclear power plants, 0.62 mSv for universities and research, 0.42 mSv for medicine, 2.15 mSv for industry and 0.27 mSv for „others".

With the introduction of the new ordinance and the new dose limits, the occupational exposure has not changed drastically. The collective dose and the average doses remained almost the same. One change in the dose distribution can nevertheless be noticed: the higher doses are pushed towards the „middle region" (about 10 mSv), probably because one is afraid to exceed the limit.

A second change can be noticed for the cases exceeding the dose limits. In the previous years they appeared mainly as isolated events, where an annual dose has been made by one single monthly dose. Now it may occur that during a normal operation with an exposure of about 2 mSv per month, the annual dose limit can be exceeded. By investigating cases above 2 mSv per month several such potential cases could be detected before they exceeded the limit. This occured mainly in the field of interventional radiology and angiography. In some cases the exposure could have been easily reduced, but in some others it was not possible. In these cases a 50 mSv annual dose limit has been approved considering the justification principle and the 5-years dose limit.

One specific problem is how to apply the dose limits to pregnant women. So far the employer has to inform female radiation workers of the danger from radiation and the dose limits during the pregnancy. In 1996 the first case exceeding this limit appeared. A woman in the luminous painting industry accumulated a dose of 5.2 mSv during pregnancy (where the limit is 1 mSv).

Luminous painting industry is the field where the women accumulate the highest occupational doses. The appropriate supervision authority put a big effort into optimizing the exposure in this field. There are a number of technical possibilities to reduce tritium incorporation, but their financing is almost unbearable for the small luminous painting companies.

The main reduction of the total collective dose (about 30%) has been achieved in 1990 due to optimizations in the field of nuclear power plants [4]. It seems that further dose reduction in this field is not very easy.

Another field with a potential for improvement of radiation protection and for exposure optimization is interventional radiology and angiography. This is a relatively new, strong developing area, with high radiation exposures because of long exposure times and small distances from the radiation sources. In addition the measured doses are underestimated because dosimeters are carried underneath protective aprons. In contrast to the classical, well established applications in medical diagnosis in this field the corresponding personnel is less educated in radiation protection and is often even not declared as occupationaly exposed. Therefore there is great need for better monitoring of the individual exposure and for better radiation protection education.

4. CONCLUSION

The introduction of the new lower dose limits for occupational radiation exposure posed no problem in Switzerland thanks to the already existing high level of the radiation protection in the country. One bigger effort to reduce the doses in the field of nuclear power plants has been done in 1990 resulting in a dose reduction of about 30% of the total collective dose. At the moment the biggest potential for further dose reduction lies in the field of interventional radiology and angiography. We believe that this can be achieved through better education of the radiation workers in this field. This would have two advantages: an occupational dose reduction on one side and lower doses for the patients due to the better consciousness of radiation exposure on other side.

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Some Problems in the Acceptability of Implementing Radiation Protection Programs

Robert H. Neill
New Mexico Environmental Evaluation Group
7007 Wyoming Blvd. NE, Suite F-2
Albuquerque, New Mexico 87109
USA

ABSTRACT

The three fundamentals that radiation protection programs are based upon are, 1) establishing a quantitative correlation between radiation exposure and biological effects in people, 2) determining a level of acceptable risk of exposure and 3) establishing systems to measure the radiation dose to insure compliance with the regulations or criteria. The paper discusses the interrelationship of these fundamentals, difficulties in obtaining a consensus of acceptable risk and gives some examples of problems in identifying the most critical population-at-risk and in measuring dose.

Despite such problems, it is recommended that we proceed with the existing conservative structure of radiation protection programs based upon a linear no threshold model for low radiation doses to insure public acceptability of various potential radiation risks. Voluntary compliance as well as regulatory requirements should continue to be pursued to maintain minimal exposure to ionizing radiation.

1. BACKGROUND

While the twentieth century has seen ionizing radiation become an indispensable tool in medicine, science, engineering and electrical power, society has been uncomfortable in recognizing and accepting risks of the inevitable low doses of ionizing radiation associated with those benefits. Additionally, the international scientific community has been less than totally successful in convincing society that the quantitative correlations of radiation insult with injury in the development of risk coefficients provide bounding limits of potential harm. Lastly, the various national and international authorities charged with the responsibility of "drawing the line" of an acceptable risk for various sources continue to be queried on the reasonableness of such determinations despite the fact that all these activities have been conducted in the public domain.

2. OBJECTIVE

Another way of stating the objectives of this conference is to consider the willingness of society to pay to reduce the risk assumed to be associated with low doses of radiation. We have a responsibility to reduce a radiation risk by the expenditure of funds. At some point the decrement in risk (dose) per increment in cost ($) becomes a poor investment as shown in Figure 1. The decision of where to draw the line for optimal radiation protection is a societal one and there needs to be better recognition that the process is a public one involving researchers in universities and laboratories, biological and epidemiological investigators, environmentalists, and regulators from both governmental and voluntary standards setting agencies. The decisions are broadly based.

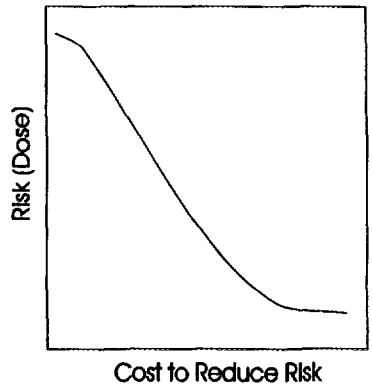

Fig. 1. Expectations to Reduce Potential Risk

3. INTERRELATIONSHIPS BETWEEN LICENSEES, REGULATORS AND RESEARCHERS

In limiting individuals and populations to radiation exposure, the prevention of exposure is always a better investment than corrective actions after a release has occurred. To this end, it is essential that regulatory control agencies, scientific research groups and the regulated licensees work together to achieve the optimal minimization of radiation exposure. It is essential that all three parties understand the strengths and limitations of the data sets and analyses. Efforts for voluntary compliance can be more cost effective, such as minimizing unnecessary diagnostic medical radiographs and encouraging the use of shorter lived radionuclides or lower energies for both diagnostic and therapeutic medical applications.

4. ESTIMATES OF DOSE

The use of estimates of radiation dose to people to determine compliance with dose-based standards is a fundamental axiom in the field of radiation protection. It enables one to quantify the absorption of electro-magnetic energy in the particular organ of interest, adjust for the biological responsiveness of the organ for a particular radiation type and energy range, and sum the insults from different radiation emissions to different organs. It is a better indicator than those used in industrial applications of the product of the concentration of a toxic chemical times the duration of the exposure. The latter has been used to evaluate exposures from the decay of radon-222 in air. Duncan Holaday defined Working Level (WL) as a concentration of radon daughters in equilibrium with 3.7 Bq (100 pCi) of radon-222/liter of air. The product of WL and the number of months of exposure provides the WLM index. Radiation release limits have also been used to supplement estimates of dose to individuals or collective dose calculations.

The following provides illustrations of the complexity and difficulty of generating estimates of dose to be measured against the yardstick of a permissible dose.

4.1. Changes with time

Airborne concentrations of radionuclides will show up in different biota at different times. It is necessary to calculate the infinite dose contribution from each and sum the results. Care must be exercised to insure that all contributors are included.

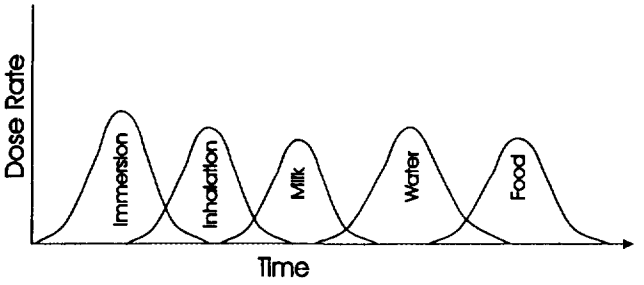

Fig. 2. Contributors to Dose from an Airborne Environmental Release with Time.

4.2. Dose as a function of age of individual exposed

Thyroidal doses from radioiodine in milk vary as a function of age of the exposed individual including the consumption of milk, fractional uptake of iodine from blood to the thyroid and the mass of the thyroid. For a given concentration C in milk, Table I shows the variability of the calculated dose as a function of age with the peak occurring at age 6-11 months. The ratio of the maximum at 6-11 months of age to a 20-29 year old is 10.5. Subsequent studies by Van Middlesworth suggest the uptake factors in the newborn may be low by a factor of 3. This would make the ratio of the dose coefficient for the 6-11 month child to the young adult equal to 32. This illustrates the importance of determining whether there is a population much higher at risk than the mean.

Table I. Dose Coefficient Values From Consumption of Milk Containing Iodine-131 as a Function of Age

Age Group	Dose Coefficient
0-1 months	20
3-5 m	83
6-11 m	105
12-23 m	78
24-35 m	72
36-59 m	62
5-9 years	45
10-14 y	28
15-19 y	21
20-29 y	10

4.3. Non-comparability of data sources

Environmental surveillance monitoring programs may be designed for different purposes which may limit the interchangeability of their data.
Examples include:

(a) Documentation of the absence of contamination
(b) Early warning (air)

(c) Focus on children (milk)
(d) Diet (ingestion)
(e) Body burden (whole body, bone)
(f) Mortality

5. SOME GENERAL OBSERVATIONS

(a) The acceptability of risk is much lower for environmental radiation than for medical radiation.
(b) Allowable radiation exposure has always decreased over the years.
(c) It does not appear that epidemiological investigations or animal studies will enable resolution in the foreseeable future of the threshold concept in dose-effect correlations.
(d) While our level of knowledge of the effects of ionizing radiation on people surpasses knowledge of other toxic substances, society does not demand more definitive studies on the latter. There are relatively few epidemiological studies of the effects of non-ionizing radiation sources such as the use of ultrasound on the fetus, UV tanning booths or microwave diathermy, or (heat) on tissue.
(e) The disposal of radioactive wastes have made it necessary to model and predict the behavior of radioactive material for periods of 10,000 to 1 million years, a new and unique set of calculations.
(f) Probabilistic analyses are becoming increasingly important in replacing deterministic calculations.

In summary, it is important that we recognize both the strengths as well as the limitations in our knowledge in the interdependent applications of radiation insult, the biological consequences of that insult and the reasonableness of the standards to limit that exposure.

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LONG-TERM HEMATOPOIETIC STEM CELL DAMAGE AFTER EXTERNAL IRRADIATION WITH X RAYS

M.T. GRANDE, F. VARAS, J.A. BUEREN
Department of Molecular and Cellular Biology,
CIEMAT,
Madrid, Spain

Abstract

We have investigated the functionality of the lympho-hematopoietic stem cells long-term (9 months) after the irradiation (X rays) of mice at different stages of development, by means of a competitive bone marrow repopulation assay. Our data revealed that a dose of 1 Gy was only capable of inducing significant long-term failures in the functionality of the primitive repopulating cells in mice irradiated at the young-adult stage (12 week-old), but not in mice irradiated at the late stages of foetus development (17 day-old foetuses) nor at the early development of the embryo (4 day-old embryos). The differential generation of long-term stem cell defects as a function of the age was confirmed in mice irradiated with 3 Gy. While no significant effects in the long-term repopulating cells were observed in 4 day-old embryos, significant repopulation deficiencies were observed in this population when mice were irradiated at the 17 day of foetus development, and more markedly at the adult stage of growth. These data offer new evidence about the influence of the developmental stage of the animal on the generation of residual hematopoietic dysfunctions by external irradiation, with particular relevance to the very primitive lympho-hematopoietic stem cells.

Introduction

All the hematopoietic blood cells are generated by a number of committed progenitors, which are characterized by a limited life-span, and which therefore depend on a very small population of self-renewing hematopoietic stem cells (HSCs). The HSC compartment is, however, a non-homogeneous population and although early data suggested that the CFU-S population represented the HSCs of the mouse, recent observations have evidenced that other more primitive populations with long-term lympho-hematopoietic repopulating capacity can be separated from the CFU-S population [1].

Marked differences in the hematopoietic damage produced by the contamination with α-emitting radionuclides or by exposures to low LET radiation have been observed during the embryonic, foetal, neonatal and adult stages of the life of experimental animals [2-6]. These studies showed that, in comparison to γ-radiation, α-particles are extremely damaging to developing hematopoiesis, indicating that a higher RBE than that considered for stochastic effects, should be given to α-particles when the number of hematopoietic progenitors is considered as a biological end-point [3]. In particular, the analysis of the CFU-S population in mice contaminated with α-emitting radionuclides suggested that the hematopoiesis of the embryo is up to 1,000 fold more sensitive than the postnatal hematopoiesis [2].

Given that the bone marrow (BM) competition assay is currently the experimental procedure which more closely defines the functional properties of the self-renewing HSCs [7], we have investigated by this procedure the functionality of the HSC compartment in mice which had been irradiated with X rays at different stages of growth.

Material and Methods

Mice and X-irradiation: B6CF1 (♀C57Bl/6 x ♂Balb/c) mice were used throughout these experiments. Pregnant females (corresponding to the 4th and 17th day of embryonic growth), and young adult mice (12 week-old) were total body irradiated (TBI) using a Philips MG 324 X-ray machine, at 300 kV, 10 mA, HVL: 3.2 mm Cu and a dose rate of 1.03 Gy/min.

Competitive Bone Marrow Repopulation Assay: To determine the functionality of the lympho-hematopoietic SCs, experiments of BM competition were conducted [7,8]. In these assays, BM cells from irradiated male mice were mixed together with equivalent amounts of BM from non-irradiated females and transplanted into myeloablated female mice [8]. Recipients of the chymeric BM were killed at 9 months post-transplantation, and their BM and thymus were dissected and processed for DNA extraction. The repopulating capacity of the irradiated BM was then determined by dot-blot hybridization using a probe for the Y chromosome (See figure 1).

Results and Discussion

Four day-old embryos, as well as 17 day-old foetuses and 12 week-old mice were irradiated with doses of 1 Gy and 3 Gy of X rays. The times at which mice were irradiated correspond to significant periods in the development of the mouse hematopoietic system [9], and were used previously to investigate the hematopoietic effects induced by the contamination with α-emitting radionuclides and irradiation with low LET radiation [2,5]. Although the previous studies have investigated the hematopoietic long-term effects induced by ionizing radiation during different stages of development, our research is focused on a long-term repopulating precursor, closely related to the self-renewing lympho-hematopoietic stem cell.

To investigate deficiencies in the functionality of this precursor as a result of the irradiation, the repopulating capacity of a test BM sample was evaluated with respect to a reference BM which was co-transplanted with the test BM. As shown in the protocol represented in figure 1, the lympho-hematopoietic cells generated by the test BM sample were distinguished from the reference and the residual surviving cells of the recipient by genetic analyses, using a probe for the Y chromosome. With the aim of evaluating long-term hematopoietic defects produced as a residual consequence of the irradiation, the functionality of the HSCs was assayed at 9 months post-irradiation. On the other hand, with the aim of investigating the functionality of a very primitive lympho-hematopoietic repopulating cell, the competitive repopulating capacity of the irradiated BM was tested, both in the thymus and the BM of recipients, also in the long-term (9 months) post-transplantation.

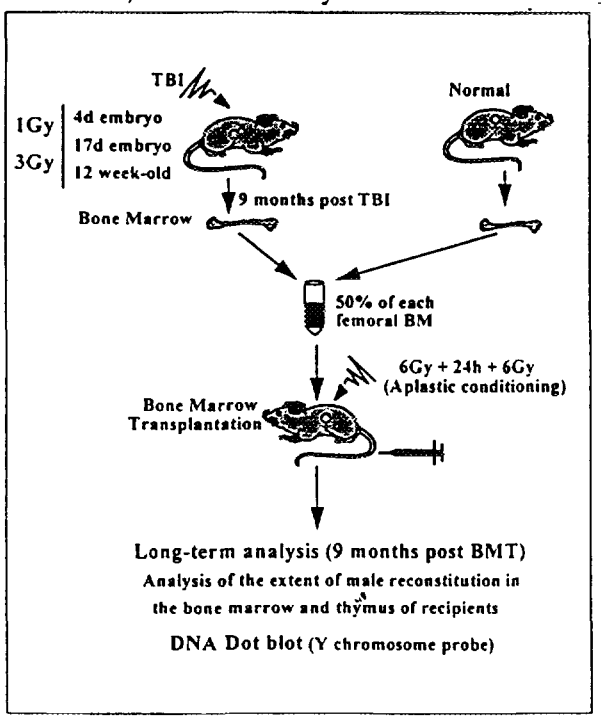

Fig. 1. Experimental procedure for evaluating the competitive repopulation capacity of bone marrow cells after irradiation of mice at different stages of development.

Data in figure 2a shows that only in the case of young-adult irradiated mice, a dose of 1 Gy was capable of inducing a residual defect in the long-term repopulating cells; an effect which was significant when the myeloid BM cells of recipients were analysed. Figure 2b shows that doses as high as 3 Gy were also uncapable of inducing residual effects in the repopulating function of the HSCs in 4 day-old embryos. However, significant residual dysfunctions in the repopulating function of the HSCs were evidenced when 17d old-embryos or adult irradiated mice were analysed. It is of significance, however, that a more marked repopulation defect was observed in the group of adult-irradiated mice than in the foetus-irradiated group, suggesting that the sensitivity of the mouse for generating functional stem cell defects is directly related to the developmental stage of the animal. Either a genetic damage in the self-renewing hematopoietic stem cells [10,11], the generation of a functional damage in the stromal microenvironment [4,12,13,14], or even a proliferative exhaustion of stem cells which survive the irradiation [15], could be involved in the HSC repopulation defects described in this study.

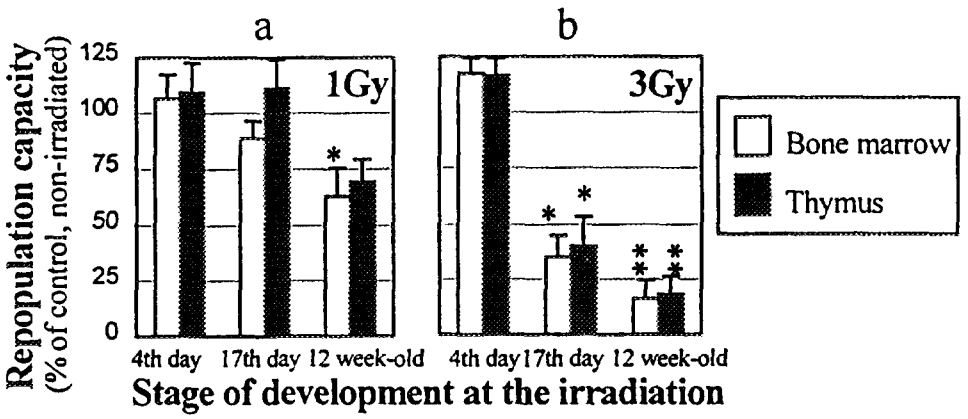

Fig. 2. Analysis of the competitive repopulation capacity of bone marrow samples obtained 9 months after irradiation of mice with a single dose of 1 Gy or 3 Gy-X rays at different stages of development (Data show the mean value ± standard error of 2-6 recipients per point. Significantly different from control, using Student's t-test: * $p<0.05$; ** $p<0.01$).

Acknowledgments

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LEUKEMIA IN THE PROXIMITY OF A GERMAN BOILING WATER NUCLEAR REACTOR: EVIDENCE OF POPULATION EXPOSURE BY CHROMOSOME STUDIES AND ENVIRONMENTAL RADIOACTIVITY

Bettina Dannheim, Anna Heimers, Boris Oberheitmann, Inge Schmitz-Feuerhake, Heike Schroder, Heiko Ziggel

University of Bremen, Dept of Physics, P O Box 330440, D-28334 Bremen, Germany

Abstract

The detection of an exceptional elevation of leukemia in children appearing 5 years after the start-up of the nuclear power plant Krummel in 1983, accompagnied by a significant increase of leukemia cases in adults gave rise for investigations of radiation exposures of the population living near to the plant The rate of dicentric chromosomes in penpheral blood lymphocytes of 7 parents of leukemia children and 14 other inhabitants in the proximity of the plant was significantly elevated and showed ongoing exposures over the years of operation This finding gives rise to the hypothesis that chronic leakages by the reactor had occured This assumption is supported by the identification of artificial radioactivity in air, rain water, soil, and vegetation registered by the regular environmental monitoring programme of the nuclear power plant Calculations of the corresponding source terms show that the originating emissions must have been well above authorized annual limits The bone marrow dose is supposed to be originated mainly by incorporation of bone-seeking β- and α-emitters

Introduction

A cluster of childhood leukemia was observed in the community of Elbmarsch in Northern Germany in 1989-91 (1, 2, 3) All five cases had been living within a distance of 5 kilometers from the nuclear power plant Krummel (KKK), located at the river Elbe about 35 km south-east of the city of Hamburg Since 1994, four additional cases in the 5 km surrounding of KKK (Fig 1) appeared All these cases occured at ages ≤ 10 years, with five of them at very early ages (1 8 - 4 years), see Table 1 Furthermore, a leukemia in a young adult and an aplastic anaemia in a child had been diagnosed there

The mean number of children (up to the age of 14) living in the 5 km surrounding of KKK between 1986-95 was about 5400 (4) Corresponding to the West German Registry of Childhood Cancer (5), the mean incidence of acute leukemia between 1980 and 1990 was $4\,3 \cdot 10^{-5}\ a^{-1}$ in individuals aged < 15 years The expected number of leukemia cases in children in the 5 km region around KKK for the period 1990-96 would be 1 6, therefore the elevation of childhood leukemia in that region corresponds to a factor of 5 6

The nuclear power plant is a 1300 MW_e boiling water reactor - the largest one in the world - and started operation in 1983 In the vicinity of this plant the nuclear research institute GKSS (Gesellschaft fur Kernenergieverwertung in Schiffbau und Schiffahrt), which was established in 1958, operated two research reactors of 5 and 15 MW (Fig 1)

The governments of the Federal States of Lower Saxony and Schleswig-Holstein had set up a board of experts to identify possible causes for the observed leukemia cluster Potential risk factors such as X-rays, chemicals and previous diseases of the affected families were investigated and could be excluded None of the parents had been exposed to occupational or unusual medical irradiation One family, however, was found to be living in a house with a mean radon concentration of 450 Bq/m^3 in their living rooms However, the only common factor remaining was proximity to the two nuclear establishments With respect to KKK not only the spatial relationship of the observed leukemia cluster to the nuclear power plant is remarkable but also the temporal correspondence The first case of malignant blood diseases was diagnosed 5 years after KKK had been commissioned

In 1994, a retrospective epidemiological study by Hoffmann and Greiser (6) showed an elevation of leukemia also in the whole population in the vicinity of KKK For the period 1984-93 they found a statistically significant elevation for males (+56%) within a radius of 5 km around the nuclear power plant The increase was restricted to the period 1989-93, i e beginning 5 years after the start-up of KKK as well

Due to these facts, a careful investigation of the possible relationship between the observed cluster and the local nuclear facilities was imperative, although whole body counting of inhabitants performed in 1991 gave negative results and analyses concerning the emission of long-lived fission products failed to demonstrate a consistent pattern of increased radionuclide concentrations in soil and vegetation (7) However, there were several isolated findings of elevated activities in different environmental media at different times (8)

To examine whether the population living in the vicinity of KKK was subjected to elevated exposures of ionising radiation, an analysis of dicentric chromosome aberrations in lymphocytes of the peripheral blood was carried out in a group of inhabitants of the Elbmarsch community In parallel, analyses of data on environmental radioactivity measurements were conducted

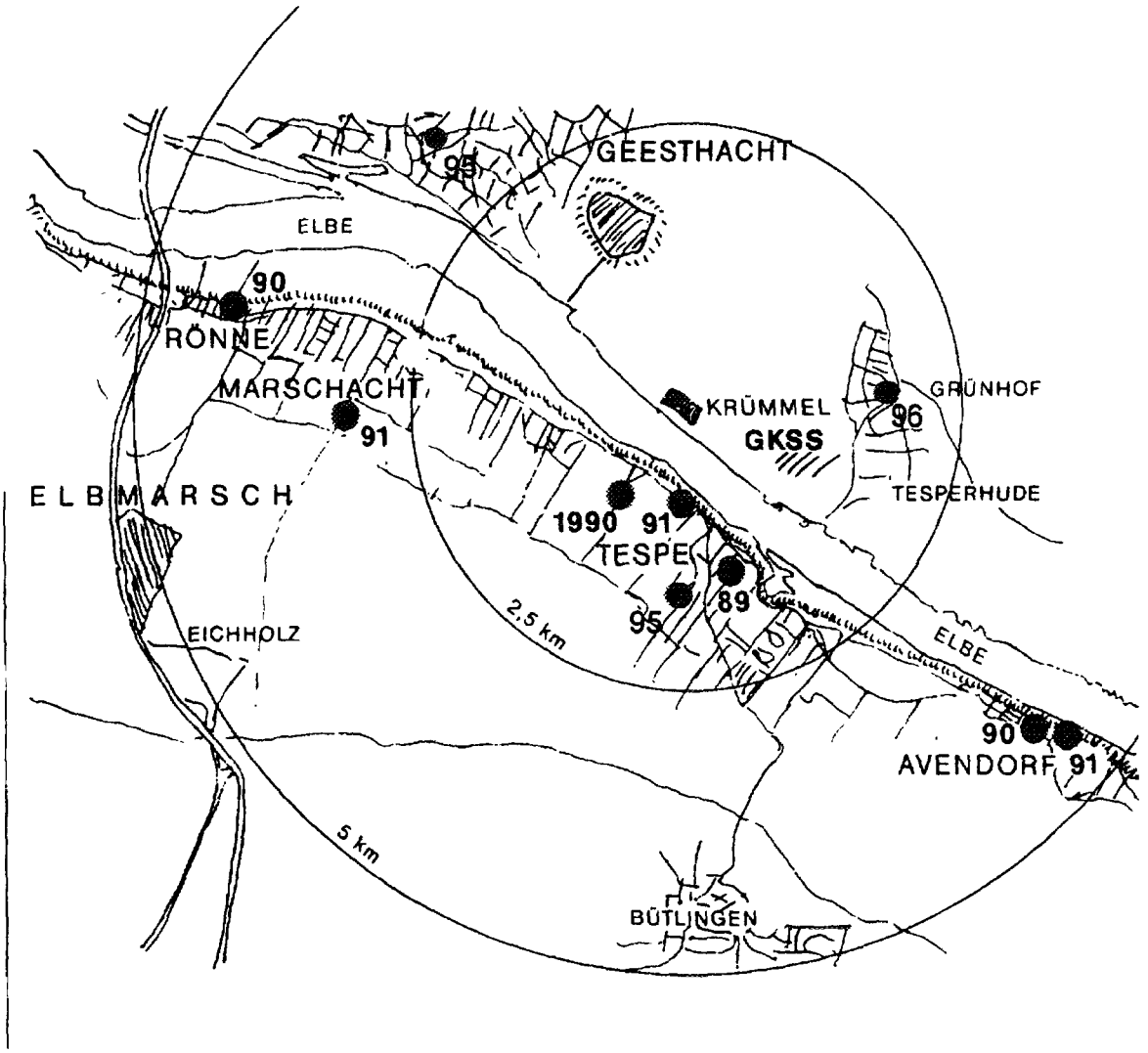

Figure 1: Map of the surrounding of the nuclear power plant Krümmel. Black Points indicate homes of leukemia cases and aplastic anaemia with year of diagnosis. Circles show the distance to KKK. (One more case of 1994 is not registered because the location is unknown.)

Assessment of radiation exposure by investigation of dicentric chromosome aberrations

The retrospective assessment of radiation exposure by chromosome aberration analysis comprised 21 individuals (19 females and 2 males), inhabitants or former inhabitants of the Elbmarsch community. All of them were residing within a distance of 5 km in the southern direction from KKK. At the time the blood samples were taken (in 1992, 1993 and 1995) these volunteers were aged 28-45 years. Four women were selected because of the fact that they had settled in the village after 1986 (Table 2A, nos. 8-11), as had one of the leukemia families (Table 2A, no. 4). Seven subjects were parents of the children having diagnosed leukemia in the community of Elbmarsch.

The control group consisted of 25 healthy adult persons (9 females and 16 males) living in the city of Bremen, 100 km south-west of Hamburg. At the time of blood sampling between 1988 and 1994 they were aged 17-57 years.

A detailed questionnaire was completed by each of the subjects. Exclusion criteria were previous occupational exposures, greater than average diagnostic medical irradiation, or exposure to chemical mutagens. Smokers (more than 10 cigarettes per day) were also excluded.

To evaluate the rate of dicentric chromosomes and centric ring chromosomes lymphocyte cultures and slide preparations were made according to standard cell cycle controlling methods (9). The collection of metaphases was facilitated by a semi-automatic computerized system which includes data management (METASYSTEMS, Sandhausen, Germany). Only first division metaphases with 46 centromeres were analysed and all structural aberrations were registered. The results are given in Table 2.

Compared to the laboratory control ($0.46x10^{-3}$) the investigated population of Elbmarsch showed a highly significant elevation of dicentric chromosomes with a rate of $1.77x10^{-3}$ dicentric chromosomes/metaphase ($p<0.01$ (10)). The highest individual number of dicentrics (excluding case no. 3 of Table 2A) was found to be 5 dicentric chromosomes in 1,000 metaphases.

Particularly noteworthy was the existence of cells with two dicentrics in the Elbmarsch group (Table 2A, subjects 5, 8, 10, and 12), in contrast to the control group (no cells with more than one dicentric). Additionally, there was one metaphase with 6 dicentrics (Table 2A, subject 3). The aberrations did not follow Poisson distribution but showed a significant overdispersion (11). This was also valid for the entire Elbmarsch population which was investigated, even if the multiaberrant cell is excluded (Table 3). Although the results of the chromosome aberration analysis give evidence that the population of the Elbmarsch community has been severely exposed to ionising radiation in the past (12) an extrapolation of the whole accumulated dose is not adequate since the exposure conditions are unknown.

Fission and activation products in environmental samples

Several media in the environment of KKK are routinely controlled for long-lived gamma emitters (13, 14). The concentration in rain water is measured periodically at three locations near KKK. One of these sampling stations which is situated in a distance of 2.2 km in the main wind direction of KKK shows a decreasing but permanent elevation of the Cs-isotopes 134 and 137 since 1986. These isotopes were elevated compared to the other locations of the KKK monitoring programme and the Cs 137-concentration was at least 10times higher than that at other measuring points in Northern Germany from the 3rd quarter of 1986 until 1993 (15). Thus, an exclusive causation by Chernobyl is unlikely. In addition, the existence of the isotope Cs 134 in these samples shows that the contaminations can not go back to the fallout from nuclear weapons testing because of the short half-life of Cs 134 (2.1 y).

Calculations and measurements demonstrate that the permitted releases of radioactivity by German nuclear facilities will not lead to detectable contamination in the surrounding (16). Therefore, the Cesium findings in rain water are an indicator for repeated releases of nuclides above permitted limits.

Elevated Cs-emissions are confirmed by the results of measurements of dry fallout at different locations near KKK (13). Compared to other locations in Germany the Cs 137 aerosol concentration in air near the ground in the vicinity of KKK was significantly elevated in different quarters in the period 1985-95. It should be noted that these measurements were carried out by three different laboratories; thus, systematic measurement errors can be excluded. Additionally, remarkable concentrations of Sr 90 were found in 1984 and 1988 which are also not explainable by other sources than by emissions of KKK.

Table 1: Observed cases of leukemia and aplastic anaemia in the 5 km surroundings of the nuclear power plant

No.	Born	Sex	Disease	Date of Diagnosis	Age at Diagnosis
1	9/82	f	AA	12/89	7
2	8/86	f	ALL	2/90	3.5
3	2/81	m	ALL	3/90	9
4	3/81	m	ALL	4/90	9
5	3/89	f	ALL	1/91	1.8
6	1970	m	AML	4/91	21
7	9/88	m	ALL	5/91	2.7
8		m	ALL	1994	
9	ca. 1991	m	ALL	1995	4
10	1985	m	ALL	6/95	10
11	1993	m	ALL	6/96	3

AA: aplastic anaemia
ALL: acute lymphatic leukemia
AML: acute myeloid leukemia
m: male
f: female

Table 2: Results of chromosome aberration analysis in adult residents of Elbmarsch (A) and in controls (B)

A) Elbmarsch group

No.	parent of leuk. child	resident in Elbmarsch	date of blood sampling	No. of analysed metaphases	No. of dicentrics	rate of dicentrics x 10^{-3}
1	yes	since <1984	Jan. 1992	1005	2	2.0
2	yes	since <1984	Jan. 1992	390	2	5.1
3	yes	since <1984	Jan. 1992	1000	3*	3.0
4	yes	<1984 -1991	Jan. 1992	1001	2	2.0
5	yes	since <1984	Jan. 1992	664	2**	3.0
6	yes	since <1884	Oct. 1995	1010	2	2.0
7	yes	since <1984	Oct. 1995	1010	0	0,0
8	no	since 1988	Apr. 1993	1002	5***	5.0
9	no	since 1987	Apr. 1993	1014	0	0.0
10	no	since 1987	Apr. 1993	1097	4***	3.6
11	no	since 1987	Apr. 1993	1034	1	1.0
12	no	since <1984	Jun. 1993	1005	3***	3.0
13	no	since <1984	Jun. 1993	1110	0	0.0
14	no	since <1984	Jun. 1993	1003	1	1.0
15	no	since <1984	Jun. 1993	1005	1	1.0
16	no	since <1984	Jun. 1993	1002	2	2.0
17	no	since <1984	Jun. 1993	1011	2	2.0
18	no	since <1984	Jun. 1993	1008	0	0.0
19	no	since <1984	Jun. 1993	1007	2	2.0
20	no	since <1984	Jun. 1993	1004	2	2.0
21	no	since <1984	Jun. 1993	1009	0	0.0
Total				20391	36	1.77 ± 0.33§

*) Excluding one multiaberrant cell with 6 dicentrics.
**) One cell contained 1 tricentric which was counted as 2 dicentrics
***) Including one cell with 2 dicentrics.
§) Standard error of the mean

B) Control group

No.	date of blood sample	No. of analysed metaphases	No. of dicentrics	rate of dicentrics x 10^{-3}
1 - 25	1988 - 1995	19775	9	0.46 ± 0.15§

§) Standard error of the mean

Table 3: Intercellular distribution of dicentric chromosomes in Elbmarsch inhabitants

	No. of dicentric chromosomes per cell								
	0	1	2	3	4	5	6	s^2/Y^*	u**
incl. multiaberrant cell									
observed	20358	28	4	0	0	0	1	1.90	92.26
expected	20349	41.91	0.04	0	0	0	0		
excl. multiaberrant cell									
observed	20358	28	4	0	0	0	0	1.22	22.58
expected	20354	35.94	0.03	0	0	0	0		

*) relative variance (Y is the mean value)
**) u > 1.96: overdispersion is significant ($p < 0.05$)

Since the start-up of KKK measurements of environmental samples show elevated activities of the nuclides Cs 137 and Sr 90 in soil and plants (13, 14). The Chernobyl accident had only lead to marginal increases of Sr 90 in the German environment (16). Nevertheless, the concentration of this isotope rose repeatly by several Bq/kg (dry mass) against the former fallout background in the grass around KKK. The highest Sr 90 contamination was registered in August 1987 at a location in 10 km distance to KKK, containing 30 Bq/kg (dry mass) which is more than 10fold of the normal concentration in Germany at that time (17). The highest concentration of Cs 137 in grass (103 Bq/kg) was measured in 1988 in a distance of 2 km from KKK (13). This corresponds to an about 100fold increase against the normal value in the vegetation (17).

The environmental monitoring programme for KKK does not demand nuclide specific and continuous measurements of pure β- and α-emitters in the controlled media, except Sr 90 in the air, nor any measurements of short-lived gamma and β-emitters. Nevertheless, there have been occasional findings of short-lived fission and activation products as well as radioactive corrosion products which are also not explainable by the Chernobyl accident. Only after damage of the fuel rods these nuclides would be detectable outside the plant. In these cases leakages of the primary cooling water will be accompanied by releases of Pu and other transuranium isotopes (18).

Discussion

Leukemia elevations have been found repeatedly in the population in the vicinity of nuclear establishments (19, 20, 21). In the case of the Pilgrim nuclear reactor in Massachusetts, a correlation between the leukemia rates in the vicinity of the plant and official information on releases of radioactivity could be established and a cause-effect relationship was derived (22). In Western Germany, an incidence study of childhood leukemia near nuclear establishments in the former countries of the federal republic lead to negative results (24). However, with respect to the innermost of the different circular regions considered (< 5km) and the group of children < 5 years at diagnosis there was a 3fold significant elevation compared to the control regions (23).

The study of Keller and coworkers (23) was restricted to the period 1980-1990, consequently most of the cases of childhood leukemia near KKK were not included. These children became diseased predominantly in very young ages (Table 1). The hypothesis of radiation induction is thus supported by the well-known fact of a higher sensivity of individuals in the prenatal stage and in very early ages. Furthermore, the predominance of diseases in boys (Table 1) corresponds to the findings in the A-bomb survivors showing a male to female ratio of 2:1 in the radiation-induced excess cases (24), while the normal ratio is 1.3:1 (5).

Further evidence of the hypothesis of radiation-induced leukemia in the Elbmarsch region is added by investigations of the latency periods for leukemia found in exposed cohorts. Children at the age of 0-15 years receiving X-ray therapy for ringworm of the scalp showed a maximum rate of leukemia about 4 years after irradiation and 50 % of all cases occured up to this point (28, 29). This corresponds to the distribution seen in the Oxford Survey of Childhood Cancers for leukemia after prenatal exposure to diagnostic X-rays (30), and to considerations about the age-dependency of latencies in the Japanese A-bomb survivors (31).

Assuming 4 years of latency and referring to the first appearance of childhood leukemia in the proximity of KKK in 1990 (Table 1), a single exposure event in about 1986 could be supposed. However, the ongoing occurence of malignancies in Elbmarsch points to continuous contamination and/or the incorporation of radioactivity with a long biological half-life.

By the medical and biological findings discussed in this paper, there is evidence that the population was affected by repeated exposures, because

(i) at least 4 of the children with leukemia were born later than 1987 (Table 1)

(ii) of the well-known decline of the dicentric chromosomes after irradiation (of about 40 % per year) (12) the rates measured in persons of the Elbmarsch do not represent an accumulated exposure Although - as discussed below - it is not adequate to derive a whole body dose from the results given in Table 2A, a dating back of the measured rates of dicentric chromosomes to a single event in 1986 or earlier would yield unrealistic high original rates

(iii) the elevated rate of dicentric chromosomes is rather similar in persons who settled at Elbmarsch before and after 1986 (before 1986 cases nos 1-3 and 5 with 2 9 10^{-3} dicentrics/metaphase, after 1986 cases nos 4 and 6-9 with 2 3 10^{-3} dicentrics/metaphase, see Table 2A)

Dose estimations based on the observed rate of dicentric chromosomes in the inhabitants of Elbmarsch are not sensible, because neither the time nor the condition of exposures are known The findings about overdispersion in the distribution of aberrations per cell give, however, additional information about the kind of exposure Overdispersion of dicentric chromosomes can be caused either by non-uniform or by high LET irradiation Such distributions have been found in blood samples of persons occupationally exposed to e g Plutonium (25), Tritium (26) or Uranium (27) In case of the Elbmarsch population this can not be proved by available data or measurements The observed overdispersion in the present study is also not to be explained by external gamma-irradiation or other kinds of low dose low LET exposure

The supervising ministry in Schleswig-Holstein has denied a relevant contribution of KKK to the exposure of the population by KKK They refer to the results of the extensive gamma monitoring in the surrounding Although there is, indeed, no indication for a severe overexposure by external gamma-irradiation in that region the supposed bone marrow dose may have been caused by incorporation of α- and β-aerosols while the gamma-submersion was negligible Scenarios which lead to such a composition of organ doses are described for accidents caused by cooling water effluent (18) In addition, fuel rod failures are a well-known problem in nuclear reactors Being the greatest boiling water reactor of the world, the Krummel nuclear power plant is a unique installation Last year, it was reported in a TV special that there had been severe problems during construction of the pressure vessel related to welding of single elements The board of experts named for the leukemia study found out information on significant leakages of cooling media from the pressurised system nearly all over the years of operation The quantities rose to 300 l per hour in the year 1986 but increased also to more than 200 l per hour in 1993 and 1996 Further investigations will consider the relevance of these leakages by analysing the pattern of observed nuclides in the surrounding

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COMPARISON OF DICENTRICS, MICRONUCLEI OR APOPTOSIS FREQUENCY IN V-79 CELLS AFTER X-IRRADIATION

M. JAMALI, R. SHUSHTARIAN, A.A. FARSHAD
Ministry of Health/Ministry of Environment,
Islamic Republic of Iran

Abstract. So far,the chromosomal studies are the most established method of biological dosimetry.We compared this method with micronucleus and apoptosis detection method simultaneously in V-79 cells.The frequency of apoptotic cells in low doses (0.1-0.5Gy) are more prominent than tow other methods in Vitro.Persumbaly, apoptosis may be chosen as a preferable alternative biological dosimetry or environmental assessment of biological effects of ionizing radiation [1].

1. Introduction

After radiation accidents or long term radiation absorption, it is important to estimate the absorbed dose by exposed persons in order to plan for their therapy or preventive implications. And even in situations where the physical measurement of dose is feasible,an independent estimation by biological methods can prove very useful.Todays,the most fully applicable biological indicator of exposure to ionizing radiation is the study of chromosomal aberrations for instance dicentrics which are readily recognizable by identifying the two centromers of the dicentric chromosomes [2].

Micronucleus assessment as an alternative reliable method to the scoring of chromosome aberrations have been suggested [3,4,5]. However, remarkable application of apoptosis in cells after irradiation, have been reported, for instance as an indicator in

intrinsic radiosensitivity [6,7] assessment of delayed reproductive death or lethal mutation [8,9,10]

We used established cells (V-79 cells) to compare the quantitative responses of three abovementioned indicators in early responses or in the progeny of irradiated cells simultaneously to find the reasonable method of radiobiological assessment.

2. Material and Methods

Experiments were performed on V79 cells obtained from Dr.B. Michael (CRC Gray , aboratory , Mount Vernon Hospital UK) as reported [8,9].

Doses of X - rays , ranging 0.1 to 12 Gy were given using a 320-kVp energy with filtration of 0.5 mm copper and the dose rate at distance of 70 cm was 0.5 Gy per min for high doses,but in low doses It was adjusted to 0.1 Gy/min, homogeneity in the field was 5% . Chromosome preparation, micronuclei (M.N) assessment and apoptosis detection as reported [8,9,10]. These three end points were assessed in appropriate times , early after irradiation or the Kinetic of their offsprings . The engulfment phenomenon of apoptotic bodies have been detected by either Giemsa or Apoptag™ metods which have been reported for first time *in vitro* [10]. In addition, the experiment was prepared to see whether after a first dose which lead to an increased frequency of delayed dicentrics, M.N or apoptosis, reirradiation of those cells would increase the frequency even more with the same dose. The protocols were planned to have enough cells one week after irradiations, from each dose point which was chosen randomly.

3. Results

The highest frequency of dicentric chromosomes, M.N were obtained 24hr and apoptosis were determined 48hr after irradiation in all ranges of doses in comparison with other assessing times. The frequency of dicentrics and M.N in low doses (0.1-0.5 Gy) were in control level (about 1%), whereas, apoptosis frequency were higher than others, but increased according to linear quadratic dose-response curve up to higher doses, but, this time dependent maximum out come for M.N were different. The frequency of cells with micronuclei increased with dose reached a peak value of approximately 50% at 4Gy, decreasing at higher dose to a plateau at around 30% [8]. The morphological criteria of apoptosis was, an intact shape of the cytoplasm which the nucleus showed condensation either margination or fragmentation [9,10].

The frequency of delayed dicentrics, delayed micronuclei and delayed apoptosis after twice the same dose given at 1 week interval more or less was the same as the delayed frequency of three end points after a single dose independent of actual doses. Interestingly, in all aimes of the study delayed responses was dose dependent up to 3 Gy and then reached a plateau (figure-2).

All experiments were repeated three times and the points in both figures are the mean value of three independent results. In order to quantity the low dose limit of this assay, all the data measured in the time course experiments at low doses up to 0.5 Gy at different times were taken and it was checked using a t-testat doses in which the fraction of three end-points would be significantly above the control that would be the most convenient factor. A significance level p of 0.05 was used in this analysis.

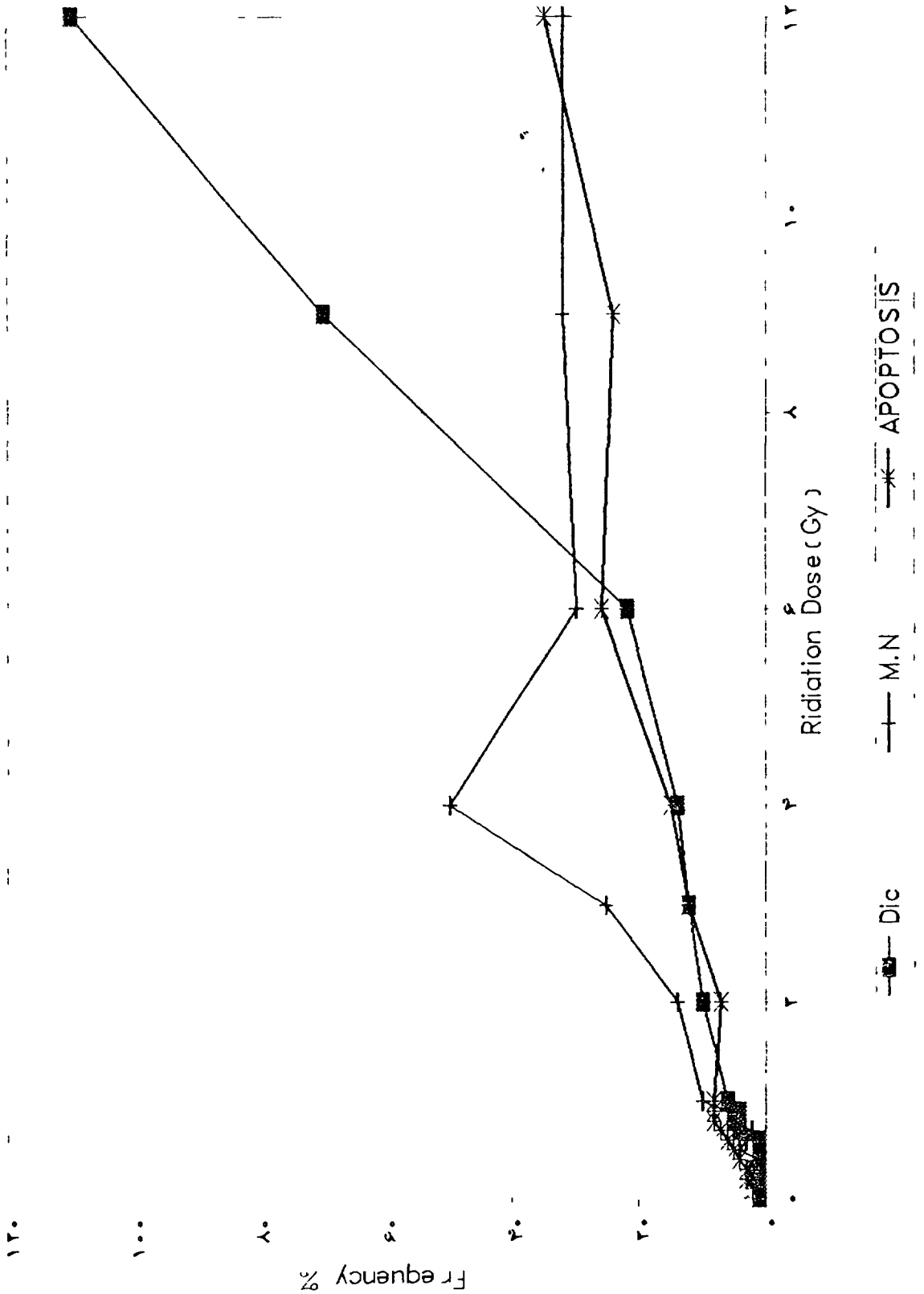

Figure.1. The frequency of dicentric chromosomes 24h, micronuclei 24h and apoptosis 48h after irradiation. The points are mean of 3 independent experiments.

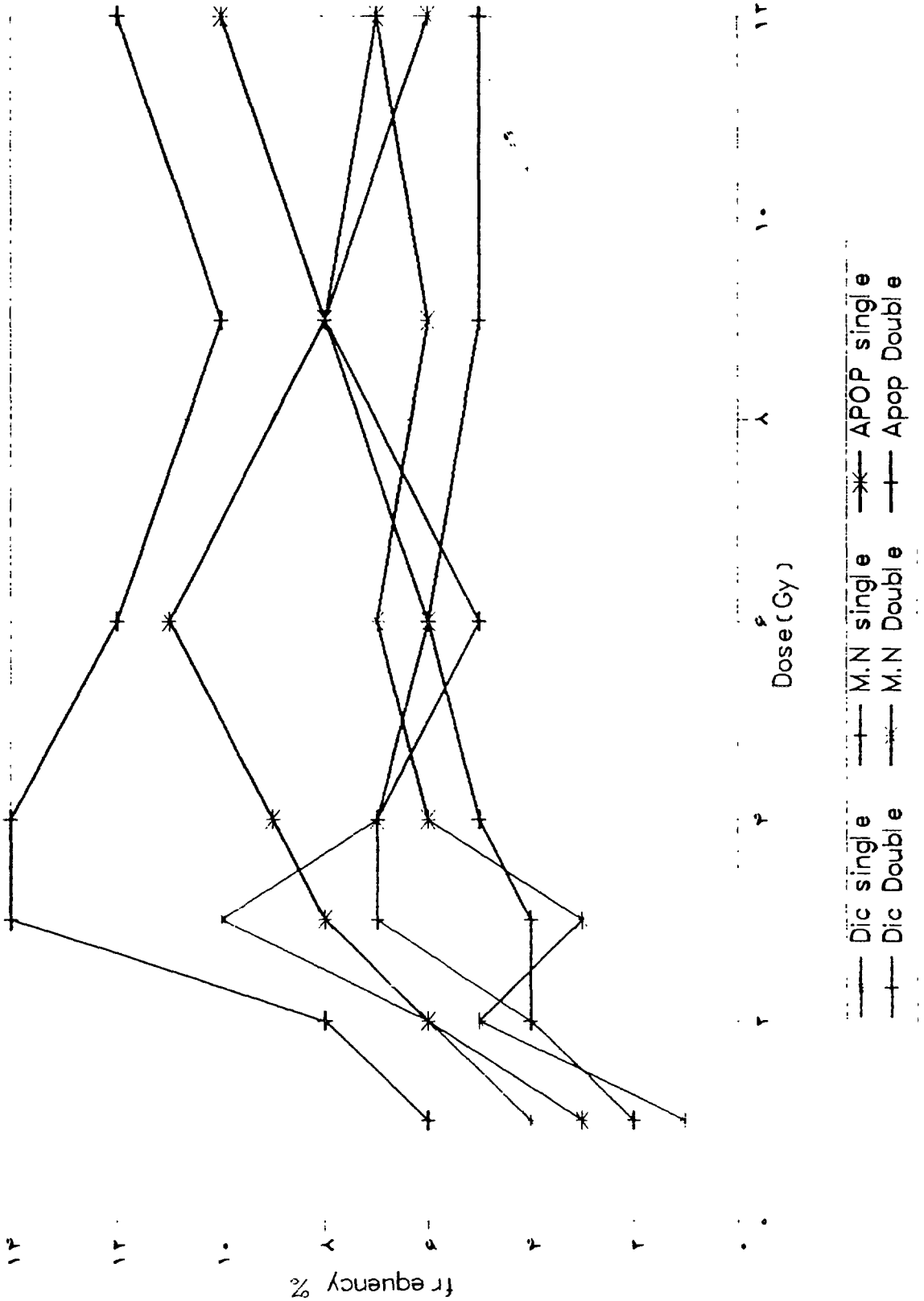

Figure.2. The frequency of dicentric chromosomes, micronuclei and apoptosis 7 days after single or twice irradiation with the same dose. The points are mean of 3 independent experiments.

4. Discussion

The dose response curve obtained in early hours after irradiation showed increased frequency of all three end-points according to increasing the dose. Whereas the frequency of dicentrics, micronucleus or apoptosis seven days after single or twice irradiation showed decrement in frequency of all three end-points 7 days after second irradiation. We performed this experiment to induce higher probability of det rimental or repair functions to quantify and compare the responses of them.

We concluded that the frequency of apoptotic cells are always higher than other tow indicators which imply that other types of chromosomal or DNA damage might occur that do not result in structural aberrations or micronuclei. The frequency of apoptotic cells might thus give a more realistic estimation of the total amount of early or delayed radiation injury in irradiated cells even in irradiated surviving cells.

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Experiences of PNRI Interaction with Licensees in Nuclear Regulatory Information Conferences

V. K. Parami
Philippine Nuclear Research Institute
Diliman, Quezon City, Philippines

ABSTRACT

The Philippine Nuclear Research Institute (PNRI) initiated various nuclear regulatory conferences with its licensees in the years 1995 and 1996. The purpose of these conferences was mainly to reach a common understanding of the provisions of the Code of PNRI Regulations (CPR) and foster openness between PNRI and licensees.

Each conference was designed for a specific category of licensees, i.e., commercial, medical, industrial (nuclear gauges), industrial radiography, research and teaching. The regulatory group of PNRI discussed the applicable regulations to each category of licensees including experiences in implementation and enforcement. This was followed by licensees' feedback on experiences in dealing with the regulatory group and complying with applicable regulations.

The outcome of these conferences brought out generic and specific issues and concerns. Majority of the general issues and concerns were directed towards PNRI. This brought to the realisation that although safety is the primary responsibility of the licensees, PNRI as the only competent authority on radioactive material and radiation safety matters, carries the bigger share of preparing the licensees for this kind responsibility.

1. Introduction

The need for collective and more focused interaction between the PNRI and its licensees has grown over the years as the number of rules and regulations the PNRI has promulgated increases. In 1959, a year after the establishment of the then Philippine Atomic Energy Commission by Republic Act 2067, the first set of regulations entitled "Rules and Regulations on the Acquisition, Possession, and Use of Radioactive Materials" was promulgated. This was followed by the promulgation of the "Rules and Regulations on the Safe Transport of Radioactive Materials in the Philippines" in 1966 and then the "Standards for Protection Against Radiation" in 1976. The first set of regulations was revised in 1989 and has evolved into various specific rules and regulations that provide requirements for licensing and safe use of radioactive materials in medicine, industry, research, and teaching.

The participation of the affected groups of licensees was rather limited to providing written comments of draft regulations. Consultative meetings with licensees and public hearings were not integral in the rule making process. Through the years, however the level of awareness in rule making has improved which can be attributed largely to the technical assistance provided by the International Atomic Energy Agency (IAEA) in the form of training, seminars, experts, safety series publications, etc.

In line with the continuing effort of PNRI to improve the regulatory system so as to be consistent with global standards, various reforms are underway. The holding of nuclear regulatory information conferences with licensees is one of these. These conferences are being held to get direct feedback, suggestions, criticisms, recommendations and opinions.

2. The Philippine rules and regulations

The Philippine regulations for licensing and safe use of radioactive materials are compiled in the Code of PNRI Regulations (CPR). The CPR consists of parts in chronological order with specific subject matter as follows:

Part 2 - Licensing of Radioactive Material
Published in Official Gazette (O. G.), Vol. 86, No. 29, 16 July 1989, pp 5337-5355
Part 3- Standards for Protection Against Radiation
Published in O. G , Vol 72, No. 14, 05 April 1976, pp. 3736-3751.
Part 4- Rules & Regulations on the Safe Transport of Radioactive Materials in the Philippines
Published in O G., Vol. 62, No 19, 09 May 1966, pp. 3209+
Part 6- Rule of Procedure for the Licensing of Atomic Energy Facilities in the Philippines
Published in O G , Vol. 3, No. 37, 12 September 1977, pp. 8691-8694.
Part 7- Licensing of Atomic Energy Facilities
Published in O. G , Vol. 70, No 22, 08 June 1974, pp. 4435-4438
Part 11- Licenses for Industrial Radiography and Radiation Safety
Requirements for Radiographic Operations
Published in O G , Vol 86, No 28, 09 July 1990, pp 5123-5131
Part 12- Licenses for Medical Use of Sealed Radioactive Sources in Teletherapy
Published in O G , Vol 90, No 39, 26 September 1994, pp 5776-5791
Part 13- Licenses for Medical Use of Radiopharmaceuticals
Published in O.G Vol 90, No.29, 18 July 1994,pp.5776-5791.
Part 14- Licenses for Medical Use of Sealed Radioactive Sources in Brachytherapy
Published in O. G , Vol. 91, No 20, 15 May 1995, pp. 3083-3094
Part 15- Licenses for Large Irradiators
Published in O G , Vol. 89, No 46, 15 November 1993, pp. 6686-6702

In addition to the above rules and regulations, IAEA Safety Series Nos. 6 and 9, Regulations for The Safe Transport of Radioactive Materials, 1973 revised edition and Basic Safety Standards for Radiation Protection, 1982 edition, respectively were adopted through an Administrative Order in 1983, for use whenever applicable.

The PNRI has recently issued policies on internal regulatory control of the radiation facilities it operates in accordance with international basic safety principles as well as standards for radiation protection.

3. Status of licensees [1]

The PNRI has only about 250 licensees involved in the use of radioactive materials in medicine, industry, research and teaching. Table 1 shows the distribution of licensees according to classification and geographical distribution.

The PNRI is engaged in various applications of radioactive materials. But since PNRI is exempt from licensing requirements it is not accounted for in Table 1. These applications include large irradiation facilities, secondary standard dosimetry laboratory, various small research facilities in health physics, chemistry, biomedical, agriculture, and teaching

Table 1. Distribution Of Licensed Users According To Geographical Location And Classification
(As of August 1997)

Region	Commercial	Hospital	Industrial Radiography	Research & Education	Physician	Industry	Subtotal
Region I	-	-	-	-	-	-	-
Region II	-	-	-	-	-	-	-
Region III	-	1	1	2	-	15	19
Region IV	-	2	-	3	-	31	36
Region V	-	-	-	-	-	-	-
Region VI	-	1	-	1	1	3	6
Region VII	-	5	-	4	-	7	16
Region VIII	-	-	-	-	-	2	2
Region IX	-	-	-	-	-	1	1
Region X	-	-	-	-	-	2	2
Region XI	-	1	-	-	-	4	5
Region XII	-	-	-	1	-	3	4
Caraga Region	-	-	-	-	-	4	4
Muslim Mindanao Autonomous Region	-	-	-	-	-	-	-
Cordillera Administrative Region	-	1	-	-	-	3	4
NCR (Metro Manila)	29	49	25	13	2	40	158
TOTAL	29	60	26	24	3	115	257

laboratories. The PNRI maintains a research reactor (not operational) and an interim low level radioactive waste repository.

4. Experiences in nuclear regulatory information conferences [2]

The PNRI in 1995 and 1996 conducted a series of regulatory information conferences to provide an opportunity for members of the regulatory staff of the PNRI and licensees to discuss the applicable Parts of the CPR and the problems experienced in implementation and enforcement by regulators and licensees.

These conferences were conducted by sector or specific applications, e.g., radiopharmaceuticals, brachytherapy and teletherapy, industrial radiography, research, etc. to have more focused approach in the discussions.

The conferences usually consisted of various topics presented by the PNRI regulatory group covering current and specific regulations applicable and relevant to the sector or category of licensees, experiences during review and evaluation of license applications, outcome of compliance monitoring discussions on proposed initiatives. Representatives of the licensees, in some cases the relevant professional organisation itself, took an active role in the discussions to facilitate the consolidation of common concerns for that specific applications group. The overall theme focused on enhancing and promoting a better understanding of the various aspects of the regulatory program as well as encouraging participation and feedback from licensees on regulatory matters affecting them.

4.1 General issues and concerns

General issues and concerns raised during the nuclear regulatory information conferences included the accreditation by the PNRI of professional organisations to certify

on the clinical aspect of use of radioactive materials. In addressing this specific issue, the PNRI has initiated the establishment of accreditation criteria for professional societies and agreed to immediately act on a long standing proposal from the Philippine Society of Nuclear Medicine, for example, to be the certifying body of practitioners in the field of nuclear medicine.

Licensees' feedback is an important input in the effort to improve the PNRI regulatory system and the capability to discharge its functions effectively. Some of the common issues and concerns included delayed issuance of licenses, sometimes resulting in expired licenses or unauthorised use of radioactive material. Some requirements were not fully appreciated for what they are worth. Examples of these were certificate of release, a requirement for radioactive consignment to be released by customs authorities, and transport certificate which is a requirement before a licensee can ship or move radioactive materials. The need to leak test sealed sources as often as specified in the regulations in certain cases was being questioned including the cost of the service and related matters.

4.2 Specific issues and concerns

In radiotherapy, the need to have a standardised calibration technique and reporting of results in full calibration of therapy machine and associated instrumentation was discussed. This included the lack of appropriate dosimetry systems for low energy calibration.

The continued use of radium sources in brachytherapy was raised and the efforts taken by the PNRI to discourage the use of these sources, together with an aggressive campaign to change from manual to remote afterloading devices, were highlighted.

The proposed requirement for medical physicists in other medical applications such as in nuclear medicine has gained overwhelming support from concerned users.

5. Regulatory challenges

The experiences gained and the lessons learned from the conduct of the nuclear regulatory conferences indicated that there is a need to continue this activity on a regular basis. The PNRI, therefore, will design another series of conferences in the following years to sustain the enthusiasm and report results of new initiatives.

The PNRI regulatory system will have to be periodically reviewed. Local experiences as well as information on other regulatory bodies' experiences should be studied and appropriately applied to become more effective and efficient.

Current regulations, especially Parts 3 and 4, will have to be reviewed and revised. Better opportunities for consultations and dialogues with present licensees and even prospective license applicants should be provided by PNRI.

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LOW DOSE EFFECTS DETECTED BY MICRONUCLEUS ASSAY IN LYMPHOCYTES

G.J. Köteles, I. Bojtor*, Gy. Horváth† and Tamara Kubasova**

* "Frédéric Joliot-Curie" National Research Institute for Radiobiology and Radiohygiene, H-1775 Budapest, P.O.B. 101, Hungary

† Institute of Public Health and Medical Research, Hungarian Home Defense Forces, H-1456 Budapest, P.O.B. 19. Hungary

Abstract. The effects of low doses of X-rays between 0.01 and 1 Gy were studied on whole blood samples of various individuals using the cytokinesis-blocked lymphocyte micronucleus assay as an end-point. The adaptive response could be induced in G_0 cells by 0.01 Gy followed by 1 Gy challenging dose within a time period of 8 hours, *in vitro*. The probability distribution of micronucleus increments in those samples which had received very low doses in the range 0.01-0.05 Gy proved to be of asymmetrical type (i.e. lognormal) - very likely to the same shape which has been verified for unirradiated (control) population - while the variable turned to be normally distributed at or above 1 Gy. Profound changes have been experienced in the main characteristics of the linear dose - response relationship and in regression parameters, as well, when successively lessened dose ranges were studied toward 0.01 Gy. In the range below appr. 0.2 Gy the responses were found to be unrelated to the absorbed dose. These findings suggest that in (very) low dose range a higher attention should be needed to biological parameters like repair, protective mechanisms and antioxidant capacities, rather than to the absorbed radiation energy only.

1. Introduction

For the understanding the biological effects of low radiation doses, experimental approaches are needed to reveal biological mechanisms and, furtherly, "epidemiological" survey is advisable to reflect individual responses at selected end-points. In the followings some relevant features of low dose-induced frequencies of micronuclei in human lymphocytes are presented.

2. Materials and methods

The lymphocyte micronucleus assay was performed as described earlier [1,2,3]. X-irradiation of the blood samples taken with lithium-heparin anticoagulant was made at the following conditions: 200 kV_p, 20 mA, 1 mm Cu filter, 60 cm SSD, 0.287 $Gy*min^{-1}$ dose rate, room temperature, 5 ml volume in Falcon plastic flasks. The effects of exogenous apoptosis inducers, mistletoe lectins (ML I, ML II, ML III) were studied on rabbits which had received dose of 1 Gy. After irradiation the animals were treated subcutaneously with various isolectins of 1 ng per kg body weight. Twenty four hours and further 1 and 2 weeks later the micronucleus-carrying cytokinesis-blocked cultured lymphocytes (CB cells) related to the total number of CB cells were scored.

3. Results and discussion

3.1. Adaptive response

The adaptive response could be induced in human lymphocytes of G_0 phase *in vitro* by a conditioning dose of 0.01 Gy and a challenging dose of 1 Gy received by the samples so that a time interval of 1 - 8 hours passed between the two irradiations (*Fig. 1*). The data demonstrate that despite of most of the earlier studies where G_1 cells were conditioned and challenged, the phenomenon of adaptive response could also be observed on G_0 cells in the whole blood. In addition, the micronucleus assay proved to be a proper end-point to study such kind of phenomena. These conditions of investigations even raise the possibility to use this biological response for assessing the individual radiosensitivities. This target was approached by studies which had been made on the radiation-induced individual increments of micronucleus frequencies in a population.

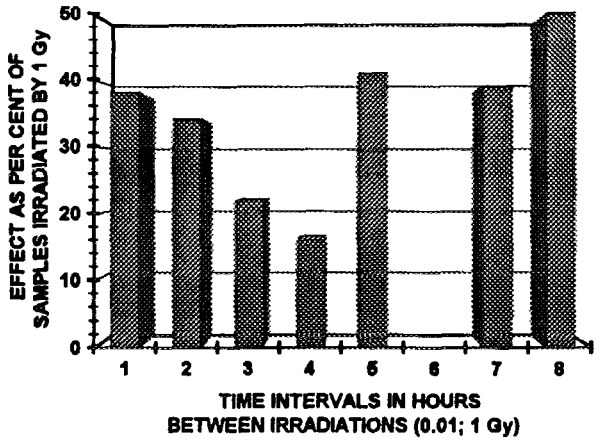

Figure 1. Adaptive response of G_0 human lymphocytes X-irradiated in whole blood, in vitro.

3.2. Individual differences in radiation-induced increments of micronuclei

The frequency in all individual samples reacted with a well observable increase against the self-control value, even at 0.01 Gy, as it has been proved by the *Friedman* analysis of variance test by ranks [3]. Profound alterations were observed in the shape of probability distribution of increments at (very) low or high doses. In samples which had received (very) low doses, the variable of increment seemed to be asymmetrically distributed: the corresponding lognormal frequency function could be fitted with far the best approximation (*Fig 2*). This type of probability distribution was found to be identical with that which had already been proved for non-irradiated control population, too.

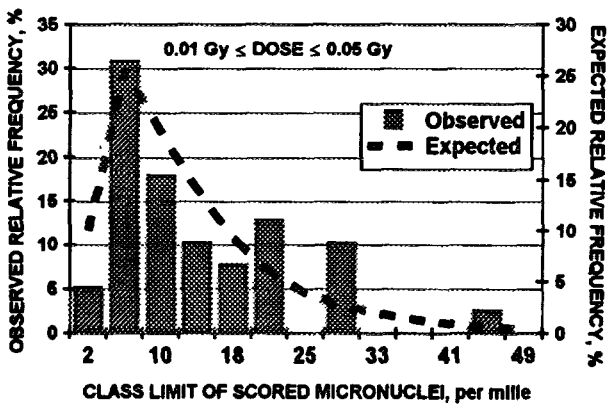

Figure 2. Frequency histograms of the observed micronucleus increments induced by very low doses of 200 kV_p X-rays and the density function of the corresponding lognormal distribution. The lognormal approximation for increments was accepted. [Calculated statistics: $\chi 2(df)=1.751(4)$; $p=0.781$; $M(raw)=13$; $M(ln)=2.3$; $SD(raw)=9.6$; $SD(ln)=0.8$; $m_e(raw)=10$; mode=6; frqucy of mode=7; skewness=1.168; curtosis=1.205]

At higher dose, i.e. 1 Gy, the pattern of distribution took a different turn: the occurrence of micronucleus increment proved to be consistent merely with the corresponding normal curve (*Fig. 3*). These findings suggest different biological protective mechanisms determining the responses. At low doses probably the individual antioxidant capacities in sera might modulate the response, while at higher doses, after the exhaustion of the antioxidant potential, the repair processes might play a decisive role in development and manifestation of an end-point.

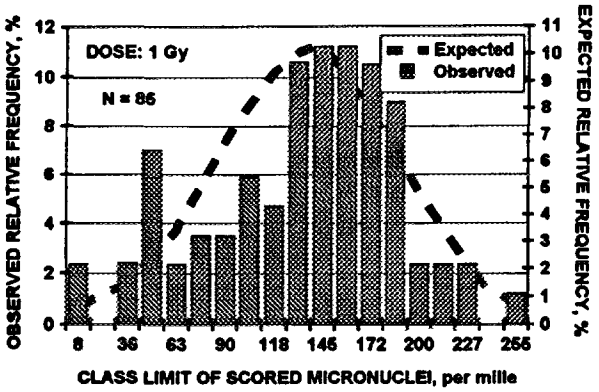

Figure 3. Frequency distribution of the observed micronucleus increments induced by 1 Gy of 200 kV_p X-rays and the expected normal curve constructed by the sample parameters. There was sufficient reason to accept the consistency. [Calculated statistics: $\chi 2(df)=15.927(10)$; $p=0.102$; $M=134$; $SD=53$; $m_e=142$; mode=166; frqucy of mode=6; skewness=-0.511; curtosis=-0.299]

3.3. Main characteristics of the linear dose - response equation

A detailed regression analysis, including that of residuals, was accomplished on the initial part of the dose - response curve. Thus, all the significant changes regarding both the correlation coefficient and slope and the proportion of variance of increment due to the dose could be revealed. Interestingly enough, when the dose range 0.01 - 1 Gy was successively cut toward the lower limit of data, in the interval *below* 0.18 Gy the slope started to "disappear" and, simultaneously, the random component of the variance became of considerable importance. In other words, the micronucleus increment was found to be unrelated to the absorbed dose in the dose range in question (*Table 1*). These results suggest that biological response-modifying factors might play more decisive role than the absorbed energy alone. The phenomenon might also explain differences in the individual adaptive response capabilities as compared with the conditioning doses in this interval.

Table I. Summary of the main parameter values and characteristics of linear dose - response equation.

Parameter	*Dose interval, Gy*						
	0.01-1	*0.01-0.7*	*0.01-0.3*	*0.01-0.22*	*0.01-0.18*	*0.01-0.13*	*0.01-0.1*
N	346	261	210	143	126	108	88
Slope, *b*	127.38	42.27	36.88	25.17	14.20	- 1.99	- 12.42
±SE, *b*	4.73	3.36	5.68	8.65	11.75	16.56	22.01
p	0.000	0.000	0.000	0.004	0.229	0.904	0.574
R	0.824	0.616	0.411	0.238	0.108	0.012	0.061
Proportion of variance of *Y* (incr) due to *X* (dose)	0.678	0.380	0.169	0.057	0.012	0.0001	0.004
No. of outliers > (±2SD), %	*Obsrvd: 7* Expctd: 5	*4* 5	*4* 5	*4* 4	*5* 5	*4* 4	*5* 5

3.4. Induction of apoptosis in radiation-damage carrying cells

Relatively low doses influence the structure and function of cell membranes [4]. In fact, differences in signal transfer leading to apoptosis between the normal and the radiation-damage carrying cells were demonstrated as the latter being more sensitive against the exogenous apoptosis inducer mistletoe lectins than the former (*Fig. 4*). This novel effect of the mistletoe lectins suggest that a scavenging mechanism is inducable. The preferential elimination of injured cells might support the efficiency of radiotherapy

allowing the reduction of treatment dose as well as the "cleaning-up" of the organism from aberrant cells. These occurrences might reduce the risks of late pathological processes.

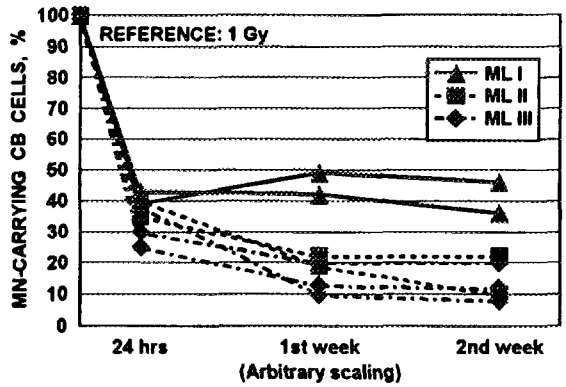

Figure 4. Reduction of radiation-induced micronucleus-carrying CB cells upon treatment of rabbits in vivo *with mistletoe lectins.*

4. Conclusions

In the (very) low dose range, as a rule, biological effects are modulated rather by biological factors or conditions than by the absorbed dose. Using cytogenetic end-points either for occupational or for accidental dose assessments, the calibration below approximately 0.2 Gy has an inherent uncertainty reflecting also the individual sensitivities. At the same time, in this dose range the biological support like the increase of antioxidant capacities and promoting the repair processes of cells and the organism might provide efficient protection. The responses in the dose range in question might be characterized by "non-linear, non-threshold" feature. Radiation-injured cells presumably carry such "*stigma*" which render them susceptible to a scavening mechanisms through apoptosis provoked either by exogenous lectins as it has been demonstrated, or any other endogenous factors. The observations and approaches presented here contribute to the understanding low dose effects and also emphasize the need of further investigations at the level of experimental cellular radiation biology with particular reference to individual reactions in human population.

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PERSPECTIVES ON DOSIMETRIC UNCERTAINTIES AND RADIOLOGICAL ASSESSMENTS OF RADIOACTIVE WASTE MANAGEMENT

G.M. SMITH
QuantiSci Ltd,
Henley-on-Thames, Oxfordshire, United Kingdom

P. PINEDO, D. CANCIO
Centro de Investigaciones Energéticas Medioambientales y Tecnológicas,
Madrid, Spain

ABSTRACT

The purpose of this paper is to raise some issues concerning uncertainties in the estimation of doses of ionizing radiation arising from waste management practices and the contribution to those uncertainties arising from dosimetry modelling. The intentions are:

(a) to provide perspective on the relative uncertainties in the different aspects of radiological assessments of waste management;
(b) to give pointers as to where resources could best be targeted as regards reduction in overall uncertainties; and
(c) to provide regulatory insight to decisions on low dose management as related to waste management practices.

1. UNCERTAINTY ANALYSIS IN RADIOLOGICAL ASSESSMENT OF WASTE MANAGEMENT

It is not the purpose here to review methods of uncertainty analysis. Extensive references have done this already; see, for example, IAEA Safety Series 100 [1] for environmental transfer models and Robinson and Cooper [2] which deals more specifically with solid waste disposal. However it is interesting to outline how uncertainties arise at each stage in the assessment process, as applied to routine releases and solid waste disposals.

Firstly, a picture of the system under assessment has to be constructed, for example, based on a list of relevant features, events and processes (FEPs). This picture can be developed into a conceptual model of the system. Conceptual model uncertainty may be investigated by alternative conceptualizations of the system being modelled; this applies as much to interpretation of groundwater flow data (eg, fractured flow or a porous medium approximation) as to alternative representations of the lung, as discussed in [3].

The conceptual description is then interpreted mathematically, to create a mathematical model. Uncertainties arise regarding the adequacy of the equations used to represent the FEPs included in the conceptual model. For example, for convenience, linear approximations may be made so as to simplify the solution.

Choices of data then have to be made for the parameters in the mathematical model. Uncertainty analysis (UA) has tended to focus on data uncertainties. For example, those systems which can be well characterized statistically are susceptible to Monte Carlo type UA approaches. Ultimately, however, it should not be forgotten that a subjective element is bound to creep into the uncertainty evaluation, even if it is the subjectivity of an expert group. It is particularly difficult to characterise the extreme ranges in parameter distributions, yet it is these extremes which may control the values of the quantities characterizing the results distribution. Furthermore, the contributions to uncertainty in the overall assessment results arising from conceptual and mathematical modelling should not be ignored. These issues have been considered in relation to a variety of radiological assessment situations in the BIOMOVS II Overview Report [4].

Sometimes included within uncertainty is the effect of variability. The appropriate value of a parameter to use in a model may be difficult to determine because of our lack of knowledge of the system being modelled but also because that system is itself temporally or spatially variable. (In this sense, a parameter value might relate to a deterministic value or to a parameter characterizing a distribution.) Sheppard and Evenden discuss [5] variations in soil to plant transfer in far future conditions, providing useful advice in site generic and site specific situations. In the dosimetry context, temporal and spatial variability correspond to age at the time of intake and distributions in body size at any particular age. The importance of the distinction between variability and uncertainty has been highlighted [1], [2], but it is also possible that the distinction becomes blurred in regulatory evaluations. If we could define very precisely the system to be assessed (the groundwater system or the exposed person) then the distinction would be clearer; however, this is very difficult for situations involving very long timescales, as in solid waste disposal assessments, or assessments of routine releases of very long-lived radionuclides.

These aspects of uncertainty arise in any kind of quantitative modelling exercise, whether directed at radionuclide movement in the ground, radionuclide migration and accumulation in the biosphere, or, more specifically, radionuclide behaviour in and radiation interactions with the human body. Inclusion of evaluation of uncertainties within a radiological assessment is increasingly regarded as important, as evidenced by the increasing body of reports on the subject. Equally, uncertainties in dosimetric models are attracting deserved attention, eg in on-going work described in [6] on internal dosimetry uncertainties and the implications for accident consequence analysis. However, it seems unusual for radiological assessments of planned waste management practices, either for effluents or solid wastes, to include evaluation uncertainties in the dosimetric models used to relate intake to dose or to relate proximity to radioactive material to external dose. Values of dose per unit intake are usually accepted, from one reference or another, as precisely correct. Proehl and Mueller [7] can be regarded more than positively, because it examines conceptual (scenario) and not just parametric uncertainty when discussing the distribution of potential individual doses arising from long term groundwater contamination. However, even here, the dose coefficient data were not assumed to vary. An interesting question arises as to whether inclusion of dosimetric uncertainty would significantly widen the distribution of results for waste management assessments, either generally or in specific instances.

Some examples are briefly considered below of specific dosimetry issues which may have significant influence on uncertainty estimates associated with waste management radiological assessments. The implications for assessment results and regulatory control are then also briefly considered.

2. SPECIFIC DOSIMETRY ISSUES

Assessments of proposed and actual waste management practices include evaluation of doses arising from a wide range of exposure pathways involving ingestion, inhalation and external irradiation as the primary exposure modes. While for any one specific scenario, one or other radionuclide and exposure pathway will turn out to be critical, it is not unusual for a range of results for a variety of different scenarios and pathways to influence decisions on waste management. In the mean time, detailed dosimetry modelling issues continue to be studied, eg assumptions about continuous as opposed to one-off intake [8] and treatment of the effects of daughter radionuclides, as in the case of Th-232 [9]. Over time, such studies contribute to widely accepted recommendations on dosimetry assumptions to be adopted in wider assessments. It is therefore inappropriate to revisit such detailed work when interpreting the broad recommendations, so long as any relevant caveats concerning their application are taken into account. However, consideration of a variety of waste management radiological assessments can identify a number of interesting issues which still require interpretation within those broadly accepted recommendations. In many cases this is because the assessment model for radionuclide migration and accumulation interfaces directly with the dosimetry model. Assumptions in one model affect or should affect assumptions in the other.

An important dosimetric issue affecting ingestion pathways concerns assumptions for gut transfer factor. It is typically assumed that the chemical form on intake is that giving rise to the highest dose, because of uncertainties about chemical conditions which will apply at the time of intake. However, when site specific data can be applied, values implying lower doses may be justifiable [10]. The reductions in dose associated with alternative chemical forms can be significant, at least for some radionuclides, that is, an order of magnitude or more [11].

Concerning inhalation, similar considerations arise as to the chemical nature of the inhaled material and the association between the radionuclides and particles of different sizes. Normally, for waste management assessment purposes, assumptions are made tending to maximise the dose, but without serious consideration of the applicability of those assumptions to the assumed conditions giving rise to the exposure.

For evaluation of external irradiation, convenient tables are provided in Federal Guidance Report No 12 [12]. Significant discussion is provided of the modelling assumptions and the related uncertainties, eg as regards treatment of the proportion of photons arising at relatively low energies and treatment of anisotropic radiation fields. Again, results are subject to uncertainties. Note that reference [12] tabulates data for effective dose equivalent and not for effective dose, because of the (then) status of decisions in the USA.

3. IMPLICATIONS FOR ASSESSMENT RESULTS

Two questions arise: are the uncertainties linked to dosimetric modelling significant in themselves and are they significant relative to other uncertainties in the assessment?

Uncertainties in dosimetric quantities such as dose coefficients arise as with any other modelled quantity. The degree of uncertainty will depend on the particular type of exposure. Also, the quality of metabolic data for particular radionuclides is bound to vary. Brief review of published data suggests, eg [11] , [13], that alternative assumptions can lead to values for dosimetric quantities which range over an order of magnitude or perhaps more in some cases. Comparisons are difficult because the quantities may not always be directly comparable even though the purpose to which the quantities are put is the same. The significance of this degree of uncertainty will depend on the purpose of the overall assessment in which the dosimetry results are being used.

Concerning the relative significance of dosimetric and other assessment uncertainties, a few examples are considered here related to solid waste disposal. It may be noted at the outset that in all these cases the levels of assessed dose are very low.

Reference [7] presents results for doses arising from agricultural use of contaminated groundwater, as may occur in the long term due to releases from waste repositories. The distributions of the potential doses cover in general about a factor of 10 - 20. The range in uncertainty in dose coefficients is perhaps comparable, and it is at least possible that inclusion of dosimetric uncertainties could widen the dose distribution. Children who are 1 year old are said to represent the critical group for most radionuclides. Bearing this in mind, it is interesting, as an example, to consider the effect of potentially high gut transfer of Th isotopes in infants, resulting in dose coefficients about 20 times higher than for adults [14]. Many waste management assessments do not consider infants, children and adults as separate critical groups.

Relatively simple dose models have been proposed for long term waste management assessments, because of the difficulty of specifying long term biosphere conditions, eg[15]. During the period of repository develop, dosimetric recommendations and regulations are bound to change. The effect of updated recommendations on [15] is considered in [16]. The differences are only about a factor of three or less, which is reassuring. However, only limited consideration was given to exposure pathways. Hazard indices based on different assumptions for radiotoxity have also been proposed, as reviewed in [17]. It is interesting to consider how robust these indices (and any decisions based on them) are to changes in dosimetry recommendations and modelling uncertainties.

Reference [18] provides results for the effect of different climate scenarios on doses. The spread of peak dose results is about 3 orders of magnitude, assuming the reference case release of radionuclides from the geosphere. Reference [19] reviews a selection of repository performance assessments, looking at modelling treatment of processes in the repository, the geosphere and in the biosphere. These and similar assessment reports would suggest that the dosimetry uncertainties, as indicated by ranges from discussion in section 2 above, are relatively small compared to the other repository assessment uncertainties. It should be noted that all these results are presented as indicators of the impacts of waste disposal rather than as absolute predictions of dose. In fact, this view of the assessment results could be regarded as an extension of the concept of effective dose as a measure of the risks associated with radiation exposure.

4. IMPLICATIONS FOR REGULATORY CONTROL AND THE FUTURE

The following points are made not as conclusions, but as preliminary observations.

Uncertainties associated with dosimetry aspects of radiological assessments, particularly long term assessments of solid waste disposal, are relatively small. However, dosimetry uncertainties, including those associated with the conceptual basis to the dose quantities, could be significant in contributing to regulatory insight and interpretation of overall assessment results. This would be especially the case where results approach a target or other regulatory criterion. It could be useful to explicitly consider dosimetry uncertainties in waste management assessments and to compare those with other uncertainty contributions, so as to guide prioritization of research efforts to reduce uncertainties. A complicating factor is that revision of regulations may be slow to follow science based recommendations. Lack of precision in regulatory guidance as to what quantities should be assessed may also contribute to uncertainties in assessment results. This precision relates to issues of critical group definition and modelling assumptions for the environment in which the group resides as well as the associated dosimetry modelling. Consistency between regulatory philosophy and radiological assessments is to be encouraged, including the consistent treatment of uncertainties when defining regulatory requirements and when carrying out each part of the corresponding assessment. Critical group issues are one of the foci of the current IAEA project, BIOMASS [20].

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IMMUNOLOGICAL STATUS OF DIFFERENT CATEGORIES OF POPULATION AFTER CHERNOBYL ACCIDENT

A.A.Chumak, D.A.Bazyka, J.N.Minchenko
Department of Clinical Immunology, Institute of Clinical Radiology, Research Centre for Radiation Medicine of the Academy of Medical Sciences of Ukraine
Kyiv, UKRAINE

Abstract

Investigation of immune status of the victims of the Chernobyl Nuclear Power Plant (NPP) accident irradiated in diferent doses was performed. Acute postradiation immunodefficiency in heavily exposed persons was changed in 6 - 24 months to the 5-7 year period of restitution and the latter was succeded by normalisation of CD3+, CD4+, CD11+ cell count and serum IgG and IgA content in certain patients, while the others revealed immunologic defficiency of the mixed type. HLA-antigenic combinations connected to the increased radiosensitivity were found out. Elaboration of in vitro tests for surface antigens expression in response to thymic peptides allowed to make adequate immunocorrection if needed.

Immune system plays a crucial role both at the early stage of radiation injury and in the realisation ot remote effects of irradiation. Immunological follow-up of different kind of victims of the Chernobyl (NPP) accident are of interest for drowing conclusions about actual health conditions and prediction of the development of different somatic diseases and functional disorders [1].

The investigations in the Department of Clinical Immunology of the Research Centre for Radiation Medicine of the Academy of Medical Sciences of Ukraine since its creation in 1987 were directed to the field of the possible mechanisms of radiation effects and the evaluation of the role of random alteration of common bone marrow progenitor cells by quants of radiation and non-lethal damage of regulatory systems, especially in the case of small absorbed doses of acute or continious partial irradiation. Immunological investigations included flow cytometry quantification of cell subpopulations, HLA-typing and humoral immunity study as previously described [2].

Person with different absorbed doses (from 0.05 Gy to the doses inducing acute radiation sickness - 1 -3 Gy) were taken into account .

A process of the three stage of the immune system recovery was seen in persons who suffered from acute external irradiation. Dynamic investigations of immune state revealed a postradiation defficiency. The cellular or/and humoral immunity disturbances included surface phenotype changes, especially in mitogen-associated subpopulations of CD3+, CD4+ and NK- cells (CD57+, CD11+16+). It was worth to mention the mozaic of injury and reparation of surface membranes of immunocompetent cells. B-cells exhibited the short-time decrease of C3+ and pan-B-antigen bearing cells subpopulations. Membrane changes at that time also evoked the difficulties in locus A, B, C HLA-typing. . First stage lasted from 6 to 24 months, the absorbed doses and the duration of irradiation, the presence of somatic and psychosomatic pathology, age at the moment of irradiation influenced greatly on this stage lasting .

The second stage was characterized by the restitution of the radiation injury, the increase of subpopulation of CD3+DR+ lymphocytes was seen , accompanied by stable

tendencies of finding in the peripheral blood of lymphocytes bearing CD4+8+ and CD1+ antigens, which normally were characteristic only for intrathymic stages of T-cell differentiation. There were the increases of B-lymphocytes count, which had such pan-B-markers as CD21, C3, late differentiation markers such as surface IgG and early antigens as CD10. These findings without leukemic reactions suggested about existence of some constrains in the immune system function and their possible role of the background of future immunopathologic processes. The decrease in expression of some antigens normally presented on monocyte cells was revealed by performed study. HLA-Dr-antigens coexpressed with LeuM3 with high fluorescence intensity (560.0+1.0) were seen only on 3.0+0.1% of cells. There were not any coincidence between CD57+ and CD11+16+ cell counts, the latter subpopulation was determined as highly active natural killers.

A study of T-cell receptor stable alterations was performed among the population of contaminated territories inhabitants and personnel of the Chernobyl NPP. A two-fold increase of aberrant cells (0.4- 0.6 per cent of the peripheral mononuclear cell) with decreased TCR expression was found in investigated contingents in 1990 - 1992.. It was accompanied by the 2 -3 fold increase of glycophorin A (GPA) aberrant red blood cells. Next years the quantity of aberrant T-cells slovly diminished, GPA mutant cells remained constant.

Major hystocompatibility typing revealed in locus I the prevalence of HLA-A1, 28; HLA-B5, 38; HLA-B16, 17; HLA-B17,18; HLA-B8, 22; HLA-B 8, 27; HLA-B 27, 35; HLA-A1, B16; HLA-A1, B27; HLA-A2, B38; HLA-A10, B38; HLA-A28, B8 in patients, who had suffered from acute radiation sickness comparing to the group of Chernobyl clean-up workers with the absorbed doses reaching or exceeding 1 Gy, but without acute radiation injury of bone marrow. These data are very important for the estimation of the radiosensitivity in individuals exposed to the lower doses and for NPP workers professional selection.

To our mind, any genetic research results could be valuable only in connection with characteristics of the given geno-geographic zone. For example, we foun out that HLA-A1,9; HLA-B8,12; HLA-B12,13; HLA-B15,35 antigen combinations were associated with thyroid pathology both in contaminated and non-contaminated regions of Ukraine with no differencies depended on radiation influence.

As a third stage of immune system recovery in five-seven years after the irradiation a heterogeneity of types of immunologic response of acute radiation sickness reconvalescents was detected. A group of patients demonstrated normalisation of CD3+, CD4+, CD11+ cell count and serum IgG and IgA content, while the others revealed immunologic defficiency of the mixed type.

Subset cell cycle analysis with propidium iodide showed the decreased prolipherative response to concanavalin A (Con A) in 18 hour cultures as well as 3H thymidine uptake in 72 hours cultures. Dose-dependent changes of enkephaline receptor on peripheric blood mononuclear cells (PMNC) and sensitisation to brain antigens accompanied by changes of TrR, RIL-2, CD10, CD23 activation antigens expression were seen in healthy irradiated persons as well. Late radiation and functional effects could be explained by neuro-humoral regulatory changes.

Clinical and immunologic investigation was performed in the group of Chernobyl clean-up workers and the personnell of nuclear power plant suffering from vegetative dysfunctions. Correlative dependencies were shown between Leu4+HLADR- cell count, on one hand, and the time of working in the zone of elevated irradiation (r=-0,72), on the other hand, Leu3a+2a+ (r=0,64), Leu3a+2a- (r=-0,68) and the absorbed doses. CD4+ cell decrease was predominantly due to Leu3a+8- inductors of antibody producing cell decrease. Subset cell cycle analysis (SOBR) showed increase of heterogenity, non-replicative DNA synthesis in short term culturewith Con A, cortisol, 5-hydroxytryptamine and epinephrine in patients with vegetative dysfunctions irradiated in low doses interval.

The presence of combined changes in immune status of various population groups irradiated in Chernobyl accident caused the difficulties in the solving the problem of individual immunocorrection necessity.

We elaborated an in vitro sensitivity assays for CD3, CD10, HLA-Dr expression in response to thymic peptides and performed them in 1120 patients. It was shown that irradiated individuals had exhibited different types of response to thymic derivatives with the dependence on absorbed doses, initial state of immunologic reactivity and the character of somatic diseases. A distinct increase of antigen expression was revealed in leukemia patients. In vitro results showed good correlation with the clinical effectiveness of above mentioned immunomodulative thymic peptides.

Comprehencive clinical and immunologic investigation of persons in various exposed groups led to the conclusion that the control of cell differentiation should be the key point in late immunological effects of irradiation. Exact mechanisms of these pathways will be a subject of future investigations.

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CHILDREN AFTER CHERNOBYL: IMMUNE CELLS ADAPTIVE CHANGES AND STABLE ALTERATIONS UNDER LOW-DOSE IRRADIATION

Dimitry A.Bazyka, Anatoly A.Chumak, Vladimir G.Bebeshko, Nadezhda V.Beliaeva
Laboratory of Immunocytology, Department of Clinical Immunology, Department of Pediatric Hematology, Institute of Clinical Radiology, Research Centre for Radiation Medicine, Kiev, Ukraine

Abstract

Early changes of immune parameters in children evacuated from 30-km zone were characterized by E-rossette forming cells decrease and E-receptor non-stability in theophylline assay, surface Ig changes. Immunological follow-up of children inhabitants of territories contaminated with radionuclides after Chernobyl accident revealed TCR/CD3, CD4 and MHC II changes with the signs of immune systems non-specific activation and G1/S-cells increase in CD3+, CD4+, CD57+ subsets, RIL-2, TrR expression and calcium channel activity. PMNC percentage with cortical thymocyte phenotype (CD1+, CD4+8+) was elevated during the first years after the accident and seemed to be of a compensatory origin. Combination of heterogenic activation and suppression subset reactions and changes in fine subset (Th1/Th2) organisation were suggested. Adaptive and compensatory reactions were supposed and delayed hypersensitivity reactions increase. as well.

Early and late effects in children were one of the keypoints in the immune system studies after the Chernobyl accident [1, 2]. Marked irradiation levels differencies and combinations of external irradiation with radionuclide incorporation were shown in those evacuated from Prypjat and 30-kilometer zone, irradiated in utero and during the 1st year of their lives, children born from the parents who had participated in clean-up works, contaminated territories and Kiev population. Early changes of immune parameters in children evacuated from 30-km zone were characterized by E-rossette forming cells decrease and E-receptor non-stability in theophylline assay, serum Ig A, G and M changes [2]. Data were controversary in different hospitals because of different investigation techniques and control groups. Adaptive and compensatory reactions were supposed on the basis of cytochemical studies and hypothesis of specific "Chernobyl" syndrome as well [3]. Clonal selection and proliferation of radioresistant cells with the final radiosensitivity decrease on the system level [4,5] were discussed earlier and the absence of negative effects below the 0,35 Sv per life dose accumulation level.

Two thousand eight hundred and ninety samples from 1050 children who lived in Zhitomir (Ovruch, Narodichi) and Kiev (Gornostajpol) regions, Kiev and Slavutych were studied between 1988 and 1997. Clinical investigation and laboratory data analysis were performed with the help of standartized criteria. Radionuclide contamination levels were in 407 - 1120 GBq per sq.km limits in investigated regions, and in 20,5 - 50 GBq per sq.km limits in control. Immune cells differentiation and activation changes were studied by flow cytometry. In 1988 only indirect immunofluorescence studies were performed with visual detection on fluorescent microscope with mercury arc lamp. From 1989 subset analysis was performed by means of flow cytometry on FACStar PLUS cell sorter (Becton Dickinson, Mountain View, CA). Monoclonal antibodies (MoAbs) were obtained commercially from Becton Dickinson (CA, USA). IMK, IMK Plus, Simulset kits were used for immunophenotyping in two-color assay. Moabs and Anti-human immunoglobulin-FITC (Boehringer) were used with propidium

iodide (PE, Sigma) in DNA-cytometry. Intracellular antigen deposition was determined after incubation with PermeaFIX (Ortho)

DNA staining list mode data were analysed with the help of FACStar PLUS software with separate subsets histograms G0-G1, M-pikes and S-phase region estimation [9,10]. For anaslysis with "DNA" software a preliminary subset data file dividing was performed with "Paint-a-Gate" multicolor graphics software. FACScan analyzer was used parallely since 1993 with HP340 workstation and LYSYS II and CELLfit software.

Subset analysis showed in 1988 - 1990 a significant decrease of T-cell content in children inhabitants of the contaminated territories. Marked differences were seen also in CD2+ population (50,0 + 0,9 % in children from contaminated territories, 63,8 + 1,1% in control group, $P < 0,05$). CD4+ cell count didn't differ in 1988/89, and starting from 1990 a tendency to decrease was shown.As for the CD8+ subset a marked decrease was detected in 1989 with a tendency to normalisation in 1990. This effect was characteristic for Leu2a+3a- cells as well as for Leu2a+7- subset.

One can think that the integral functional reaction of the immune system to non-lethal irradiation isn't the result of parralel cell changes but the combination of heterogenic activation and suppression subset reactions, i.e. CD4+ cells activation limit is considered to be 0,01 Gy, and CD8+ cells inhibition are seen at 0.2 Gy [4,5]. Immunologic parameters normal ranges estimation in this new situation is closely related to immunologic defficiencies and onco-hematological pathology diagnosis, especially when the question of treatment with thymic derivatives or growth factors is considered to be of beneficial effect.

Certain immune system changes which were reported previously showed E-receptor positive cells decrease with serum immunoglobulin content deviations [6,7]. Tendencies of partial normalisation of E-rossette forming cells percentage were seen in 100 Prypjat children evacuated to Belaya Cerkov city (Kiev region) after sanatory rehabilitation . Minimal T-cell figures associated with normal EAC-forming cell content were shown in elderly boys evacuated to Harkov [8]. In some speculations prominent T-cell changes with T-suppressor inhibition are thought to be related with immune complex pathology [8]. A significant decrease of CD2+, CD3+, CD4+ cell con- tent and CD4+/CD8+ ratio associated with HLADr+ and alpha-chain of LFA positive cells content was revealed in 26 children from Brjansk (1987) and 30 from Zhitomir (1989), but all figures were within nor- mal ranges of deviation [8].

A slow tendency for normalisation was revealed in cytotoxic and NK cells. Parallel investigation with Moabs to HLA-Dr (ICO-1, anti-HLADR , OKIa) showed no differences but most of cells were Leu4+ and Leu4- cell quantity decreased. These data didn't correlate with the results of B-cell surface immunoglobulins. CD10+(CALLA) cell count in investigated groups varied, but mean figures elevation was seen in 1989. These patients were at first considered as a group of a high risk of leukemia, and a sophisticated diagnostic assays were performed in the Department of Pediatric Haematology. Signs of haemopoetic and immune systems non-specific activation were detected but none of leukemia. CD10+ positive cells showed a low fluorescence intensity. During 1990-1992 a decrease of CD10+ cell count was revealed in this group. Interleukin-2 receptor positive PMNC count varied (0,89 + 0,18 %, 0,21 + 0,36% in control, $P > 0,05$), Transferrin-receptor positive cell count decreased (2,38 +0,57 %, 6,69 + 0,52 % in control; $P < 0,05$). CD1+ cell content was found to be increased (1,9 + 0,4% in exposed group, 0,9 + 0,1% in control, $P < 0,05$), as well as double stained CD4+8+ cell percentage. During 1991 - 1992 immunophenotype was studied in 393 children, 225 were born in 1981 - 1986 and 168 in 1987-1992 . Deviations in T-cells subsets were shown, a low CD4+8-/4-8+ ratio was characteristic for 26%. The percentage was out of normal range. At the age from 1 to 5 years the frequency of lower ratios was two-fold higher (44,5%); Lower figures were associated with the high CD8+ values.

Correlations were shown between the Enkephalin receptor expression and elevated DNA nonreplicative synthesis, related changes in Leu4, Leu3a, TrR cell proportions and antigens expression, dysproportion of non-speciphic mitogens and allergens responce decrease detected by means of DNA-cytometry and migration inhibition assays and elevated cells counts on the early stages of activation. To our opinion these were the signs of T-cell activation and showed functional possibilities. This suggestion is confirmed by 3H-TdR uptake studies in this laboratory.

In Kiev children who were considered to be the control group a low CD3+ cell count was detected beginning from the age of 6 years. In children who were born in 1985 a significant decrease of CD3 antigen fluorescence intensity was showed on CD4+ and CD8+ cells, those who were born after 1987 showed lesser deviations.

Difficulties of obtained data comparison and summation to obtain the whole picture of ionizing radiation effects on immune system in child are enlarged to our mind by methodologic assays aspects and control group differencies. Prospective studies are the only way to valuable achievements. I.e. immune status investigation of 56 exposed children from Luga and 43 from Radomishl (control group) districts of Zhitomir region in 1989 showed in exposed group T and B-cell content decrease as comparing not only with control group but with previous study in 1988. A stable immunologic deficiencies formation was reported in children who had showed transitory changes in 1988. Similar changes were seen during this investigation. Various speculations could be made about the nature of cellular changes after continious low level irradiation. Peripheral PMNC changes seem to be related with the age at the moment of accident. Cell activation and differentiation deviations were the frequent event. PMNC percentage with cortical thymocyte phenotype (CD1+, CD4+8+) was elevated and according to Beverley (1986) [9] was considered to be of a compensatory origin .

The data obtained during the 10 years of patients follow-up could be explained by the adaptatin process. Additional confirm was obtained after apoptosis studies which is supposed to be the important self-regulation factor of the cellular population. A significant increase of CD95+ cells was detected in almost all of the investigated the groups. These findings coinsided with the detected increase of apoptotic bodies by image analysis.

Most of the patients showed in this study a two-fold TCR abberant CD3-4+ cell content increase suggesting some stem cell alterations. The implementation of recently developed biological dosimetry assays shows now the way to connect late non-stochasic immunologic effects with irradiation. A significant decrease of variant cells counts was seen in 1991-1995 in the groups of children evacuated from Pripjat and the inhabitants of controlled territories. Dose -effect curves and two- years mutations half-life period were the signs of the insignificant new irradiation loads. From 1996 a slow increase of TCR-CD4+ cells was shown in the group of inhabitatnts of contaminated territories. The decrease of the nutrition control and the increased radionuclide incorporation due to the contaminated foods ingestion were considered to be the main purpose and this fact semmed to be of the first line problems due to scientific and practical importance. Other flow cytometric assays could help in testifying of this suggestion [10]. A thorough investigation is needed in such cases with the estimation of activation and differentiation changes and especially of CD69, TrR, IL-2R and CALLA-expression elevation. Prognostic valuability of this data will be the topic of future study and estimation.

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MEDICAL CONSEQUENCES OF CHERNOBYL DISASTER IN UKRAINE

Andrei M.Serduk, Olga A.Bobylyova

Ministry of Public Health of Ukraine
Grushevsky str. No 7, Kiev 252021, Ukraine

ABSTRACT

Some aspects of health deterioration in population of Ukraine affected after the Chernobyl accident are presented. The survived population division in groups, peculiarities of morbidity incidence and prevalence are described. The dynamics of some medical demography parameters are discussed concerning adults and paediatric population. The precise values of incidence and prevalence for the main classes of diseases are shown in comparison of 1995 - 1996 to 1987.

INTRODUCTION

The Chernobyl Nuclear Power Plant (NPP) accident in 1986 led to the severest radioecologic disaster in human history. As the result nearly 8 % of population of Ukraine were affected: 3.2 million people are resident now on contaminated territories, 350,000 participated in accident cleaning up, 130,000 are migrants from contaminated zone. Children born during post-accidental period from parents - accident survivors constitute the high radiation risk group. Separately are presented the mortality tendencies and values in affected population compared to the whole Ukraine.

The revealed health status disorders genesis reasons can be connected both to the unfavourable radioecological situation (as the result of thyroid irradiation, CACCP general overexposure and several years-long effection of low radiation doses in population resident on contaminated soils) and unfavourable non-radiation origin factors effection (life conditions deterioration, dietary shortenings, prolonged psycho-emotional strain).

DATA AND DISCUSSION

In Chernobyl disaster health consequences estimation the prior medical attention should be drawn to 700,000 of paediatric population in Kiev, Zhitomyr, Chernigiv, Volyn, Rivno, Vinnitsa, Cherkasy, Ivano-Frankivsk, Chernivtsy, Ternopyl provinces both with group of migrants with thyroid exposure to radiation. The 772 cases of thyroid cancer are registered among this population group, 782 children are recognised as disabled persons because of diseases related to Chernobyl disaster.

The Chernobyl accident consequences cleaning up participants (CACCP) represent the second group requiring prior medical attention. Today according to Expert Councils' conclusions, the "reason-consequence" interrelation between disease and Chernobyl disaster consequences is fixed in 61,000 persons. The total number of disabled persons is nearly 47,000 (data of January 1, 1997).

The number of ill persons increased significantly during 1995-1996 compared to 1987: for 278 % among CACCP, for 255.5 % among children born since 1986, for 59.2 % among the contaminated territories residents, for 37.1 % among the evacuated persons (migrants).

In persons - CACCP the nervous system diseases are present in 11.4 % of all newly registered cases (499.4 per 10,000), cardiovascular system pathology - in 11 % (430.4), digestive system diseases - in 10.3 % (280.9). The pathology prevalence in some nosologic groups among CACCP is rather exceeding the average values for Ukraine: for vegetative-vascular dystonye in 5.6 times (244.3 and 43.7 respectively), peptic ulcer - in 4.3 times (72.6 and 16.9 respectively), endocrine system diseases - in 3.2 times (133.4 and 41.6 respectively, blood and hemopoetic organs - in 2.1 times (27.3 and 12.8 respectively).

The hematologic pathology requires much more attention in CACCP. The myeloblastic syndrome is registered by Radiation Medicine Scientific Centre of Ukrainian Medical Sciences Academy in 1994 - 1996 more and more often among sick CACCP.

The leukaemia diagnosis was made in 90 persons (in 17 of them in 1996). The 500 persons fixed in State Register are considered as the high risk group because of hematologic stable biases.

In health status analysis among adults and adolescents affected after the Chernobyl NPP accident the general tendency is markable during 1987 - 1995 for total morbidity and nosologic morbidity annual growth. The integral morbidity value increased in 3.8 times and consisted 5204.8 per 10,000 of respective contingent in 1995.

The all diseases classes morbidity and pathology prevalence is registered since 1987. For some diseases classes the morbidity among adults and adolescents - Chernobyl accident survivors significantly exceeds the values of all the adult population: for blood and hemopoetic organs - in 2.4 times and consists 30.5 per 10,000 in survivors (12.6 for Ukraine); for endocrine system - in 1.7 times - 70.0 (41.6 for Ukraine); for digestive system the morbidity is higher with 39.8 % (313.9 and 24.5 respectively), for cardiovascular system - with 36.4 % (445.8 against 326.7 respectively).

The malignant morbidity increased more than in 2 times in 1996 compared to that in 1987. The thyroid malignancy in affected adults and adolescents is in 2.5 times more frequent than in 1989 (no registration slots were provided in statistical reports before that). That exceeds the average value for Ukraine with 43.9 % (0.59 and 0.41 per 10,000). The lymphatic and hemopoetic tissue malignant neoplasmas prevalence grew in 2.2 times since 1987 (6.7 per 10,000 for respective contingent in 1996 and 3.0 - in 1987).

The cardiovascular system diseases posses one of the leading ranks in morbidity structure - 9.6 % (531.1 per 10,000 survivors), the digestive system diseases - 9.3 % (516.9), nervous system - 8.8 % (487.3), bone - muscular system - 4.3 (239.1). The vegetative-vascular dystonye morbidity among the evacuated persons exceeds the average Ukraine value in 4.2 times (185.9 per 10,000 survivors); that of blood and hemopoetic organs - in 4.2 times (54.3); of endocrine system - in 3.4 times (141.2); of digestive system - 2.3 times, including peptic ulcer disease - in 3 times (50.1). The bone-muscular system and joining tissue diseases prevalence is in 1.7 times higher (1284.2), that of cardiovascular system - in 1.5 times higher (4666.0) than for Ukraine.

The blood and hemopoetic organs diseases are more frequently registered in contaminated territories residents than among the whole Ukraine - in 2.4 times (30.2 per 10,000 survivors), that of vegetative-vascular dystonye - in 1.6 times (68.5). For 31.8 % the exceed of cardiovascular pathology incidence is present (430.4), that of endocrine system - for 30/3 % (54.2), of digestive system - for 25.2 % (280.9), of bone-muscular system - for 7.7 % (333.0).

The children health status estimation indicates the diseases prevalence progredient growth since 1987 annually concerning all the diseases classes both with separate ones. If the pathology prevalence value in 1987 consisted 786.6 and the morbidity one - 455.4 per 1,000 children, in 1995 those values increases in 2.1 and 2.5 times respectively. At the same time the diseases prevalence and morbidity incidence decreased for the whole Ukraine: prevalence from 1571.8 in 1988 to 135.8 in 1995 (declination for 15.0 %); incidence from 1309.03 to 1037 per 1,000 children (declination for 20.8 %). Therefore for January 1, 1996 the morbidity in affected paediatric population substantially exceeded the average value for Ukraine.

In morbidity analysis for diseases classes the neoplasmas class possess the leading place in pathology growth structure (due to thyroid cancer), the second rank is proprial to congenital abnormalities, that is followed with nervous system and sensory organs diseases, than - blood system pathology, digestive system diseases and genitourinary tractus ones. That is remarkable, the morbidity of the affected paediatric population for the first years after the accident remained lower in spite of its growth than morbidity of the whole paediatric population in Ukraine. The step-by-step excess was first fixed somewhere in 1992 - 1993.

From the diseases classes with substantial growth the congenital malformations are to be marked, as the morbidity level increase in 5.7 times was observed since 1987 to 1995. That of nervous system and sensory organs - in 5.7 times, for blood system and hemopoetic organs - growth in 5.4 times is present.

The mortality rate among the affected contingents as before is of tendency to increase. Values in 1996 were: CACCP - 9.06 ‰, face number - 2297; the workable population of Ukraine mortality rate is 6.5 ‰, that for the evacuated population is 11.6‰, face number - 684; for the contaminated territories residents - 18.42‰, face number - 34,079. The mortality rate for Ukraine consists 15.2. The 3178 death cases according to Expert Councils conclusions can be connected to Chernobyl accident consequences; 773 cases among CACCP in 1996.

CONCLUSIONS

The revealed health status disorders genesis reasons can be connected both to the unfavourable radioecological situation (as the result of thyroid irradiation, CACCP general overexposure and several years-long effection of low radiation doses in population resident on contaminated soils) and unfavourable non-radiation origin factors effection (life conditions deterioration, dietary shortenings, prolonged psycho-emotional strain).

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SOME ASPECTS OF THYROID SYSTEM STATUS IN PERSONS EXPOSED TO THE CHERNOBYL ACCIDENT

Anatoly K.Cheban, Dmitry E.Afanasyev, Olga Y.Boyarskaya

Paediatric Endocrinology Department, Endocrinology Departmant
Radiation Medicine Scientific Centre of Ukrainian Medical
Sciences Academy
Melnikova str. No53, Kiev 254050, Ukraine

ABSTRACT

The thyroid system status estimation held in post-accidental period dynamics among 7868 children evacuated from the 30-km Chernobyl zone and resident now in Slavutich city (Cs-137 contaminated area), among contaminated regions permanent residents, among native kievites and evacuated from 30-km zone. The thyroid pathology incidence dependence on residence place during Chernobyl Accident and after that was revealed. The immune-inflammatory thyroid disorders are characteristic for 30-km zone migrants, goitre different forms - for the radionuclides contaminated territories residents. No thyroid function abnormalities frequency confidential increase was registered during the research activities run. The total serum cholesterol level application unavailiability is revealed in Chernobyl accident survivors thyroid hormones metabolic effects estimation. Data concerning Chernobyl accident consequences cleaning up participants (CACCP) presented additionally.

INTRODUCTION

The thyroid gland and thyroid system in general posses the important place among nuclear facilities accidents. That is particular in case of Chernobyl nuclear power plant accident (CNPPA) [1].

Because of radioiodine high content in CNPPA fallout and iodine metabolism features the thyroid irradiation doses can exceed 10 - 20 Gy [2]. That unavoidably leads to thyroid pathology risk amplification [3]. Children are characteristic with higher thyroid irradiation doses compared to that in adults [4].

The radioecologic situation after the CNPPA in Ukraine is peculiar with extreme irregularity of present soil contamination level and radioiodine-produced thyroid irradiation doses in 1986. The differences in radionuclides spectrum content (including the variety of iodine radioactive isotopes) both with improper stable iodine profilaxys created the unpredictable situation concerning the possible pathology amount growth in survivors.

MATERIALS AND METHODS

The study of 9068 children and adolescents age 4 - 17 years old (0 - 10 years at the moment of accident) was held. Ist study group consisted from 1952 persons evacuated from town Pripyat in 1986, now resident in Slavutich city - Cs137 contaminated area); IInd study group was presented with 2664 Chernigov province residents (mild radionuclide contamination with no iodine dietary abnormalities in pre-accidental

period). The IIIrd study group contained the 2440 Kiev province Ivankov region residents (moderate soil contamination with mild goitre endemy - environmental iodine insufficiency). The 812 children - Kiev city residents were involved (400 native kievites and 206 migrants from town Pripyat) as the IVth study group. The Vth study group was presented with Rivno province residents - 1200 persons (remote territories with the severe radioactive contamination). The 260 persons - CA CCP of 1986 - 1987 years period were examined as the comparison group with high absorbed thyroid and total irradiation doses.

The study program contained:

- complex clinical examination;
- thyroid ultrasonography (mobile echo camera "Aloka-260" during the field works or unit "Aloka SSD-500" in clinic;
- thyroid hormones assay with immunofluorescent method on DELFIA unit ("Wallac Co");
- radiation anamnesis reconstruction;
- total serum cholesterol and malonic dialdehyde assay [5] as the thyroid function metabolic marker (first one) and lipids peroxydation index (second one).

RESULTS AND DISCUSSION

The Ist study group was characteristic with only inhalation mode of radioiodine incorporation because of evacuation during few days after the accident and almost absence of local origin food products in diet. The further residence in contaminated location contributed the low radiation doses effection here.

The contaminated territories residents IInd group was characteristic with long-term chronic radionuclides incorporation. The joint alimentary-inhalation mode of radionuclides incorporation was present.

The 1991 - 1995 years study results indicated that the amount of thyroid pathology increase with the age. The wave-like dynamics was surveyed from year-to-year. The average values consisted 1.6 - 5.0 %. The cases with goitre of IB degree were considered as the risk group. The mentioned quota consisted from 24.2 - 37.5 % during 1991 - 1995. At present no further thyroid pathology growth is registered. No clinical signes of thyroid function abnormalities were revealed. Some cases with neuro-emotional lability and termoregulatory abnormalitied were related to autonomous nervous system functional pathology.

The carried out hormonal studies revealed the hypothyroxinemia in 0.8 % of cases (Ist study group) with TSH increase in 0.2 % of cases. On the background of clinical pattern absence that was qualified as the laboratory hypothyroidism.

The clinical cases of hypothyroidism absence is not corresponding to the expected [6].The present results may indicate the distinct peculiarities of exposed paediatric population in Ukraine (i.e. ethnic features, dietary peculiarities, unproper iodine prophylaxis etc.) with delayed onset of expected pathology in the future.

The thyroid ultrasonography revealed no confidential differences in thyroid volume and frequency of structural disorders between native kievites and persons evacuated from town Pripyat - present Kiev residents.

The thyroid gland status in both Kiev residents groups is presented in Table I.

The study results among Rivno province residents indicated the high prevalence of thyroid cancer cases (both newly detected and already treated ones) - 0.7 % of cases, diffuse goitre - 0.4%, nodular goitre - 0.2 %, subacute thyroiditis - 0.4 %, chronic thyroiditis - 4.5 %, hypothyroidism - 0.5 %. The rather enough prevalence of

thyroid cancer and hypothyroidism prove the unfavourable significance of combination of radioiodine irradiation, contaminated zone residence and goitre endemy as the background.

In 86.2 % of Chernobyl 30-km zone residents the hypercholesterolemia was revealed. No correspondence to thyroid hormones serum content and clinical pattern was fixed. The sharp variability of parameter in native kievites is remarkable. The serum cholesterol level and malonic dialdehyde content directly correlated (r=0.34) in children age less than 7 years old at the moment of Chernobyl accident.

Table I.
Thyroid gland status in children - Kiev residents

Thyroid gland status	Chernobyl zone migrants		Native kievites	
	n	%	n	%
No goitre	112	28	118	28,5
IA stage	102	25,5	100	24,5
IB stage	176	44,5	186	45
Diffuse goitre II stage	2	0,5	2	0,5
Nodular goitre	2	0,5	2	0,5
Chronic thyroiditis	8	2	6	1,5
Subacute thyroiditis	10	2,5	2	0,5

In the comparison study group of CACCP of "iodine period" with the most complicated mode of thyroid and total body exposure to radiation during the all the survey period the progredient realization of the non-stochastic effects was registered. Those were presented with "euthyroid" hyperthyroxinemia, chronic thyroiditis with autoimmune component and hypothyroidism resulting outcome. The research data are proved with epidemiological statistics.

CONCLUSIONS

1. Thyroid pathology in children - Chernobyl accident survivors is registered with different frequency depending on place residence during accident and further period.
2. The thyroid cancer and hypothyroidism are more frequently present in persons with thyroid irradiation, resident on radioactively contaminated territories with environmental iodine deficiency.
3. The immune-inflammatory disorders are more characteristic for Chernobyl 30-km zone migrants; the certain forms of goitre are proprial to the contaminated territories residents.
4. No confidential difference revealed between native kievites and town Pripyat migrants resident now in Kiev (i.e. kievites are also affected after the CNPPA and resident in unfavourable environment).
5. The revealed morphological changes in thyroid gland tissue in 34 % of all cases are to be considered as the premorbid status with high risk of pathology outcome.
6. The serum cholesterol level in case of ionising irradiation is not corresponding to thyroid status and not available for biochemical estimations application.

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CYTOGENETIC EFFECTS IN CHILDREN BORN TO PARTICIPANTS IN THE CLEANUP OF THE CHERNOBYL ACCIDENT CONSEQUENCES — ACUTE RADIATION SYNDROME SURVIVORS AND CHILDREN EVACUATED FROM PRIPYAT

Eugenia I.Stepanova, Janna A.Misharina
Radiation Medicine Scientific Centre of Ukrainian MSA Melnicova str. №53, Kiev 254050, Ukraine

ABSTRACT

The cytogenetic study of 87 children was held. Age of involved kids ranged from 5 to 14 years old. The I-st study group was presented with 17 kids born in 1987-1988 from the Chernobyl accident consequences cleaning up participants (CACCP) who survived the Acute radiation syndrome (ARS) of I - II severity degree in 1986. The II-nd study group was consisted from the 45 children born in 1983 - 1985 resident in town Pripyat with thyroid exposure doses from 65 to 616 sZv and total irradiation doses from 0.2 to 13.2 sZv. The 25 children born in 1983 - 1988 and resident in radiation situation - favourable region of Ukraine constituted the Control (III-rd) group.

The aberrant cells number and chromosomal aberrations amount mainly due to chromatide type ones confidential increase compared to that in control was revealed among the children born from CACCP - ARS servivors.

In children exposed to ionising radiation during infant and early childhood age the aberrant cells number and chromosomal aberrations quantity was elevated also but due to both chromosomal (dicentrics and rings) and chromatide types.

INTRODUCTION

The chromosomal apparatus status study represents one of Chernobyl disaster actual medical aspects for radiation effection bioindication both with feasible stokhastic and non-stokhastic effects risk estimation [1]. The children are of particular interest here as the most sensitive to radiation factor effection part of the survived population [2].

MATERIALS AND METHODS

The 87 children age from 5 to 14 years old were inviolved. The I-st study group was presented with 17 kids born in 1987-1988 from the Chernobyl accident consequences cleaning up participants (CACCP) who survived the Acute radiation syndrome (ARS) of I - II severity degree in 1986. The II-nd study group was consisted from the 45 children born in 1983 - 1985 resident in town Pripyat with thyroid exposure doses from 65 to 616 sZv and total irradiation doses from 0.2 to 13.2 sZv.

The 25 children born in 1983 - 1988 and resident in radiation situation - favourable region of Ukraine constituted the Control (III-rd) group.

The cytogenetic study was held after the complex clinical examination and medical-genetic consulting of children both with their families. That enabled to exclude the factors suspected to effect the cytogenetic study results (prophylactic vaccinations, viral and bacterial infections, reparation diseases in family etc.).

For the lymphocytes metaphasal chromosomes preparations the 0.5 ml of heparinizated venous blood was added to 4.5 ml of RPMI-1640 cultural medium (containing 15% fetal calf serum, 2.5% of FGA, 1% of L-glutamine and antibiotics). Incubation was carried out for 48 - 50 hours under 37 degrees santigrade in plastic vials. The preparations were received with standard method. The heated up to 37 degrees 0.075 M KCl solution was applicated for hyposmolarity, the methyl alcohol and glacial acetic acid in 3 : 1 ratio were used for fixation. The preparations were placed in trypsin before dying (50 mg : 100 mL of distilled water) for 47 seconds. The Gimza dye was applicated. The coded preparations were microscoped with oil immersion under the x900 magnification. The 100 - 400 metaphases containing 46 ± 1 chromosome were analysed in every person. The Yunis method [3] was applicated for differentially dyed earlymitosed chromosomes obtaining.

The following types of chromosomal aberrations were taken into account: dicentric and ring chromosomes, single and double fragments. The analysis results were fixed in the standard registry protocol. The dicentrics and rings were taken into account for the exchange aberrations frequency calculation. The free fragments not relevant to the exchange type aberrations - for the fragments frequency calculation respectively.

The data concearning irradiation doses values, clinical and cytogenetic studies results were fixed in the Data base and processed with Excel software on PC.

RESULTS AND DISCUSSION

According to the received results the aberrant cells and chromosomal aberrations are present with the same frequency (1.45 + 0.22%) among the Control group.

The chromosomal type aberrations were presented mainly with double fragments (0.90 ± 0.1%) and dicentrics (0.01 + 0.01%). The chromatide type aberrations number consisted 0.55 ± 0.90%.

Thus the somatic cells mutations level among children of Control group is not different from data of other researchers [4, 5].

In children born from the CACCP - ARS survivors the aberrant cells and chromosomal aberrations were revealed with frequency of 2.38 ± 0.23% and 2.40 ± 0.24% respectively, that exceeded the control value ($p<0.001$). The chromosomal type aberrations value (double fragments, dicentrics, ring chromosomes) consisted 1.00 ± 0.19% and not exceeded the control one. The chromatide aberrations frequency was 1.40 ± 0.20% that is confidentially higher ($p<0.01$) than in Control group (table).

Table - Chromosome aberrations frequency in Study groups

Parameters	Study groups		
	Born from CACCP-ARS survivors	Evacuated children	Control group
Number of children	15	45	25
Cells with chromosome aberrations (%)	2,38±0,23*	2,70±0,28*	1,45±0,22
Cromosomal aberrations (%)	2,40±0,24*	2,70±0,28*	1,45±0,22
Dicentrics & rings (%)	0,08±0,03	0,23±0,03*	0,01±0,01
Double fragments (%)	0,92±0,19	1,00±0,12	0,90±0,10
Single fragments (%)	1,30±0,18*	1,22±0,17*	0,55±0,90

* - confidential difference from control ($p<0.01$)

Consequently the aberrant cells and chromosomal aberrations were confidentially more frequent in children born from CACCP - ARS survivors compared to that in control. The chromatide type aberrations presented the significant quota of all the chromosomal aberrations.

The aberrant cells and chromosomal aberrations number was equal (consisting 2.70 ± 0.28%) in children exposed to ionising radiation effection in town Pripyat during infant and early age. That value exceeded the control one ($p<0.001$). The unstable chromosomal aberrations of exchange type (dicentrics and rings) were revealed with frequency of 0.23 ± 0.03% and were over the control levels ($p<0.001$). The double fragments number consisted 1.00 ± 0.12% here, and 0.90 ± 0.10% in control ($p>0.05$).

So the children evacuated from town Pripyat have the cytogenetic status distinct peculiarities characterised with aberrant cells and chromosome aberrations (both chromosomal - dicentrics and rings, and chromatide - single fragments) frequency increase compared to control.

For possible interrelation revealation between total irradiation dose and cytogenetic study data the correlational analysis was applicated. The confidential correlational relationships presence were fixed between the aberrant cells total number, chromosomal type aberrations (double fragments, dicentrics) frequency and total irradiation dose. The correlation parameters value consisted 0.48 - 0.54 (figure).

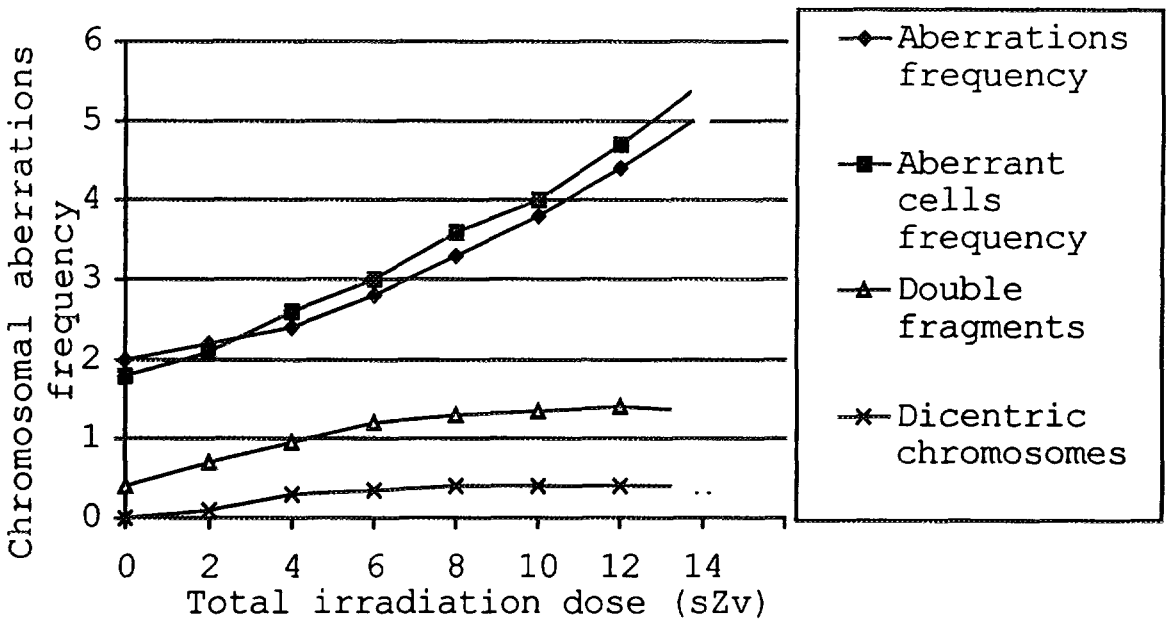

Fig. - Chromosome aberrations frequency distribution depending on total irradiation dose

Therefore radiation effection cytogenetic markers are revealed during the remote post - accidental period in children exposed to ionising radiation total exposure doses range 0.20 - 13.2 sZv. That may indicate the damage on the stem cells - precursors level and mutant cells clones initiation.

We consider the aberrant cells number and chromosome aberrations increase both with that of chromosomal type (dicentrics and rings) and chromatide type (single fragments) in children born from Chernobyl accident consequences cleaning up participants - acute radiation syndrome survivors and in children evacuated from town Pripyat, indicate the chromosome apparatus instability. That may occur the risk factor for stokhastic effects during the postaccidental period remote terms.

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CLINICAL EFFECTS IN CHILDREN IRRADIATED PRENATALLY: 11 YEAR SURVEY RESULTS

Eugenia I.Stepanova, Valentina G.Kondrashova, Tatyana Ya.Galichanskaya, Olga A.Davidenko, Vitaly Yu.Vdovenko, Natalia A.Stakhurskaya

Radiation Medicine Scientific Centre of UMSA, Melnikova str.No53, Kiev 254050, Ukraine

ABSTRACT

The 11 years-long survey results indicated the amount of children increase with disconcordant development signs, thyroid structure and function disorders both with that of somatic status. Majority of blood and immune system quality and quantity parameters deviations been present during the "acute iodine period" among children exposed to acute irradiation gradually reached the control level. The hemopoetic and immunocompetent system function substantial deviations are continued being registered among children born in zone of radionuclide contamination.

INTRODUCTION

The high radiosensitivity is characteristic for organism on stage of development and differentiation. Therefore children represent themselves the critical population group mostly affected after radiation accidents especially in case of ionising radiation effection during antenatal ontogenic period [1 - 3].

MATERIALS AND METHODS

The 1104 children born in 1986 were surveied during 11 years of post-accidental period. The Ist study group was presented with children born from women pregnant at the moment of Accident and evacuated from town Pripyat - 340 kids; IInd - children born and resident in radionuclide contamination zone - 169 persons; IIIrd - control group - 595 persons respectively. The fetal thyroid irradiation doses consisted 0.1 - 334.0 sZv, total irradiation doses in Ist study group - 10 - 376 mZv, in IInd - 4.7 - 33 mZv respectively. The thymus and red bone marrow irradiation dose values in Ist study group were 10.0 - 300.0 mZv, in IInd - 4.2 - 25.9 mZv and 4.7 - 35.5 mZv respectively.

The clinical, hemetological studies were carried out, the neutrophyles functional properties were tested with alkaline (AlPh) and acid (AcPh) phosphatases, myeloperoxydase (MP), $NADH_2$ and $NADPH_2$ dehydrogenases (DG) activities evaluation; lipids (LP) and glicogene (Gl) content [4], phagocytosis percentage (PhP), phagocytic index (PhI) assessment; NBT-test parameters in spontaneous and stimulated variations (percent of formazane-positive cells - PFPC, average cytochemical index of tetrasolreducting activity - ACITA) [5] estimation. The blood cells ultrastructure and superficial architectonics were estimated with transmissional (TEM) and scanning (SEM) electrone microscopy. The immunocompetent cells subpopulations content was studied on lazer flow cell sorter FACStar PLUS ("BECTON DICKINSON" Co.) with LT - series monoclonal antibodies application (produced in Moscow Institute for Immunology). The serum immunoglobulines A, M, G content was assaied with

immunodiffusion in agar gel method. The thyroid structure evaluation was held with echo camera "Aloka-SSD-500". The hormonal studies were completed via immunofluorescent method on DELFIA unit ("Wallac" Co.). The mathmethods complex was applicated for children health deterioration risk estimation.

RESULTS AND DISCUSSION

According to the received data, the average physical development parameters in newborns from Ist and IInd study groups corresponded to control. The personal parameters analysis indicated the more frequent (7.6%) than in control (2.9%) birth of children with "low for term" body mass in IInd group ($p<0.01$). No cases were registered in newborns of head circumference lower than normal age values. In children from IInd study group the lower body mass was registered at age of 1 year. The amount of children increase with disconcordant physical development was fixed in further years, especially in IInd study group (Table I) both with that of thyroid goiter of IB - II degree (Table II).

Table I. - Children with disconcordant physical development quantity in post - accidental period dynamics (per cent).

Study group	Years of survey				
	1989	1991	1993	1995	1997
I	6,2	8,3	12,7	16,9	27,4
II	9,1	13,2	19,8	27,6	49,3
III	4,7	6,9	11,1	15,1	17,1

Table II. - Thyroid gioter frequency in post-accident period dynamics among children irradiated in utero (per cent).

Goiter	Ist group					IInd group					IIIrd group degree				
degrel	1989	1991	1993	1995	1997	1989	1991	1993	1995	1997	1989	1991	1993	1995	1997
0	72.3	60.7	11.4	10.2	40,3	87.0	57.7	16.1	15.1	25,9	92.6	87.0	83.6	54.5	71,7
I-A	26.8	37.9	80.4	75.2	38,5	12.5	39.7	72.1	70.2	47,2	7.4	13.0	13.2	34.0	11,2
I-B	0.9	1.4	8.2	14.6	20,3	0.5	2.6	11.8	14.7	25,4	0.0	0.0	3.2	11.5	17,1
II	0.0	0.0	0.0	0.0	0,9	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	0,0

Thyroid structure irregularity during year 1989 studies was revealed in 51 % of children of Ist, in 41 % of IInd and in 19 % of control group respectively; that in 1997 consisted 37 %, 43 % and 21 % respectively. Cyst and nodular degeneration of thyroid tissue in 1997 was registered in 0.8 % of Ist and in 1.7 % of IInd study groups, no cases were fixed in control. No clinical signes of hypothyroididsm were detected. The hyperthyroidism of mild degree was registered in 1997 among 0.2 % of children from IInd study group, autoimmune thyroididtis - in 1.2 % among children from Ist, in 1.8 % among children from IInd and in 0.2 % in control group respectively. The THS deviations from normal age values were registered in 2.4 - 5.1 % among Ist and IInd study groups; no deviations were registered in control.

The lower compared to control hemoglobine, WBC and platelets content was proprial to the children irradiated in utero during the early post-accidental period. The leucogram deviations were more frequent too. Those biases normalised in Ist study group at the age of 9 - 10 years old, in IInd one - still remained.

The blood cell ultrastructure estimation indicated the decreased volume cells presence among RBC with cytoplasmic gemmations of "apoptose bodies" creations - type, membranes focal loosening or condencing. The WBC content with functional activity morphological signes was increasing. The number of cells with peculiar nuclei forms, perinuclear space

dilatation, increased vacuolization and membranes microclazmatosis increased too. The mitochondria with enlightened matrix and partial crists desorganisation were registered more often. The "active" neutrophyles quantity increased. The autophagocytosis signs were revealed with cytoplasmic pieces registration in phagocytic vacuoles. The described disorders involuted in dynamics but not disappeared totally. The blood cells superficial architectonics changed substantially. The discocytes number was decreased to 62.5 - 59.8 % with transition, pre-hemolytic and degeneration-changed forms number synchronous increase. The amount of lymphocytes with relatively plain and villial surface decreased and increased with that of complicated surface type.

The neutrophyles metabolism among children from both main study groups in 1988 - 1989 was characterised with activation of AlP (127.5 ± 6.40 ut., in control - 79.08 ± 3.63 ut., $p<0.001$); AcP (156.37 ± 5.92 ut., in control - 88.08 ± 3.45 ut., $p<0.001$); $NADH_2$-DG (9.47± 1.81 gr./cell, in control - 4.83 ± 0.27 gr./cell, $p<0.01$) and $NADPH_2$-DG (3.38 ± 0.47 gr./cell, in control - 1.93 ± 0.11 gr./cell $p<0.001$); LP content increase (276.44 ± 7.71 ut., in control - 240.17 ± 6.48 ut., $p<0.001$) and Gl increase (274.00 ± 4.68 ut., in control - 249.75 ± 2.30 ut., $p<0.05$). In further years the parameters graduent decrease was revealed, in Ist study group control values were reached up to 1995. In children of IInd group the intracellular enzymes, energetic and plastic substances depot exhaustion was observed. The neutrophyles function instability occured to be revealed on that background.

The immunologic parameters deviations in both Ist and IInd main study groups were of simmilar tendency and presented mainly with T-branch supression, immunoregulatory subpopulations disbalance and disimmunoglobulinemia. The personal parameters were rather variable with high frequency of deviations over the physiologic range. The three types were picked out from all the deviations variability. The first one was characteristic with CD8+ decrease, CD16+ and CD72+ - cells, immunoregulatory index increase, elevated Ig G and Ig M content (activational type). That one was present in 18.9 % of all children and manifestated with allergy syndrome. The second type was peculiar with CD3+, CD4+, CD16+, CD72+ - cells, Ig G and Ig A content decrease. This one was registered in 17.4 % of children and was presented with immunologic insufficiency infectional syndrome. The third type was characteristic with various combinations of immunologic parameters deviations without precisely describable clinical pattern. This undifferentiated type of immunologic disorders took place in 19.8 % of cases. The CD3+, CD4+ and CD8+ - cells content in children from Ist group turned to control values up to years 1995 - 1997, but the CD4+/CD8+ ratio remained more high ($p<0.05$). No real positive dynamics was revealed in IInd study group. The immunologic status more severe disorders were present in children irradiated during first 15 weeks of gestation.

The mathanalysis indicated the more intensive increase of children with chronic pathology quota among irradiated in utero (Fig.1). The most sharp dynamics was in kids exposed in early gestation terms (Fig.2). The confidential dependence was fixed between health status, total irradiation dose, thymus, red bone marrow irradiation doses and some studied parameters with multiple correlation indices of 0.5754 - 0.8463. The health deterioration risk most informative criterions were: average absorbed dose (β=0.058), thymus (β=0.031) and red bone marrow average equivalent doses (β=0.047); RBC content (β=0.027); neutrophyles to lymphocytes ratio (β=0.031); $NADPH_2$-DG activity (β=-0.018), PhI (β=-0.035); PFPC (β=0.011); ACITA (β=-0.028); Ig A content (β=-0.046) and Ig M content (β=0.046); immunoregulatory index (β=0.037). The group health deterioration risk in children irradiated in utero consisted 1.63 - 2.94, with 0.85 - 1.13 value in control.

The integral index reflecting unfavourable biases as the result of Chernobyl accident radiation and non-radiation factors effection during ontogenesis antenatal period is presented with practically healthy children quota reduction among population from 35.7 % in 1987 to 5.0 % in 1996.

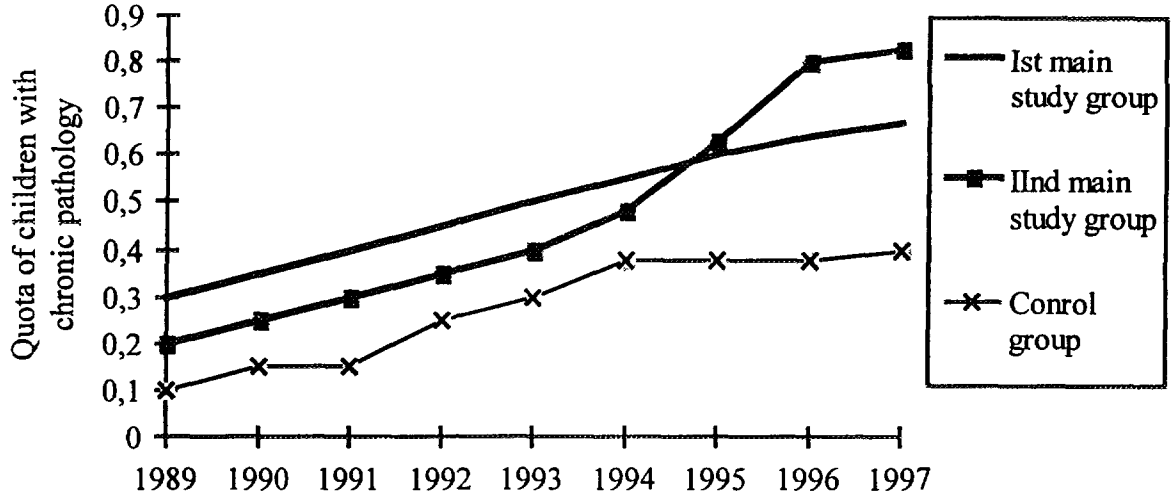

Fig.1. Quota of children with chronic pathology in dynamics after Chernobyl NPP accident

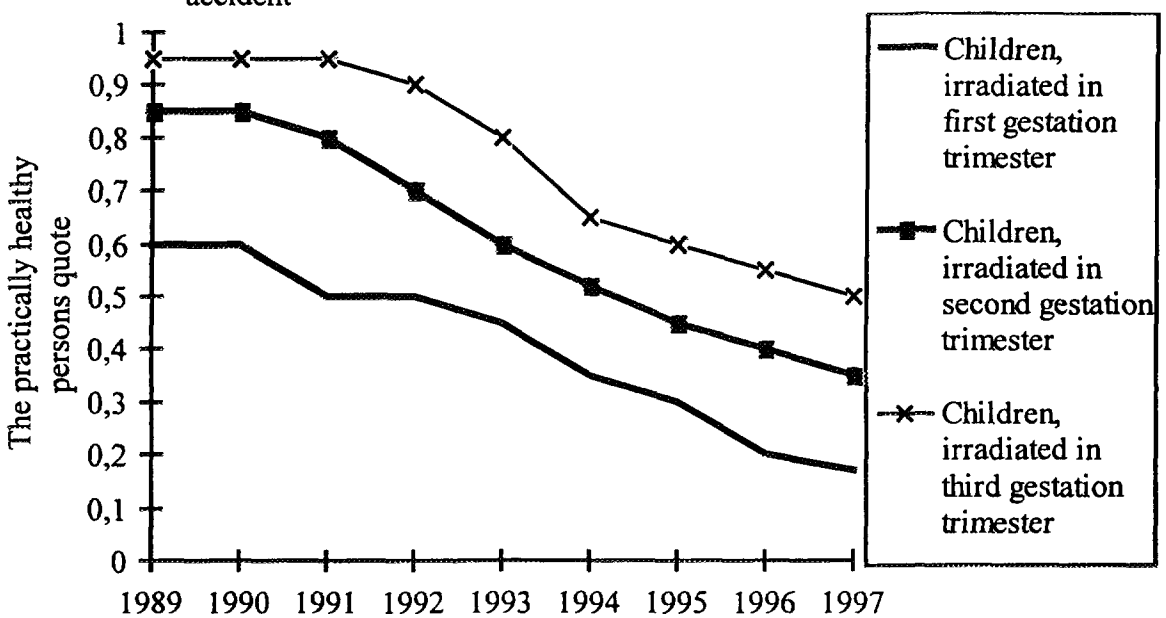

Fig.2 . Quota of healthy children in dynamics after Chernobyl NPP accident depending on various gestation term

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BIOLOGICAL EFFECTS OF LOW DOSES OF IONIZING RADIATION: CONFLICT BETWEEN ASSUMPTIONS AND OBSERVATIONS

P.C. KESAVAN AND T.P.A. DEVASAGAYAM

Biosciences Group, Bhabha Atomic Research Centre, Trombay, Mumbai - 400 085, INDIA

Abstract. Recent epidemiological data on cancer incidence among the A-bomb survivors and more importantly experimental studies in cell and molecular radiobiology do not lend unequivocal support to the "linear, no threshold" (LNT) hypothesis; in fact, the discernible evidence that low and high doses of ionizing radiations induce qualitatively different/opposite effects cannot be summarily rejected. A time has come to examine the mechanistic aspects of "radiation hormesis" and "radioadaptive response" seriously rather than proclaiming one's profound disbelief about these phenomena. To put the discussion in a serious scientific mode, we briefly catalogue here reports in the literature on gene expression differentially influenced by low and high doses. These are not explicable in terms of the current radiation paradigm.

1. Introduction. The current radiation paradigm assumes that for genetic effects induced by ionizing radiation, there might not be any "threshold dose", and a "linear, no threshold" relationship between dose and adverse genetic health effect (mutations in offspring, cancer in the exposed survivors) would therefore be expected to increase following exposure to even very low doses. A backward extrapolation from the high to low regions of the dose-effect curve has seemed justifiable. It must, however, be noted that actual experimental as well as epidemiological studies have not provided unequivocal support to the "linear, no threshold" (LNT) hypothesis; instead there has been growing evidence that low dose ionizing radiations induce "hormesis" [1], radioadaptive response [2,3] which are clearly not explicable by the current radiation paradigm. So far as cancer incidence among the A-bomb survivors is concerned, 'hormetic effect' among those exposed to about 8 cGy has also been suggested. A similar trend has also been inferred with regard to the inhabitants of high natural background radiation areas in China [4]. Since epidemiological data are often vitiated by several confounding factors, these are not powerful enough, to constitute the premise for "paradigm shift". There are, however, appropriate data from cellular and molecular radiobiology, to infer that low and high doses elicit *qulitatively* different responses. It is often noted that low and high doses do not simply activate (or inactivate) the expression of genes in quantitative manner, but exert opposite effects on different genes of the genome. The other major observation is that only small conditioning doses induce radioadaptive response, whereas higher doses do not. This again shows that low and high doses induce widely different molecular and cellular events in the cell. We propose to catalogue in this brief review only such major aspects which seem *not* readily explicable on the basis of LNT hypothesis.

2. Induction of gene expression. *a : Proteins* Low and high doses of radiation exert widely varying effects on expression of different genes invloved in synthesis of proteins, control of apoptosis and immunomodulation. Twelve X-ray-induced transcripts differentially expressed, 8 to 230-fold, in X-irradiated versus unirradiated radioresistant human melanoma cells. All transcripts were transiently expressed and induced by lower, but not higher (>600 cGy) doses of radiation. X-ray-inducible genes may function in damaged cells to regulate DNA repair, apoptosis etc. [5]. Such an expression also shows a pleiotropic response. X-irradiation (up to 8

Gy) induced 3 different types of responses in proteins (XIPs, X-ray induced polypeptides) in human malignant melanoma cells. Class I proteins were induced linearly with increasing X-ray doses. The synthesis of class II proteins (a majority of XIPs) increased linearly with low doses, but plateaued at higher doses of 1.5 to 2.5 Gy. In contrast, the expression of class III proteins, decreased with increasing X-ray doses [6]. Mice chronically exposed to 4 cGy γ-rays for 4 weeks showed an increase in the expression of stress proteins (HSP70, HSC70, HSP72) in splenocytes. A higher dose of 10 cGy, however, did not induce these proteins [7]. Low dose irradiation (25 and 50 cGy) stimulates the SH group of membrane proteins and enhances the $Na^{+}K^{+}$-ATPase activity, while doses above 100 cGy significantly decreased enzyme activity, in rat cerebral cortex [8]. (Please see Table 1. for comparative effects)

Table 1. Influence of dose of ionizing radiation on differential gene expression

Parameter	Low dose & effects	High dose & effects	Ref.
1. Expression of X-ray-inducible genes	<6Gy; 12 genes (transcripts) are induced	>6 Gy; no induction of gene expression	5
2. X-ray induced polypeptides -Class I	up to 1.5 Gy; increase	above 1.5 Gy; no change	6
Class II	up to 1 Gy; decrease	above 1 Gy; no change	
3. Expression of stress proteins	4 cGy; induced expression	10 cGy; did not induce expression	7
4. $Na^{+}K^{(+)}$-ATPase activity in brain	25 & 50 cGy; increased activity	100 cGy; decreased activity	8
5. Thymocyte apoptosis	<20 cGy; reduced below control levels	>50 cGy; increased above controls	9
6. Con-A induced mitogen response	5,10 cGy; increased	>25 cGy; reduced response	13

b: Apoptosis. There was a significant reduction in apoptosis rate, below control levels, with doses below 20 cGy and a dose-dependent increase with those above 50 cGy in thymocytes of whole body irradiated mice and in EL4 cells. A typical J-shaped dose-response curve was observed for X-ray (1-1000 cGy) induced apoptosis in EL4 cells. Only doses above 50 cGy caused an increase in apoptosis and values of 5 dose points were below that of the control and among these 3 were statistically significant from control [9]. Accumulation of p53, the product of tumor suppressor gene involved in the regulation of apoptosis, occurred in the adrenal glands and pancreas of mice exposed to 25 and 50 cGy but not 100 cGy of X-rays [10].

c: Modulation of immune system. 7.5 cGy X-rays enhanced signal transduction in lymphocytes. There was increased mobilization of $[Ca^{2+}]_i$ and activation of protein kinase C in response to ConconavalinA (ConA) and anti CD_3 McAB [11]. In rats exposed to 5 and 10 cGY, ConA-induced mitogen response increased significantly whereas doses above 25 cGy reduced such response [12].

(ii) Adaptive response and the mechanisms involved. Preexposure of cells to a low dose of gamma-ray (1 cGy) caused a decreased susceptibility to gene deletions and rearrangements after a challenging radiation with a high dose [3]. In bone marrow cells of mice exposed to a challenging dose of 1 Gy, adaptive response observed was time-dependent and a lower dose of 2.5 cGy induced a longer-lasting adaptive response as compared to 5 cGy [2]. In human lymphocytes a dose of 1 cGy induced an adpative response, in terms of decrease in the frequency of mironucleated binucleate cells, when exposed to a challenging dose 1 Gy of gamma-rays (Fig. 1) [13].

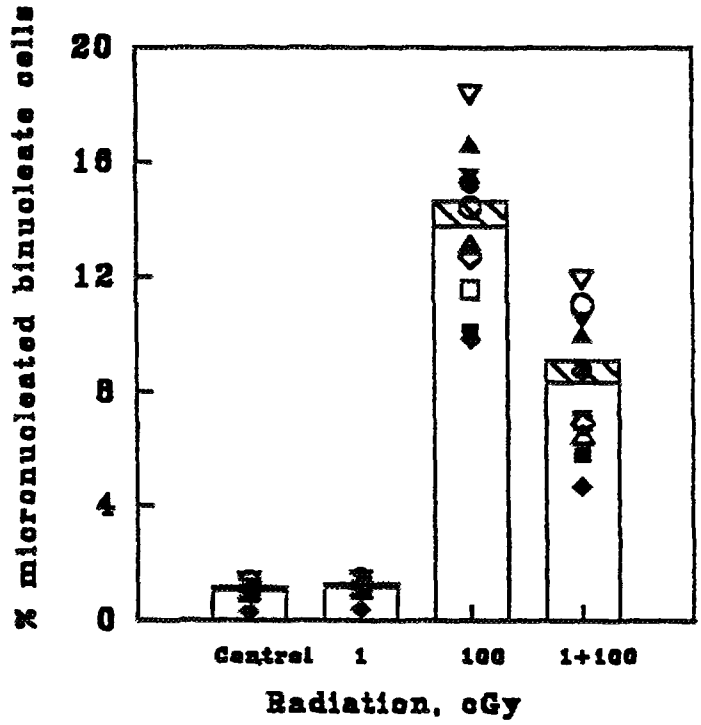

Fig. 1. Effect of pre-exposure to 1 cGy gamma radiation on 100 cGy radiation induced mn-BNCs in human lymphocytes *in vitro* male subjects. Symbols denote different individuals and bars represent pooled mean values [13].

Protein kinase C-mediated signalling pathway is a key step for the transduction of the low-dose-induced signal responsible for adaptive response. Low-dose may trigger changes in the expression of several genes whose products, though most of them are still not identified, would be related to DNA repair and/or control of cell cycle progression [14].

It is likely the the qualitative difference in the responses observed with low and high doses of radiation may be due to the differential response of the signalling pathways. One such pathway deals with reactive oxygen intermediates. They are known to influence apoptosis and membrane functions. It is likely that the quantitative and qualitative differences in the generation of these reactive species may be some of the major factors responsible for the contrasting effects observed with high and low doses. There is a paucity of data in this aspect and further studies are needed to examine the molecular mechanisms involved.

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Knowledge of Doses from Radiumtherapy for Skin Hemangioma in Childhood

SHAMSALDIN A.*♣, DIALLO I. *♣, LIGOT L.*♣, CHAVAUDRA J.*, DE-VATHAIRE F.♣

* Institut Gustave-Roussy/Physics department (IGR/Phys.), Villejuif/France
♣ Research Unit of Cancer Epidemiology (U351 INSERM), Villejuif/France

Abstract

Before 1974 about 5000 children were irradiated at the *Institut Gustave-Roussy* for a skin hemangioma of whom 20% were treated with radium applicators. To evaluate the absorbed doses to these patients at any site, we have developed a software program wh)ch permits simulation of the actual patient and treatment conditions.
Part of this software is devoted to constructing an Individual Computerised Tomographic Anatomy (ICTA) based on real human transverse slices and auxological tables. From the generated phantom, 160 anatomical sites of epidemiological interest are defined and localised according to a Cartesian co-ordinate system.
The gamma doses at all sites from Ra-226 applicators are calculated by an algorithm which permits separation of the radiation paths in air, tissue, and lungs. It includes a correction for attenuation and scatter in infinite and semi-infinite mediums. To evaluate the factor $\varphi(r)$ for these corrections at any distance or position from the applicator, we have modelled the results from several Monte Carlo simulations.
In the range of 1 to 10 cm, the $\varphi(r)$ values obtained from our model showed good agreement with those obtained by published methods. For several cases, the absorbed doses at points in water and patients from radium applicators estimated by this software, were compared to those measured and estimated at the Karolinska Hospital. The results showed good agreement.

Introduction

Earlier studies to monitor the long-term radiogenetic risk after radiumtherapy for skin hemangioma in childhood confirmed a high risk [1-4]. In these studies, the dose estimation from radiumtherapy was based on standardised phantoms and treatments. To increase consideration of the strong graduation of the dose in the vicinity of the radioactive source, we initiated development of a more precise program for dose estimation in epidemiological studies. Initially, the program is used to evaluate radiation doses to a cohort of about 5000 children irradiated at the *Institut Gustave-Roussy* (IGR) for a skin hemangioma before 1974.
In this paper we describe briefly the anthropomorphic phantom established by this software, and the approach we have used to evaluate the effective transmission factor, and to calculate absorbed doses to various sites of patients.

Phantom

The first part of the program is devoted to constructing an Individual Computerised Ttomographic Anatomy (ICTA) based on real human transverse slices [5]. These slices were combined to construct a 3-D phantom. The phantom is segmented into 5 sections defined by x (left-right width), y (distance up-down), and z (post-ant thickness). In co-operation with paediatricians, we have defined and localised 160 anatomical sites of epidemiological interest.

When the information about a patient is introduced, the program calls auxological tables to select the reference parameters (mediastinal diameter, head width and thickness, bi-acromial and bi-iliac widths, and the distance from the base of the heel to the: chin, breast, gonad, and knee) corresponding to the sex and the age of the patient at the time of treatment, using the method described in [6]. The 5 sections of ICTA are thus adapted and the anatomical sites are relocalised. Figure 1 shows the frontal projection of ICTA phantom adapted to: 1, 12, and 24 month female children constructed by this software.

Applicator model

In the second part of the software, the radioactive applicators (type, geometry, and dimensions) are modelled. Precise 3-D positioning of the applicator (needles, tubes, flat sheets) and the shape of the treated region are considered. Once the phantom is adapted to the patient, the applicators are positioned according to available information, i.e. drawing, photograph, etc.. This information is saved independently of the dose calculation module, allowing for further extensions and improvements in dose calculation procedures.

Dose calculation

The gamma doses from radium applicators are calculated by an algorithm which forms the third. part of the software. The well known quantisation approach described in [7], is adopted. The active volume is divided into small elements, equal in size. The number of the elements depends on the source length (or surface area for radium plaques), and the distance source-point of interest, such that each element could be considered as a point source. The absorbed dose at any point is calculated from the widely used equation recommended by CFMRI* [8], which is based on the ICRU recommendations [9]. In this equation, the correction for attenuation and scattering in the medium is performed using the effective transmission factor $\varphi(r)$. To evaluate this factor, we have modelled the results of several Monte Carlo simulations using the EGS4 code system.

Results

In figure 2, we represent the variation of $\varphi(r)$ with distance (r) from the source. In the range of 1 to 10 cm, the $\varphi(r)$ values obtained by this model showed good agreement with those calculated by Meisberger [10]. For further distances our model extrapolates exponentially, permitting the continuity of the variation, as was suggested by an other author [11]. For the superficial sites, a correction is introduced to take into account the semi-infinite nature (lack of scattered radiation). Consideration of this correction is particularly important in our study as the radium applicators were applied on the skin surface. The sites located near the skin surface and on the same side of the treated region (e.g. breast when the treated region is the anterior abdominal region), receive lower doses as compared to points located at the same distance from the source and situated inside the body (e.g. heart). This algorithm estimates the photon path length separately, in air, tissue, and lung, which influence the attenuation and consequently the absorbed dose.
The absorbed doses at several sites within the patients and in water, estimated by this software, showed good agreement with those estimated and measured at Karolinska Hospital.

Discussion

The ability of our software to adapt ICTA to each patient allows for a precise estimate of (r).This factor is of major influence in estimation of the absorbed dose at any site. Evaluation of $\varphi(r)$ at any distance and at any position with a single model, not only simplifies the individual dosimetry, but

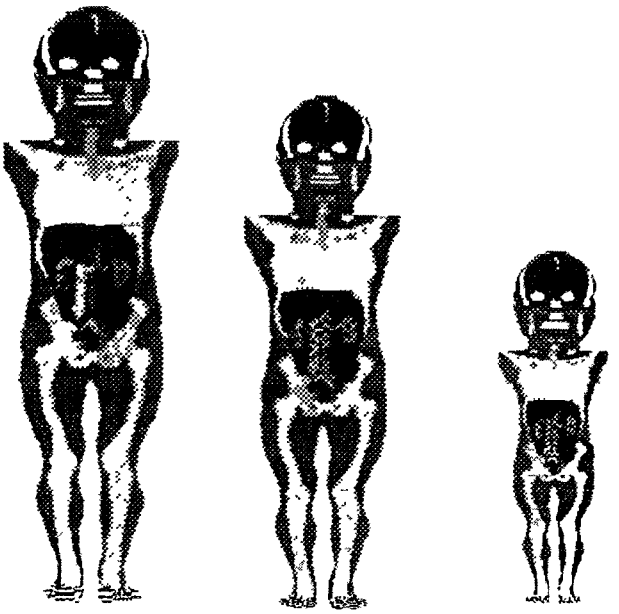

Figure 1. Frontal projection of ICTA phantom adapted to: 24, 12, and 1 month female children.

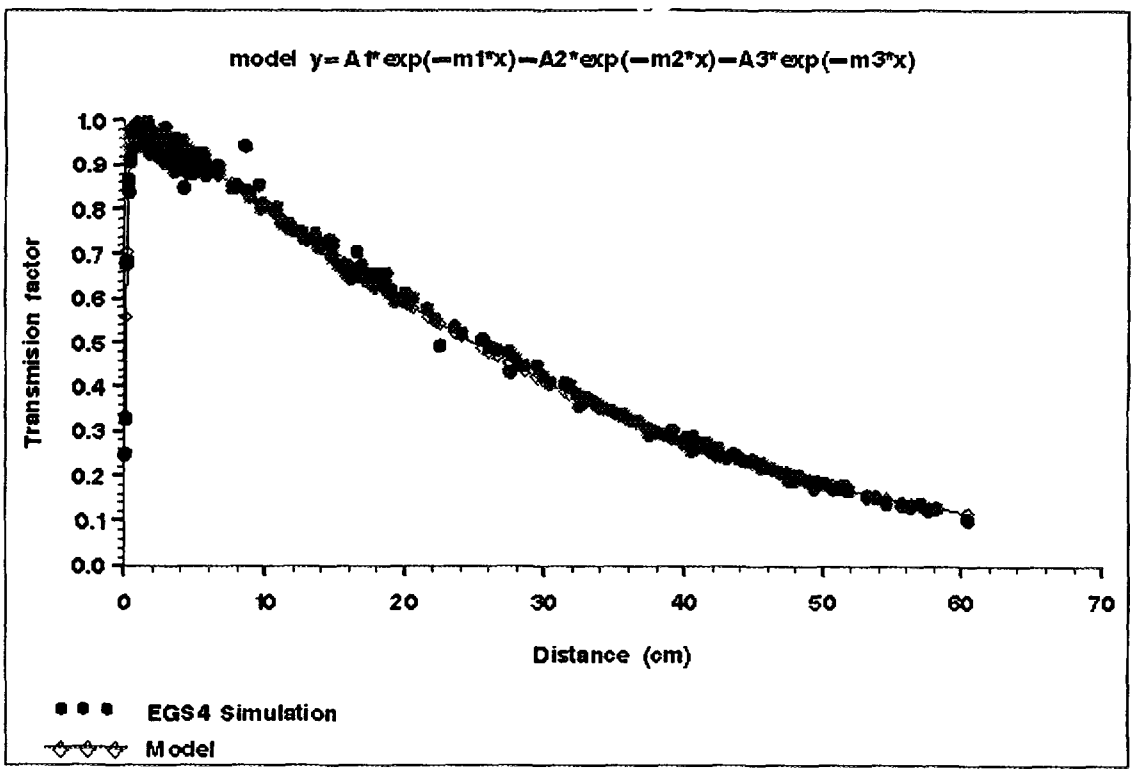

Figure 2. The transmission factor φ(r) as a function of distance, based on Monte Carlo simulations using the EGS4 code.

also allows for accurate estimation of the absorbed doses at points very close to the source (< 1 cm) and at distances larger than 10 cm, limits of other available models. Moreover the software can be easily handled, not only to input the information required for retrospective dose estimation (sex, age at the time of treatment, characteristics of the applicator, time of treatment) but also to localise the applicators correctly according to the drawings, photographs or any available information in the treatment records. This software can be easily adapted for dose calculations for any other radioactive source applied on the skin surface, or within the body.

Finally, our approach is a useful tool for individual dose estimation, particularly when large groups of patients are analysed. It is also useful when knowledge of the absorbed doses to numerous sites is required. The database constructed by our model could lead to evaluate dose-response relationship, and can help to improve knowledge of low dose-effects for the radiation protection purposes.

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Knowledge of doses from external radiotherapy for a cancer in childhood

SHAMSALDIN A. *♣, GRIMAUD E. .*#, HARDIMAN◊ C. *♣, DIALLO I. *♣,
DE-VATHAIRE F. ♣, CHAVAUDRA J.*

* Institut Gustave-Roussy/Physics department (IGR/Phys.), Villejuif /France
♣ Research Unit of Cancer Epidemiology (U351 INSERM), Villejuif/France
\# Institut de Formation Superieur de Biology Médical (IFSBM), Villejuif/France

Abstract

Radiation doses outside the radiotherapy treatment field are of radiation protection interest. Available studies investigating such doses, focused on specific sites, standard target volumes, and a few radiation beams or treatment conditions. We present a software package designed to perform individual dosimetry in retrospective studies. It was developed for a European cohort study of over 4400 patients who were younger than 17 years when treated for a primary solid cancer in childhood at 8 French and UK cancer centres. The methodology adopted by this software enabled the anatomical data for all patients in the cohort who were between a few days to 16 years of age, to be taken into account. It includes the characteristics of all machines used to treat the patients from 1942 to 1992. The absorbed doses are estimated directly in volum% and the lung heterogeneity is considered. Based on actual measurements, all principal sources of scattered radiation, sources of doses to out-of-beam sites, are modelled and introduced. For each patient, absorbed doses to 151 anatomical sites were calculated, according to radiation beam energy with a range of energy from 50 kV to 31 MV for photons and 4 to 32 MeV for electrons. Such a tool can provide dose estimation sufficiently accurate for radiation protection purposes.

Introduction

A cohort study of 3-year survivors of a first cancer in childhood was initiated by our group to evaluate the long-term risk of a second malignant neoplasm [1]. It included 4400 patients treated for various solid cancers in 8 French and British centres, of whom 2827 underwent radiotherapy. This study required precise individual dose calculation, for which we have developed a software package, Dosimetry Electron_Gamma (Dos_EG), able to simulate all patients and treatments in the cohort. It enabled us to estimate the radiation doses delivered to a wide range of sites, permitting the construction of a useful database for radiation protection purposes and enhancing understanding of low dose-effects. In the present paper we describe briefly, the software Dos_EG, and a few examples of absorbed doses to a few sites estimated by this software.

Materials and Methods

Population

Patients included in this study were treated for various primary solid cancer (Ewing's sarcomas, osteosarcoma, soft tissue sarcoma, Wilm's tumour of the central nervous system, retinoblastoma, Hodgkin's disease, non Hodgkin's lymphoma, etc...) from 1946 to 1992, at 8 different centres, as described in [2,3]. Therefore the population includes a wide range of different anatomical data for both male and female patients aged between a few days to 16 years at the beginning of their radiotherapy.

Patient and treatment simulations

The individual dose calculation, required for this study was performed with a software package, Dos_EG, which was developed for retrospective studies at the IGR [4]. It includes two major algorithms. The first is devoted to generating an anatomy mathematically equivalent to each patient and computes the organ positions using auxological methods as described in [5]. The parameters required to construct this anatomy, are the sex and height or age of the patient at the time of treatment. The anatomy so generated is adapted to the patient using recorded anatomical information

about the patient, i.e.; lateral diameter of different sections of the body, ant-post thickness, and organ heights. This anatomy is a considerable improvement on the previous model described in [5], in that: (1) the individual phantom is articulated allowing thus for trunk inclination and back extension of the head as for mantle treatments, (2) the parameters used to adapt the generated phantom to the patient, increase to 12, allowing for better adaptation (3) it localises 151 anatomical sites using a Cartesian co-ordinate system against 64 in the previous method. Once the individual anatomy is constructed the treatment conditions are simulated using the recorded information, i.e; total dose delivered to the target volume, the number of fractions, the time from first to last fraction, the type of the treatment machine, type of radiation (photon, electron) and energy, source-skin distance, field size and shape, beam direction and wedges if any, and weighted dose from each beam. Dos_EG allows the input of the complex form of each field when shielding blocks are present.

The second algorithm is devoted to dose calculation inside and outside the beam up to 180 cm from the field edge. It takes into account all principal sources of radiation doses outside the treated volume, i.e; the actual leakage radiation from the collimator and the head of the treatment machines, and radiation scatter from the collimators, beam modifiers, walls and other obstacles. Radiation scattered inside the patient from the irradiated volumes, is also considered [6]. The penetrant bremsstrahlung radiation produced by high energy electron beams is taken into consideration both inside and outside of the useful beam. This algorithm represents a considerable improvement on the previous one developed at the IGR and described in [7]. Not only does it take into account a wide range of photon energies (50 kV to 31 MV), electron beams from 4 to 32 MeV and treatment machines (38 machines used in 8 treatment centres), but also lung heterogeneity, shielding block and wedge modifications, and all possible field shapes and sizes. The distance at which the dose could be estimated was extended from 50 cm to 180 cm from the central axis, permitting the calculation of doses to all sites of all patients from all treatments. In addition, Dos_EG, uses the measured spectrum emitted by the treatment machine in the estimation of the energy flux, for all beam energies from conventional orthovoltage tubes, Cobalt, Van der Graff, linear accelerators, and betatron equipment.

Results and discussion

The absorbed doses to 151 anatomical sites were estimated for every patient in the cohort using their appropriate treatment conditions, machine and energy. In Table I, we present an example of absorbed doses at selected sites, for a female patient who underwent 5 courses of radiotherapy for lymphoma between the ages of 5.5 and 12 years. According to our methodology, her actual anatomy at the time of each course of radiotherapy and the actual treatment conditions were all considered when doses were calculated. For the treatments with electron beams (16 and 8 MeV) from two different machines, all these sites received doses lower than 0.1mGy which are here, considered negligeable (N), but received very variable doses from the Cobalt and kV beams, reflecting the influence of the patients size, beam energy, and all treatment parameters.

For the whole population in this study, we represent the distribution of absorbed doses to the brain (figure 1) and to eye lenses (figure 2). These distributions showed that most of them have received very low doses (about 0.1 Gy) at both sites. The absorbed doses to the brain showed another peak around 20 Gy, but at 5 Gy to eye lenses.

In several examples, the estimated doses by our model showed good agreement with those measured at the IGR at several sites in an Alderson-Rando phantom.

To our knowledge, no study has supplied estimated organ dose distribution with a model fulfilling the requirements of epidemiological studies to such an extent as do Dos_EG, and may help to improve knowledge of low dose-effects for the radiation protection purposes. However several studies investigated doses to out-of beam sites, but they were either based on measurements in adult phantom, standard treatment conditions (e.g. uterine cervix), and specifique radiation beams (e.g. photon beams below 10 MV) and accessories (e.g.wedge and blocks), or focused on particular sites [8-12].

Table I. Absorbed doses (cGy) from 5 courses of radiotherapy received by a female patient between 5.5 and 12 years of age.

Treatment conditions	beam & energy	TV Dose* (cGy)	oesophagus (cGy)	stomach: upper-lower (cGy)	pancreas (cGy)	colon (cGu)	rectum (cGy)
chest AP/PA (28x23 & 28x18 cm) lung & humerus shields	Cobalt	2500	2446	1163-4056	934	28	22
upper chest-neck 2 opposed lat. (11.5x11.5 cm)	16 MeV Betatron	2500	N	N	N	N	N
lower neck, left lat. (10x10 cm)	250 kV	1050	6	2	2	1	1
neck left lat. (10x10 cm)	8 MeV linac	2500	N	N	N	N	N
head 2 opposed lat. (10x13 & 9x13 cm) facial shields	Cobalt	5200	15	24-16	7	3	3

* dose delivered to the target volume, N is negligible dose (below 0.1 mGy).

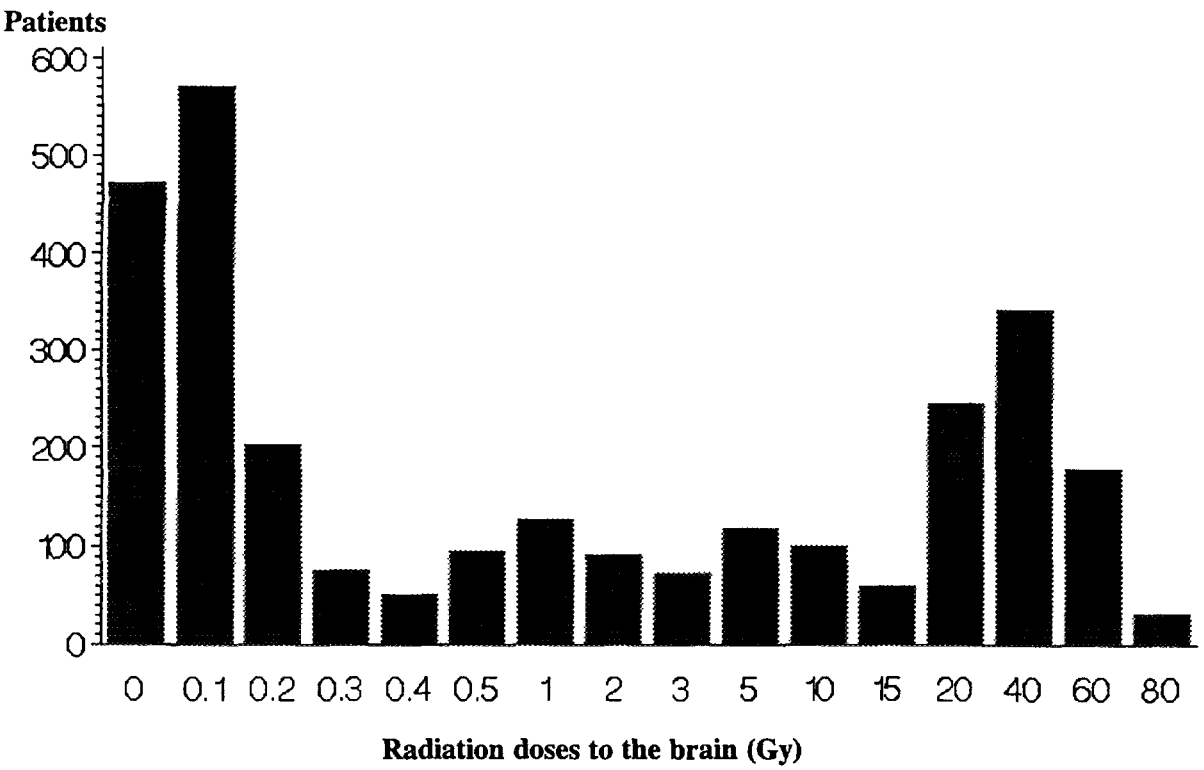

Figure 1. Distribution of absorbed doses to the brain from external radiotherapy.

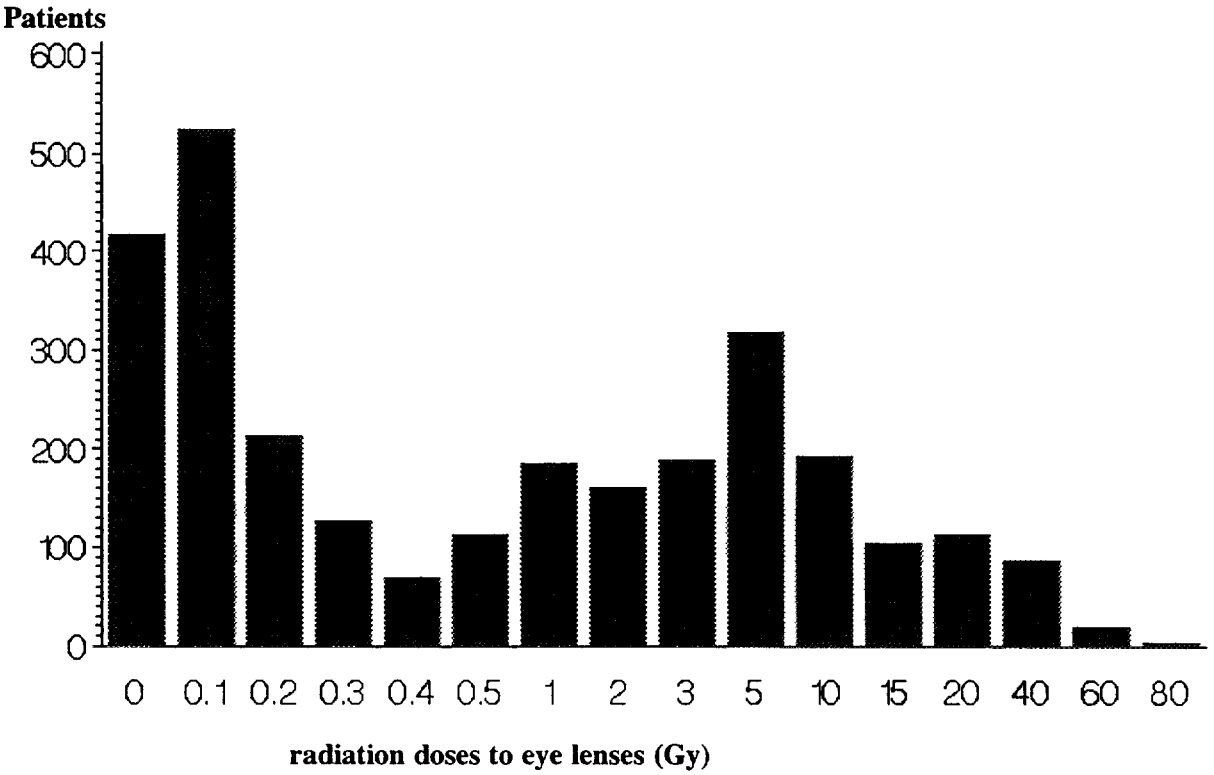

Figure 2. Distribution of absorbed doses to eye lenses from external radiotherapy.

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PROTRACTED RADIATION-INDUCED ALTERATIONS IN HEMATOPOIETIC REPAIR AND RECOVERY

T.M. SEED, T.E. FRITZ*
Armed Forces Radiobiology Research Institute
Bethesda, MD 20889 U.S.A.
Argonne National Laboratory*, Argonne, IL 60439 U.S.A.

Abstract

Pathologic predisposition of beagle dogs under chronic, low daily dose (7.5 cGy day^{-1}) whole-body gamma irradiation has been studied relative to molecular repair and hematopoietic competency. Molecular repair, assessed by a microscopy-based unscheduled DNA synthesis (UDS) response, was measured within proliferative and nonproliferative marrow myeloid elements of dogs with markedly different hematopoietic capacities (low capacity, aplasia-prone [AA^+] versus high capacity, myeloproliferative disease-prone [MPD^+]) under protracted radiation stress. Results indicated that protracted exposure elicited a net increase in UDS-repair capacity that was largely independent of exposure duration. This enhanced capacity resulted from the increased strength of the UDS signal together with an expanded number of positively responding cells. The combined response was strong in primitive blasts and weak in more differentiated myelocytic cells. The UDS repair response of the MPD^+ dogs was significantly greater than that of the AA^+ animals and was clearly modified relative to the controls. These results suggest that both resiliency and pathologic potential of the hematopoietic system under protracted radiation stress is, in part, associated with an augmentable DNA repair within the more primitive myeloid marrow elements.

1. INTRODUCTION

There is increased awareness concerning the relationship(s) between repair sufficiency and the potency of a given toxicant to cause pathology [1]. In a number of well documented genetic diseases of man (e.g., xeroderma pigmentosum, ataxia telangiectasia) insufficient repair capacity has been related clinically to a hypersensitivity to a variety of physical and chemical toxicants, as well as with predisposition to several significant pathologies, including cancer [2].

In the above mentioned pathologies, preexisting genetic/epigenetic lesions are clearly tied, and perhaps drive the noted changes in toxicant-directed repair capacity. This statement, however, begs the question as to the nature and meaning of toxicant-mediated repair responses within 'normal' individuals outwardly lacking signs of genetic/epigenetic-based disease. It appears that the normal individual's repair capacity, in terms of both magnitude and fidelity, can be differentially altered under varying parameters of toxicant exposure [3,4]. However, the late pathological consequences of this toxicant-elicited repair modifications are unclear and need to be clarified.

We have previously identified subgroups of experimental dogs having distinct predispositions to several types of radiation-induced pathologies [5], and related differences in the magnitude and plasticity of hematopoietic repair under chronic toxic stress [6].

In this study we have utilized UDS as a repair correlate in an attempt to monitor and quantitate repair capacity within essential bone marrow progenitors of individual animals subjected to protracted irradiation and prone to several major pathologies of interest.

2. METHODS

Young adult beagle dogs (17) were segregated into control (nonirradiated) groups (6) and test (chronically irradiated) groups (11). Test animals were given whole-body, ^{60}Co gamma irradiation, delivered in a near continuous mode at a daily dose rate of 7.5 cGy day^{-1} (22 hrs each day) for duration of life. Average times of testing (day zero = radiation initiated) for the various irradiated subgroups, along with age-matched controls were as follows: AA^+, 116 $\pm$ 4 days; preleukemic syndrome variant of AA (AA/PLS), 116 days; control #1, 112 $\pm$ 6 days; MPD^+, 1117 $\pm$ 184 days; nonMPD, 965 days; and control #2, 1098 $\pm$ 208 days. Control animals were comparably caged and handled, but maintained in a shielded anteroom during the course of the experiment. Exposures (and sham exposures) were started when the animals were approximately 400 days of age. Descriptions of animal husbandry, the radiation exposure facility, and dosimetric methods have been given in detail in previous publications [5,7].

Blood samples were taken on a periodic basis, with blood cell counts and differential counts determined by standard procedures. Marrow samples were collected and processed as previously indicated [5,8,9]. The measured endpoints included: blood cell counts and selected marrow functions; i.e., repair, assayed by a microscopy/autoradiographic UDS-based technique [8]. Nuclear grain counts ranging between 1-100 grains per nuclei were scored as UDS positive; nuclear grain counts above 100 were considered to S-phase; zero grains per nuclei were recorded as UDS negative [8].

3. RESULTS

3.1 Blood response patterns under protracted radiation exposure

Figures 1A-E illustrate differences in blood response patterns exhibited by the various irradiated subgroups relative to the nonirradiated control group. These differences were substantial. The aplastic anemia-prone (AA^+) subgroup, along with the AA/PLS variant, exhibited low hematopoietic capacity under protracted irradiation, as indicated by the progressive, ultimately fatal, pancytopenic condition following relatively short exposure (<300 days). The myeloproliferative disease-prone (MPD^+) subgroup, and the nonMPD variant, showed high hematopoietic capacity, as indicated by the resistance to acute anemia and by partial restoration of vital leukocytes and platelet blood levels.

3.2 Change in net UDS capacity of myeloid elements

Figures 2 A-D illustrate the change from normal in net UDS capacity of the marrow elements of dogs under protracted irradiation. All irradiated subgroups exhibited increased net UDS capacity at the level of the primitive marrow progenitors (marrow blasts), but not at the level of mature myeloid cells. Only in one subgroup, the AA/PLS variant, was the net UDS capacity of immature myeloid cells elevated relative to unirradiated controls (Fig 2B).

Distinct response patterns were evident for irradiated animals with different preclinical disease. The AA^+ subgroup (Fig 2A) showed the smallest overall gain in net UDS capacity; whereas the AA/PLS variant (Fig 2B) showed the greatest gain. MPD^+ and the nonMPD variant patterns (Fig 2 C&D) were characterized by substantial gains in net UDS capacity elicited under low UV-dose-induction; but smaller gains in capacity were noted at high dose. The nonMPD variant, in contrast to all other subgroups, exhibited the largest increase in net UDS capacity following low dose UV induction, and the lowest following high dose UV-induction (Fig 2D).

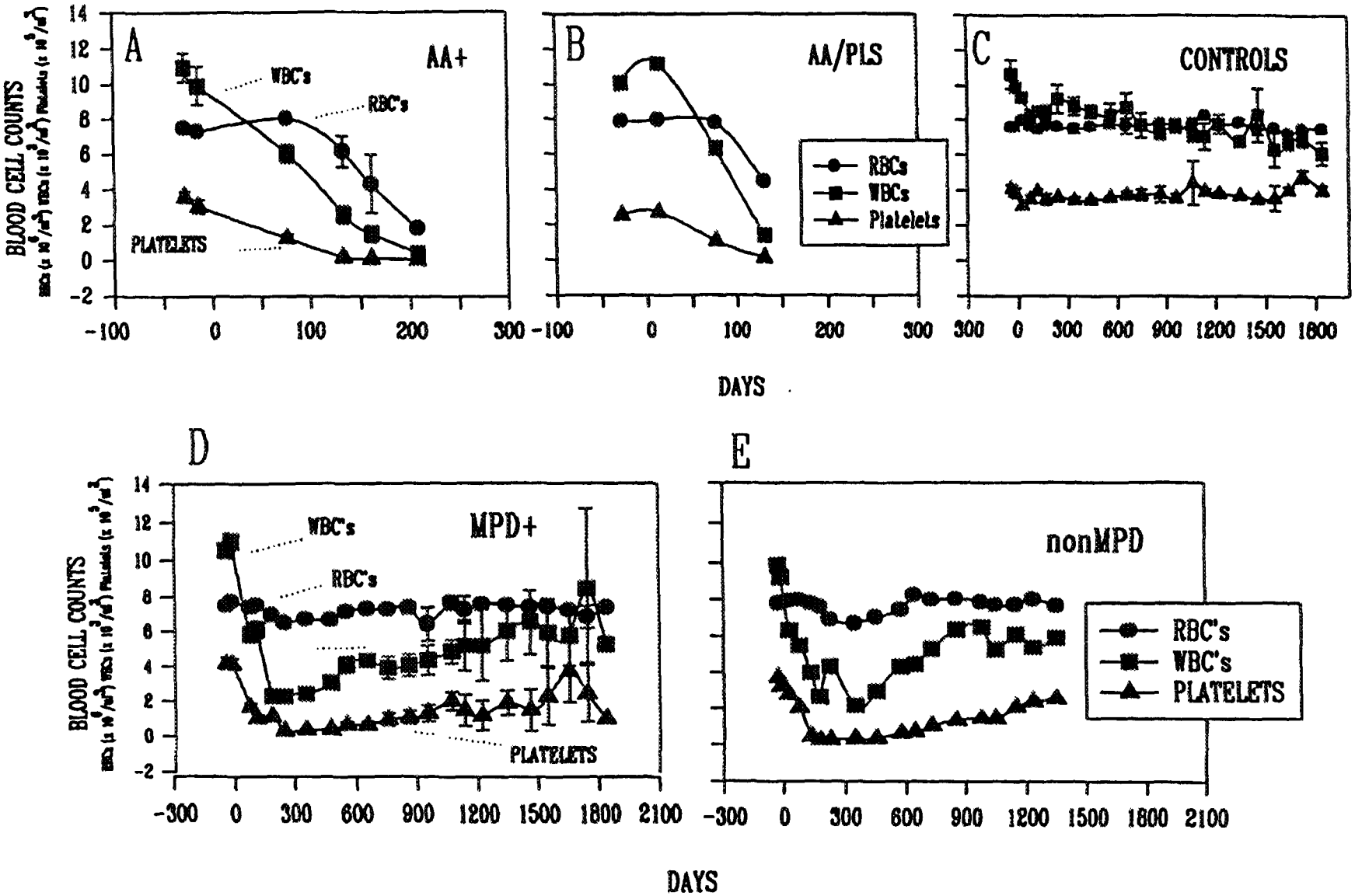

Fig 1. Blood responses of chronically irradiated dogs versus nonirradiated dogs: A) AA^+; B) AA/PLS; C) controls; D) MPD^+; and E) nonMPD.

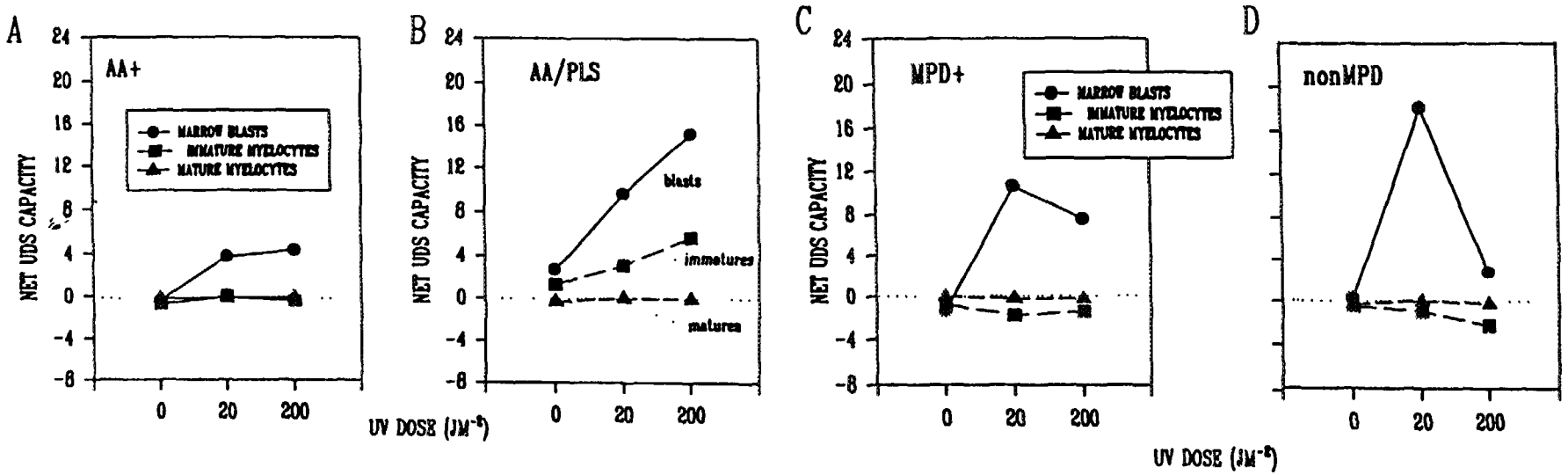

Fig 2. Net difference in UDS repair capacity between irradiated and nonirradiated subgroups: A) AA^+; B) AA/PLS; C) MPD^+; and D) nonMPD.

4. DISCUSSION

This study examined the change in hematopoietic repair as a function of protracted gamma irradiation and the preclinical state of evolving hematologic disease. Using net UDS response as a measure of repair, we surveyed several different subgroups of animals with marked differences in survival and hemopathologic tendencies under protracted chronic radiation exposure. Our results showed that the net UDS repair response changed both qualitatively and quantitatively as a consequence of both exposure and the type of developing pathology. The radiation- and pathology-associated changes in the UDS patterns noted in this study are consistent with previous work demonstrating marked differences between these irradiated subgroups when assessed for other hematopoietic repair correlates. The MPD^+ subgroup is in sharp contrast to the AA^+ subgroup in terms of repair proficiency of vital marrow progenitors, as manifested by the marked differences in proliferative capacity, radioresistance, split-dose recovery responses, and DNA repair [5,6,8,9]. Repair capacity, acquired under protracted irradiation, is linked temporally to the spontaneous hematopoietic recovery response exhibited by MPD^+ animals during the initial preclinical phase transition [13]. Both cellular repair and organ system recovery seem to be coordinately constrained by several radiological parameters, most notably by the time of exposure, cummulative radiation dose, and exposure rate [9]. Causal linkages between acquired cellular/molecular repair functions and overall hematopoietic recovery remain uncertain and need to be further developed. Our observations made here with the short lived preleukemic variant (AA/PLS) tend to argue against simple causal relationships between elevated UDS repair signals and hematopoietic recovery under protracted irradiation. The markedly elevated UDS repair signals expressed by this AA/PLS variant in the absence of an effective, sustained hematopoietic recovery response adds to the uncertainity of the causal role played by the UDS response in hematopoietic repair and its misrepair under protracted irradiation. Clearly additional work is needed to resolve these relationships.

With the assumption that the measured UDS response is a reasonable correlate of repair capacity within hematopoietic elements, it then follows that the major differences in UDS patterns exhibited by the various subgroups reflected major differences in the magnitude and inducibility of repair, and also in the resiliency related to both continued toxic insult and saturation.

5. CONCLUSIONS

Protracted gamma exposure elicited an enhanced UDS-repair response within the marrow of beagle dogs. The enhanced UDS repair is confined largely to marrow blasts. With the exception of the AA/PLS variant, the enhanced UDS response is virtually absent in both mature and immature myelocytic elements. The magnitude of the change noted in UDS repair appeared more related to the pathologic status of the subgroup, rather than to the duration of exposure. The resiliency of the hematopoietic system under protracted irradiation does, nevertheless, seem to be associated with distinct patterns of augmentable DNA repair within more primitive myeloid marrow elements.

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POPULATION-RELATED GENETIC ASPECTS OF THE LOW DOSES RADIOLOGICAL RISK AND MELANIN INFLUENCE ON GENETIC RADIOSENSITIVITY

Mosse I.B., Plotnikova S.I., Kostrova L.N., * Dubovic B.V., Subbot S.T., Maksymenia I.P.
Institute for Genetics and Cytology of the National Academy of Sciences, Minsk, Belarus
* Scientific Medical Radiological Centre, Russian Academy of Med. Sciences, Obninsk, Russia

Abstract

From the genetic point of view, radiation sensitivity is a quantitative character, and the distribution of individuals in the population with different radiation sensitivities is characterized by a binomial curve. Thus rise in irradiation dose firstly results in a very slow increase in the number of sensitive genotypes, and then in a sharp rise. Since quantitative characters are dependent on several polymeric genes, and their manifestation is strongly affected by external conditions, radiation sensitivity of the organism depends on many hereditary and environmental factors. One of them is the presence of melanin pigment in cells. In particular, we have shown that the introduction of exogenous melanin into the organisms of mice reduces (2-4 times) the frequency of mutations, induced not only by acute, but also by chronic irradiation. It was also established, that mutational load, accumulated in drosophila populations, irradiated within 125 generations, has been decreased under melanin influence almost to the control level. Antimutagenic action of melanin is also manifested on cultured human cells. So, it was shown by the example of melanin, that it's possible to increase the radiation resistance of individuals, and in the first place of the population highly sensitive fraction.

Introduction

The problem of radiological risk assessment is extremely complicated: several factors must be taken into account, one of which is different radiosensitivity of individuals belonging to populations of the same species. This population-related genetical aspect of radiosensitivity has been very poorly studied, and is practically not taken into consideration when carrying out radiological risk assessment. From the genetic point of view, radiation sensitivity is a quantitative character, and the distribution of individuals in the population with different radiation sensitivities is characterized by a binomial curve. In fact, 50% of individuals have mean radiation sensitivity ($x \pm 0.67\ \sigma$), while 95% of the population have radiation sensitivity within the range $x \pm 1..96\ \sigma$. Only 5% of individuals have extreme values of this character (2.5% are highly sensitive and 2.5% are highly resistant). This means, that the number of individuals sensitive to irradiation increases not proportionally to the radiation dose, but rather in accordance with a "bell-shaped" curve; moreover, rise in irradiation dose firstly results in a very slow increase in the number of sensitive genotypes, and then in a sharp rise.

The presence in the population of a small fraction of highly sensitive individuals obviously explains the contradictory data about the existence of a "threshold" in the biological action of radiation: if one analyses samples that are not very large, or uses methods that are not very sensitive, then the apparent "threshold" is observed at an irradiation dose, preceding the sharp increase in the number of sensitive individuals. Naturally, this dose is precisely the maximal tolerance dose, so one can take advantage of this principle to set standards for ionizing radiation action for man.

Hereditary differences between individuals for their radiosensitivity are due to the interaction between several pairs of polymeric genes responsible for a whole range of physiological and biochemical peculiarities of the organism. Differences between genotypes may be the following: contents in the cells of autoradioprotectors and autoantimutagens such as endogenic antioxidants and sulfur-containing radioprotectors which are present or get synthesized in the cells under the irradiation impact, rate of repair processes, etc.

Since quantitative characters manifestation is strongly affected by external conditions, radiation sensitivity of the organism depends on many environmental factors. The diet is important for the individual resistance: food rich in vitamins, microelements, adaptogens, etc. favours the increase in individual radioresistance [1]. Besides nutritional conditions, the level of radiosensitivity depends on physical activity, nervous and psychological state, hormonal balance, presence of non-genetical diseases, etc.

The genotype and environment influence on radiosensitivity may be clearly demonstrated with melanin pigment. It is well known that one of its functions consists in the protection of cells against ultraviolet radiation. It has been shown in several publications that high contents of endogenous melanin (particularly in the case of melanoma), as well as the addition of exogenous melanin promote the increase in the radioresistance of cells and organisms [2-4]. We have studied the influence of melanin on ionizing radiation genetic consequences; it has been demonstrated that melanin injections or feeding with this pigment result in the decrease by 2÷4 times of the frequency of radiation induced mutations in germ animal cells (drosophila, mice) and cultured human cells [5]. Besides melanin was shown to be able to reduce the mutation load accumulated in the populations as a result of the irradiation of many generations [6].

Methods

The influence of melanin isolated from animal hair on genetic effects of acute and chronic irradiation in mice and human lymphocytes has been studied. Mice males of 2.5 months and 22g weight were used. The starch gel or melanin suspension in it were injected into stomach every day with a special needle. Melanin was supplied in concentrations from 0.3 to 30 mg/kg. Mice were exposed to 1-3 Gy of γ-rays of Cs^{137} at the dose rate of 0.007Gy/h (chronic irradiation) and 420Gy/h (acute one). Animals were killed 2.5-3.0 months later when the exposure was stopped. This interval was necessary for repairing irradiated spermatogonia. The levels of reciprocal translocations in metaphase of spermatocytes were analysed cytologically.

Human cells were cultured according to a standard method. The culturing time was 52h at 37°C. Colchicin was injected 2 hours before cells fixation with ethyl alcohol and glacial acetic acid mixture. Blood was taken from practically healthy people of 25-45 years old in special medical hospital.

Melanin was added to culture media at G_1 and G_2 stages in the following concentrations: 0.1; 0.3; 1.0; 3.0; 10.0; 30.0 mg/l. Human cells were exposed to acute irradiation (0.5Gy of γ-rays) 40 min after melanin injection. The cytological test included dicentric-ring- and fragment- analysis.

Results

Investigations of melanin influence on spontaneous mutation level has demonstrated that melanin itself doesn't possess a mutagenic activity in all concentrations used, even being supplied for 30 days.

Melanin in all concentrations was shown to reduce effectively mutagenic action of acute γ-irradiation. The melanin influence on genetic effect of chronic irradiation was even more

effective The data presented in fig 1 show that the pigment in all concentration used greatly reduced the percentage of induced mutations at different doses of chronic irradiation.

It's very difficult to compare antimutagenic activity of melanin under acute and chronic irradiation because in the first case one injection of melanin has been used, but in the second case melanin has been injected many times (once a day for 10-20 days). Nevertheless it is possible to draw a conclusion that melanin is no less and even more effective under chronic irradiation than under acute one.

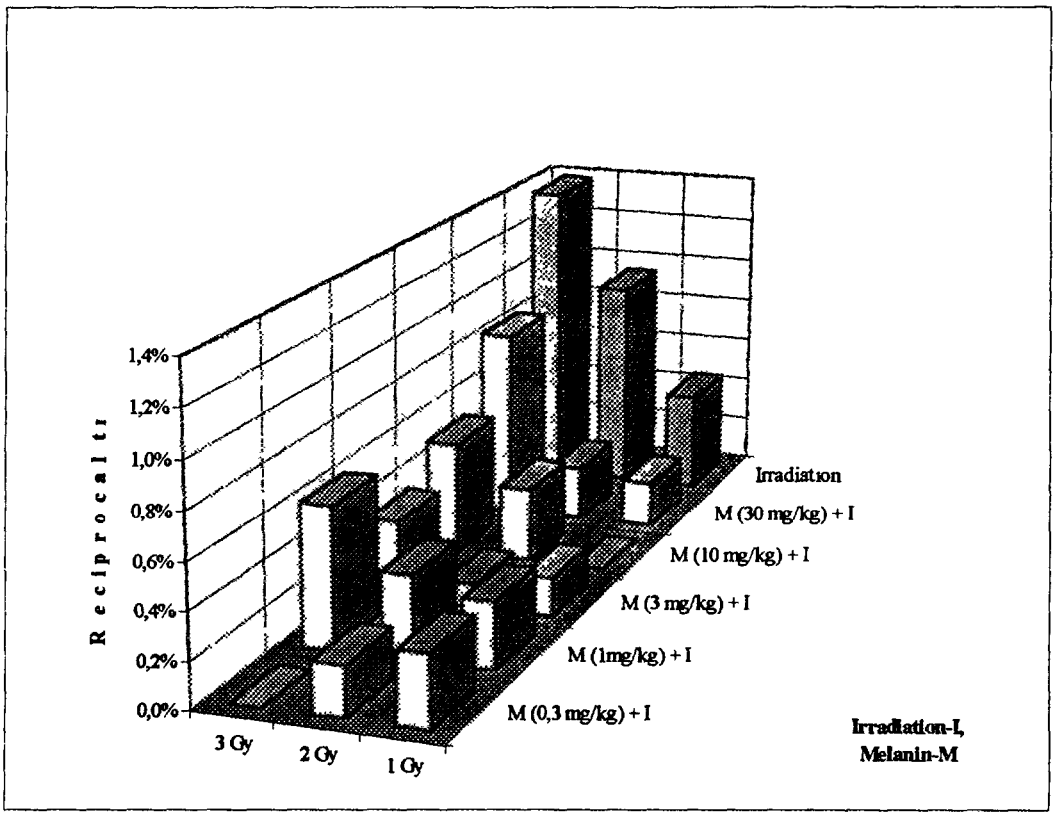

Figure 1. The melanin influence on chronic irradiation induced mutation frequency in mice germ cells.

The investigations of melanin action in human lymphocytes have shown, that melanin in all used concentrations (from 0.3 to 3 mg/l) was able to decrease the mutation level (fig. 2), but not so effectively as in mice. Strict concentration effect correlation was not observed either in human cells or in mice. There are some proofs that only small amount of melanin can penetrate into cells, and melanin quantity inside cells doesn't increase with rise in outside melanin concentration - this fact can explain absence of such correlation

Antimutagenic effect of melanin has been revealed to be the same under irradiation at G_2 stage as at G_1 one. These results demonstrate that melanin action doesn't depend (or little depends) on the repair system. The same conclusion was drawn earlier, when melanin had been investigated in drosophila and mice [5] Complete toxicological tests have been conducted.

Conclusions

According to our data the radiogenetic risk depends upon the melanin contents in the body Melanin is able to reduce genetic consequences of chronic irradiation and decrease mu-

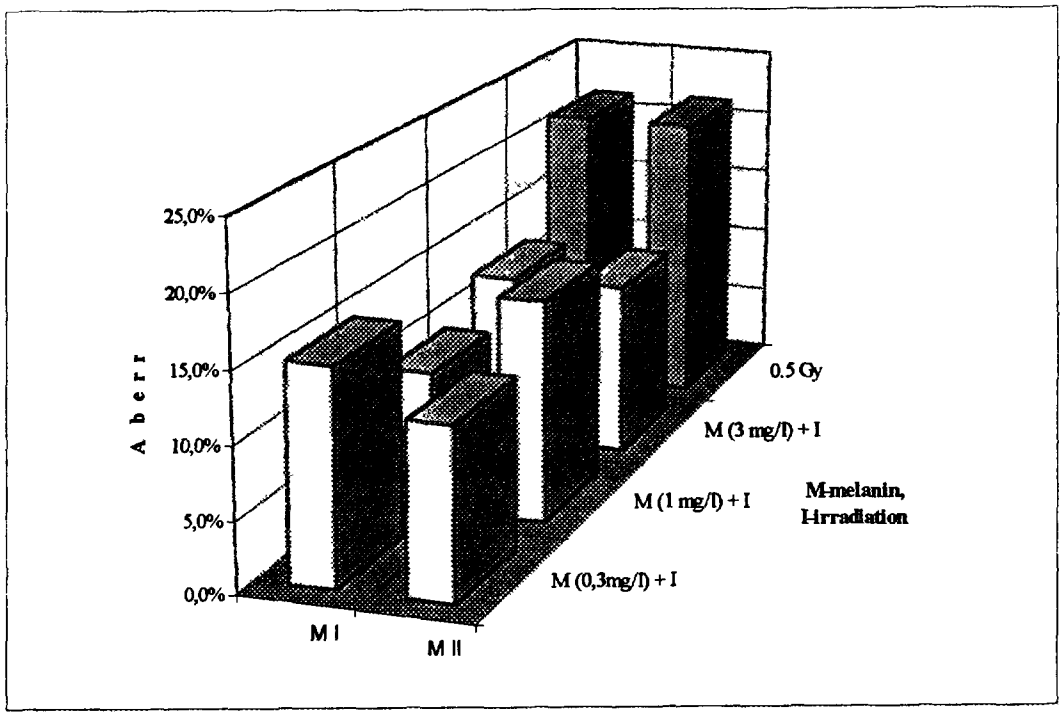

Figure 2. The influence of melanin on radiation induced mutation frequency in human lymphocytes

tational load, accumulated in populations, irradiated within many generations. So, melanin could be used in medicine for people protection against genetic consequences of irradiation.

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INTERRELACION ENTRE EL RESULTADO DEL CONTROL DOSIMETRICO INDIVIDUAL Y EL CONTROL REGLAMENTARIO EN CUBA

Díaz Bernal, E. D.; Jova Sed L. A.; Capote Ferrera E. y López Bejerano G. M.
Centro de Protección e Higiene de las Radiaciones, Calle 20 No. 4109, La Habana, Cuba

RESUMEN

El uso creciente de las diversas aplicaciones de las radiaciones ionizantes en Cuba determinó la necesidad de crear un sistema armónico de instalaciones que garantizará la seguridad radiológica de los trabajadores, el público y el medio ambiente. Así, se creó en 1985 el Centro de Protección e Higiene de las Radiaciones (CPHR). Posteriormente, en 1991, se creó el Centro Nacional de Seguridad Nuclear al que se asignaron las funciones de regulación y supervisión de la seguridad radiológica y nuclear. Desde 1987 se estableció de forma centralizada por el CPHR el control dosimétrico individual. La introducción de este servicio ha permitido al órgano regulador contar con una herramienta de control sobre la situación existente en las entidades registradas o licenciadas. En el trabajo se exponen los resultados del servicio en el período 1994-1996 y su comparación con años anteriores. Los resultados obtenidos reflejan que el sistema de supervisión en su conjunto ha garantizado en general, mantener bajos niveles de dosis. Los valores de dosis registrados demuestran la posibilidad real de establecer en el país como límite de dosis, un promedio anual de 20 mSv y nunca mayor de 50 mSv en un año, sin tener que realizar costosas inversiones y haciendo énfasis en las medidas organizativas.

1. INTRODUCCION

El uso creciente de las diversas aplicaciones de las radiaciones ionizantes en Cuba determinó la necesidad de crear en el país un sistema armónico de instalaciones que garantizara la seguridad radiológica de los trabajadores, el público y el medio ambiente. Así, con el Decreto Ley No.56 de mayo de 1982 para las Regulaciones del Uso Pacífico de la Energía Nuclear en Cuba [1] se otorgó a la Secretaria Ejecutiva para Asuntos Nucleares el carácter de Autoridad Nacional Competente (ANC) en materia de seguridad radiológica y nuclear. Con posteririodad, en el año 1994, estas funciones pasan al Ministerio de Ciencia Tecnología y Medio Ambiente.

En el año 1985 se crea el Centro de Protección e Higiene de las Radiaciones (CPHR), como centro técnico, rector de la protección radiológica; encargado de organizar el sistema de supervisión de la protección radiológica en el país. Posteriormente, en 1991, se crea el Centro Nacional de Seguridad Nuclear, al que se asignaron las funciones de regulación y supervisión de la seguridad radiológica y nuclear, quedando el CPHR como centro de apoyo científico-técnico al órgano regulador.

2. CONTROL REGLAMENTARIO

Desde su constitución, la ANC ha prestado especial atención a la elaboración de la base regulatoria en materia de protección radiológica. A partir de la promulgación en 1981 de las Reglas Básicas de Seguridad [2], se estableció por primera vez en Cuba una forma para la limitación de dosis a los trabajadores (50 mSv al año) y el público (1 mSv al año). Esta norma responde al principio de garantizar que toda exposición a las radiaciones ionizantes este justificada y que no se sobrepasen los límites básicos de exposición establecidos, así como disminuir la dosis de exposición hasta los niveles más bajos que se pueda razonablemente conseguir. Este documento se encuentra en un proceso de revisión, atendiendo a las recomendaciones de la Comisión Internacional de Protección Radiológica

[3], las Reglas Básicas de Seguridad para la Protección contra las Radiaciones Ionizantes y la Seguridad de las Fuentes de Radiación [4] y la experiencia nacional recopilada durante 15 años de trabajo.

Consciente de la necesidad de controlar el uso de las radiaciones ionizantes y con ello las dosis a la que pueden estar sometidos los trabajadores y el público, la ANC desde el inicio estableció un Sistema de Notificación, Registro y Licenciamiento para la autorización del empleo de las radiaciones ionizantes, el cual se ha ido perfeccionando y profundizando con la experiencia adquirida. Paralelamente se realizó un censo nacional para la determinación del universo de aplicaciones y fuentes radiactivas que se encontraban en el país. Estas medidas han permitido en primer lugar, tener un control de ubicación de todas las fuentes de radiaciones ionizantes desde su introducción al país y por otro lado las entidades usuarias de radiaciones ionizantes se han visto en la obligación de crear las condiciones constructivas, organizativas y de preparación del personal para garantizar la protección radiológica de los trabajadores, la población y el medio ambiente. En la actualidad la casi totalidad de las prácticas que se realizan en el país están autorizadas y reúnen los requisitos de protección radiológica.

Por otro lado, como este proceso tiene cerca de 15 años, la mayoría de las entidades han tenido que renovar su autorización al menos una vez, lo que ha permitido ir adecuando las condiciones de protección radiológica a las nuevas exigencias. A esto ha contribuido también la realización de inspecciones por parte de la ANC, las que se realizan teniendo en cuenta el riesgo que implica la práctica, así como las condiciones concretas de la entidad y la cultura de seguridad alcanzada. Otra medida importante que ha contribuido a la reducción de las dosis que reciben los trabajadores ocupacionalmente expuestos (TOE), ha sido la recogida centralizada y sistemática que se realiza por parte del CPHR de las fuentes radiactivas en desuso del país.

3. CONTROL DOSIMÉTRICO INDIVIDUAL

En el CPHR se han consolidado importantes servicios científicos-técnicos de seguridad radiológica en apoyo a la labor de la ANC; pero en primer lugar cabe mencionar el servicio de vigilancia radiológica individual, establecido centralizadamente en el país desde 1987, para todas las prácticas, con excepción del diagnóstico con rayos X. El servicio brindado incluyó el control de la exposición externa mediante el empleo de dosímetros fílmicos y el control de la contaminación interna por mediciones "in vivo" e "in vitro". La descripción de los aspectos técnicos y organizativos del servicio ejecutado ha sido abordado en [5, 6]. Es necesario señalar que en el caso de nuestro país, cuando las dosis evaluadas son menores que el nivel mínimo detectable (NMD), se registra una dosis igual al propio valor del NMD, lo que conlleva a un incremento de las dosis acumuladas. En el caso de dosímetros perdidos o cuyas evaluaciones sean imposible de obtener, la dosis registrada es igual a la dosis máxima recibida por el individuo durante los tres últimos períodos controlados.

4. RESULTADOS Y DISCUSIÓN

La introducción del servicio de vigilancia radiológica individual ha permitido al órgano regulador contar con una herramienta de control sobre la situación existente en las entidades registradas o licenciadas. Como se puede apreciar de la Tabla I, los valores de dosis efectivas medias anuales por esfera de aplicación en ninguno de los casos sobrepasan el valor de 2.1 mSv. La contribución de la dosis por contaminación interna a la dosis colectiva en las aplicaciones medicas no supera el 0.1%, siendo los valores de dosis individuales inferiores a 0.5 mSv. Las medidas tomadas por las entidades a exigencias del órgano regulador han permitido mantener bajas la dosis promedio por prácticas. En comparación con las dosis recibidas en otros países [7], se puede concluir que las de Cuba se encuentran en un rango aceptable.

Tabla I: Resultados del control dosimétrico individual por esfera de aplicación. Dosimetría externa y contaminación interna.

Esfera de Aplicación	Año	Número de TOE controlados	Dosis efectiva media [mSv]	Dosis Colectiva [Sv-h]	TOE con dosis superiores a 15 mSv	Dosis Colectiva, S(>15) [Sv-h]
Medicina	1994	357	1.48	0.53	1	0.02
	1995	300	2.07	0.62	2	0.04
	1996	327	1.96	0.64	6	0.13
Industria	1994	110	1.07	0.12	0	0
	1995	139	0.70	0.10	0	0
	1996	158	1.20	0.19	0	0
Investigación + Docencia	1994	115	0.71	0.08	0	0
	1995	127	1.12	0.14	0	0
	1996	174	1.32	0.23	1	0.05
Otros	1994	217	1.73	0.38	2	0.04
	1995	218	1.68	0.37	2	0.05
	1996	216	1.58	0.34	2	0.04

La dosis media total en el período 1987-1996 oscila entre 1.1 y 2.6 mSv (Tabla II). Por otra parte, la disminución brusca de la dosis media a partir del año 1991 con respecto a los anteriores muestra claramente el efecto que provocó la extensión del tiempo de utilización de las películas hasta 3 meses y la significación que tiene la asignación de un valor de NMD en los casos de dosis evaluadas inferiores a este valor. Así por ejemplo, durante un intercambio mensual un trabajador que recibiera una dosis evaluada por debajo del NMD en cada uno de los períodos de control podría acumular al año una dosis tres veces mayor que la que recibiría en las mismas condiciones de trabajo pero con un intercambio trimestral. Otro efecto de esta política de asignación de dosis es el aumento de las dosis individuales acumuladas.

Tabla II: Resultados del control dosimétrico individual de la exposición externa.

Años	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Número de TOE controlados	1263	1475	1714	1542	1459	1079	1002	820	770	857
Dosis efectiva media [mSv]	2.47	2.38	2.48	2.55	1.28	1.53	1.16	1.36	1.57	1.61
Dosis Colectiva [Sv-h]	3.11	3.51	4.25	3.93	1.86	1.66	1.16	1.12	1.21	1.38
TOE con dosis superiores a 15 mSv	2	2	9	11	4	8	6	3	4	9
Dosis colectiva , (S>15) [Sv-h]	0.03	0.03	0.17	0.29	0.09	0.20	0.12	0.06	0.08	0.21
Dosis máxima [mSv]	16.8	16.1	24.2	42.7	44.2	34.8	22.8	26.4	29.9	53.0

Solo un trabajador ha sobrepasado el límite permisible de dosis de 50 mSv establecido para un año. Los casos que sobrepasan los 15 mSv son reportados al Órgano Regulador, que ha establecido este valor como Nivel de Investigación y que exige una investigación del hecho, la elaboración de un informe y la toma de medidas para evitar su repetición. En cualquier caso, la dosis efectiva máxima registrada es de 53 mSv.

La frecuencia de casos de trabajadores con dosis anuales por encima de los 15 mSv (razón de la distribución del número de trabajadores, NR_{15}, [7]) oscila entre 2 y 11 trabajadores por año, cifras que

representan entre 0.2 y 1% del total del personal controlado. Por su parte, la fracción de la dosis colectiva para estos trabajadores (razón de la distribución de la dosis colectiva anual, SR_{15} , [7]) no es superior en ningún año a 0.1, valor que pudiera considerarse aceptable si tenemos en cuenta que la fracción por encima de 15 mSv en una distribución de referencia debería estar entre 0.05 y 0.5 [8].

Valorando los aspectos expuestos anteriormente, se puede afirmar en primer lugar, la posibilidad real de establecer como límite de dosis en el país, el valor de 20 mSv como promedio en 5 años, aunque nunca mayor de 50 mSv en un año, sin tener que realizar costosas inversiones. Por otra parte, la realización de inversiones costosas para reducir las dosis en las condiciones socioeconómicas del país no se justifican. Sin embargo, se pueden optimizar las dosis en algunas prácticas con medidas organizativas.

5. CONCLUSIONES

No se observaron en ninguna de las esferas de aplicación tendencias significativas de aumento en las dosis media en el período analizado. Los niveles de dosis se encuentran en un rango aceptable, en comparación con los niveles de dosis a nivel internacional. Hubo un decrecimiento en el nivel de la dosis media total a partir del año 1991, influenciado fundamentalmente por la extensión del período de control. La política de asignación de dosis aplicada actualmente aumenta los valores de dosis acumulada. Los bajos valores de dosis media evidencian que las condiciones y exigencias de Protección Radiológica existentes en nuestro país garantizan evitar dosis por exposición externa y/o incorporaciones de radionúclidos significativas. Para las aplicaciones de las radiaciones ionizantes analizadas se evidencia la factibilidad de pasar a un límite primario de dosis más restrictivo que el vigente actualmente de 50 mSv.

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Molecular Mechanism of Radioadaptive Response: A Cross-Adaptive Response for Enhanced Repair of DNA Damage in Adapted Cells

Takaji Ikushima
Biol. Div., Kyoto University of Education, Fushimi, Kyoto 612, Japan

Abstract

The radioadaptive response (RAR) has been attributed to the induction of a repair mechanism by low doses of ionizing radiation, but the molecular nature of the mechanism is not yet elucidated. We have characterize RAR in a series of experiments in cultured Chinese hamster V79 cells. A 4-h interval is required for the full expression of RAR, which decays with the progression of cell proliferation. Treatments with inhibitors of poly(ADP-ribose) polymerase, protein- or RNA synthesis, and protein kinase C suppress the RAR expression. The RAR cross-reacts on clastogenic lesions induced by other physical and chemical DNA-damaging agents. The presence of newly synthesised proteins has been detected during the expression period. Experiments performed using single-cell gel electrophoresis provided more direct evidence for a faster and enhanced DNA repair rate in adapted cells. Here, using single-cell gel electrophoresis, a cross-adaptive response has been demonstrated for enhaced repair of DNA damage induced by neocarzinostatin in radio-adapted cells.

1. Introduction

After cells are pre-exposed to very low-dose radiation, they become less sensitive to subsequent a high dose of radiation for induction of genetic damage. This phenomenon has been termed the radioadaptive response (RAR) [1]. Following the finding of RAR for chromatid aberrations in human lymphocytes [2], we have obseved RAR for the induction of micronuclei and sister-chromatid exchanges in cultured Chinese hamster V79 cells pre-exposed to very low-dose radiation [3]. Thereafter, the RAR has been characterized in a series of our experiments [1, 3, 4, 5]. The RAR can be caused by a narrow window of low doses (cGy level). A 4-h interval is required for the full expression of RAR, which decays rapidly with the progression of cell proliferation. The RAR expression is suppressed by treatments with inhibitors of poly(ADP-ribose) polymerase, protein- or RNA synthesis, and protein kinase C. The RAR cross-reacts on clastogenic lesions induced by other physical and chemical DNA-damaging agents. Proteins are newly synthesised concurrently with the development of the RAR. The similar characteristics have been noticed in human lymphocytes, too [e.g. 6].

These observations suggest that RAR may be attributed to the induction of novel, efficient repair mechanism for chromosomal DNA damage. To verify this hyposesis, we have analysised repair kinetics of DNA double-strnad breaks in adapted cells pre-exposed to low doses using single-cell gel electrophoresis, and provided evidence for a faster and enhanced DNA repair rate in adapted cells [7]. Here, we report the results of experiments performed to ascertain whether RAR cross-reacts for the repair of DNA damage induced by neocarzinostatin, a radiominetic chemical [8].

2. Materials and Methods

Chinese hamster V79 cells were maintained as monolayers in exponential growth by subculturing twice a week in alpha-modified Eagle MEM culture medium (Sigma) supplemented with 10% fetal bovine serum (Bio Whittaker), 20 mM HEPES, 100 U/ml penicillin and 100 μ g/ml streptomycin, at 37 °C in a humidified atomosphere of 95% air/5% CO_2.

The cells cultured to semi-confluence as a monolayer in a tissue culture flask were irradiated with ^{60}Co γ -rays at dose-rate of 5 cGy/min for adapting doses. After the adapting exposure to 5 cGy, the cells were allowed to express fully the adaptive response at 37 °C for further 4 h prior to the challenging treatments with 0.2 U/ml of neocarzinostatin (Kayaku, Japan) for 1 h. The repair kinetics of DNA strand breaks were monitored for 120 min after the neocarzinostatin challenge using single-cell gel electrophoresis. The single-cell gel electrophoresis was performed as described previously [7]. The elongated length of tails was used as semi-quantitative measure of DNA double-strand breaks.

3. Results and Discussion

The neutral gel electrophoresis was applied to the assay of double-strand breaks in chromosomal DNA. The mean length of the elongated comet's tails was increased with increasing concentration of neocarzinostatin, and in the assay immediately after the neocarzinostatin treatments, there was no significant differences in the initial yield of DNA double-strand breaks between non-adapted and adapted cells as shown in Fig. 1. The present data indicate that RAR does not enhance the cellular capacity to suppress the production of initial DNA damge by neocarzinostatin challenge.

To test whether RAR can be explained in terms of DNA repair, the repair kinetics was monitored over 120 min after 0.2 U/ml of neocarzinostatin challenge. As shown in Fig. 2, the rate of rejoining of DNA double-strand breaks induced by neocarzinostatin was higher in adapted cells by pre-exposure to 5 cGy than in non-adapted cells. The enhancement of repair rate was more remarkable in the early phase than the late phase of repair, and less damage remained in adapted cells than non-adapted cells. The results indicate that RAR caused by pre-exposure to low-dose radiation may cross-react on chromosomal DNA lesions produced by neocarzinostatin for enhanced DNA repair.

We have demonstrated that pre-exposure to low doses results in a faster and enhanced repair of DNA damage induced by a subsequent high dose of radiation. From the present results, it is inferred that pre-exposure to low-dose radaition may bring about a faster and enhanced repiar of DNA damage, at least double-strand breaks, induced by subsequent treatments with DNA damaging agents other than radiation as well. For the induction of cytogenetical damage, such a cross-adaptive responses have been reported in several combinations of adapting and challenging treatments [4, 9].

The RAR is effectively suppressed by 3-aminobenzamide, an inhibitor of poly(ADP-ribose) polymerase, which plays an important role in the rejoining of DNA strand breaks [1]. The RAR requires 4 to 6 h to express fully [5, 10], and this response accompanies de novo protein synthesis during this period [5, 11]. The development of RAR is also blocked by protein kinase C inhibitor [5]. These facts suggest a possible intracellular process of RAR that pre-exposure to low-dose radiation generates a signal of small amount of DNA damage, and the signal, through a signal transduction pathway mediated by protein kinase C, is sent back to the nucleus. This chain of events may trigger the activation of a set of genes encoding repair enzymes and/or factors leading to de novo protein synthesis, and enhance the repair capacity of

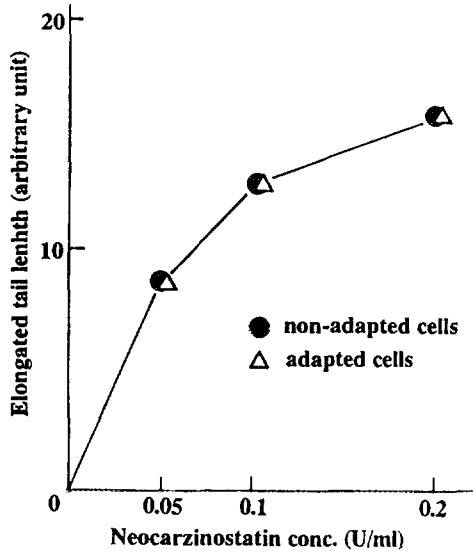

Fig. 1. Induction of DNA double-strand breaks by neocarzinostatin in adapted and non-adapted cells.

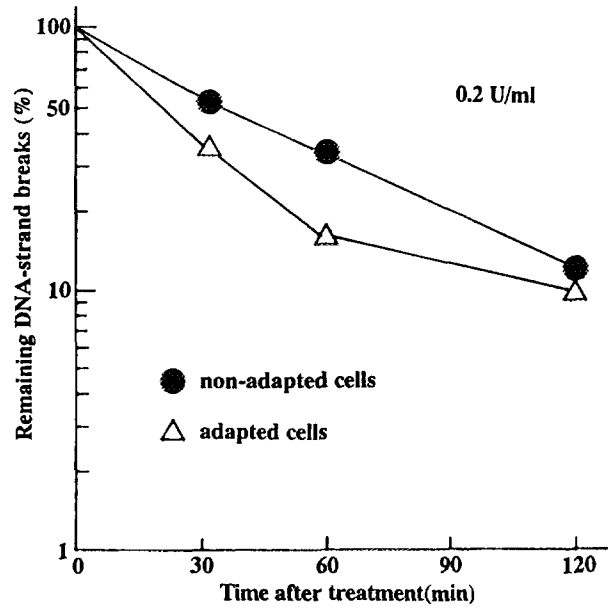

Fig. 2. Repair kinetics of DNA double-strand breaks induced by neocarzinostatin in adapted and non-adapted cells.

the serious DNA damage induced by a subsequent challenge by radiation or other mutagens as depicted in the previous papaer [7]. It is intresting whether Ku protein and DNA-PK are involved in this process [12]. This hypothsis is worthy to be explored further.

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EFFECT OF LOW DOSE RADIATION IN LYMPHOCYTES FROM CHILDREN EXPOSED TO IONIZING RADIATION AFTER THE CHERNOBYL ACCIDENT. CYTOGENETIC, CHROMOSOME PAINTING, GPA AND ADAPTIVE RESPONSE STUDIES

Padovani L , Appolloni M., Anzidei P., Spanò M , Stronati L., Testa A. and Mauro F

Environmental Department ENEA Casaccia, Rome, Italy

Abstract

The present study concerns the monitoring of some children coming from Byelorussian, Ukrainian and Russian republics, exposed to the fall-out, or to the initial acute dose of radiation with the aim of assessing the effects of ionizing radiation on human health and of verifying the persisting of chromosomal damage several years after the accident. Both structural chromosomes damage (conventional cytogenetic and chromosome painting) and molecular mutation (GPA) have been investigated, moreover the possible induction of an adaptive response has been tested.

INTRODUCTION

Several studies have demonstrated the occurrence of chromosomal aberrations in peripheral lymphocytes from individuals exposed to low doses of ionizing radiation. Following the explosion of the Chernobyl nuclear power station some studies reported an increased frequency of chromosome aberration, both for individuals exposed to a high acute dose and to a chronic low dose [1,2,3,4]
Since 1991 with the coordination of some humanitarian organizations more than 1000 children have been coming in Italy for a 1 month stay; they all underwent medical examinations and analyses, carried out in the laboratories of collaborating hospitals.
During the 1st week of some children stay, the internal contamination from ^{137}Cs and ^{134}Cs was measured by WBC (Whole Body Counter) and urine toxicological analyses in the laboratories of ENEA (National Agency for New Technology Energy and the Environment). Besides on 83 children, selected for their WBC values and the area of origin, conventional cytogenetic analyses have been performed
Other studies have been carried out on random subsets of subjects in order to reveal stable chromosome damage

- Chromosome painting by FISH, Fluorescence in Situ Hybridization, has been performed on 13 children in order to focus our attention on long term stable markers of exposure (reciprocal translocation), which are difficult to investigate with the conventional methods

- Mutations on the gene for glycophorin A (GPA) have been investigated by the flow cytometry approach GPA is expressed on the RBC membrane and occurs in two major allelic forms that define the M and N types of the MN blood group In a somatic cell a mutation affecting this gene remains remarkably stable even long time after the exposure to the mutagenic agent Thus we adopted this test for bio-monitoring the stable chromosome damage in a somatic cell line One variant cell type, the N/O variant has an hemizygous phenotype, such cells may arise by single base changes, deletion or inactivation of the GPA^M allele, or loss of the chromosome carrying the allele The variant N/N has not only lost the expression of GPA^M allele but also expresses the GPA^N allele twice the heterozygous level, these variant cells might be generated by chromosomal loss and duplication, gene conversion, or mitotic recombination in erytroid precursor cells

Several studies report that cells appear to become less susceptible to the induction of radiation damage if a challenge exposure to ionizing radiation is preceded by a low «adaptive» dose [5,6,7]. As contradictory results have been reported about the conditions under which the phenomenon can be evidenced, in our work we have analyzed 13 children subjected to a chronic low «adaptive dose» due to the intake of contaminated foods, to assess if the phenomenon really exists out of laboratory conditions.

MATERIAL AND METHODS

SUBJECTS

A total of 83 children, with age ranging between 8 and 12 years, and without evident signs of pathology due to radiation exposure, arrived in Italy during the last six years. Most of them were coming from areas exposed to the fall-out of the Chernobyl accident, while a small number of children was living near the power station during the explosion and had been exposed to the initial acute dose. 11 subjects came from an area (Smolensk) which is considered to be not contaminated, they showed internal contamination values quite normal (<70 Bq), so that we used them as control group.

CULTURE CONDITION

Blood sample were collected from all children at the time of the WBC analyses. Whole blood was cultured at 37 °C, 5% CO2 for 48 hrs, in RPMI 1640 medium (Flow), supplemented with 10% fetal calf serum (Gibco), 2% phytohoemoagglutinin (Murex) and penicillin-streptomycin. For each subject, three different cultures were set up for independent cytogenetic scoring. Metaphases were obtained according to standard procedures.

CYTOGENETIC

The slides were coded and blindly analyzed by three different observers, for most of the subjects a total of 600 metaphases were scored (a total of 52,217 metaphases have been scored) and the frequency of chromosome aberrations typically induced by ionizing radiation (dicentrics, acentrics, fragments and rings) was evaluated.

CHROMOSOME PAINTING

On 13 subjects (4 contaminated, 6 subjected to a single acute dose and 3 controls) chromosome painting was achieved, DNA probes specific for whole human chromosomes 2, 3 and 4 (Cambio) were used. Bound probes were detected with avidin-FITC and biotinylated goat anti-avidin antibody (Vector).

When possible 900 painted metaphases per subject were analyzed by different observers.

The total genomic translocation frequency per cell (FG) can be calculated from the frequency of translocations per cell detected by chromosome painting (FP) according to the equation:

$$FP = 2.05\ fp(1 - fp)\ FG$$

where fp is the fraction of human genome investigated (fp = 0.22)

GPA

After blood collecting 33 MN sample were typed using the Ortho Diagnostic Systems (Raritan, NJ, USA) blood grouping reagent kit (rabbit anti-M and anti-N) according to the manufacturer protocol. Fixation was carried out overnight at room temperature in PBS solution containing 3.4% formaldehyde and 8.4 μg/ml SDS, successively cells were stored in GPA staining mixture. Monoclonal antibodies anti-GPA(M) 6A7-PE and anti-GPA(N) BRIC-FITC were added and incubated for 1 hr. The day after samples were processed with Facstar Research Plus flow cytometer using standard band-pass filter for FITC and PE fluorescence. As far as the FCM GPA A analysis is concerned, we have analyzed 21 subjects (17 contaminated and 4 controls) and 5 million events were accumulated per each sample at a rate of about 2,000 cells/sec.

ADAPTIVE RESPONSE

13 children with internal contamination ranging from 664 to 26617 Bq were investigated to assess if the chronic exposure they have been subjected to, after Chernobyl accident, could induce a major cell

resistance to a subsequent acute high dose. Each sample was treated with a challenge dose of 1.5 Gy of gamma rays (dose rate 0.10 Gy/min) 48 hours after PHA stimulation and incubated for other 6 hours; furthermore a parallel cell culture, soon after the exposure, was treated with 3AB (3-aminobenzamide, 2mM), an inhibitor of the poly(ADP-ribose)polymerase function affecting mammalian cell radiosensitivity during the last stage of chromosome repair.
The same protocol was utilized in the lymphocytes cultures (4 subjects) of the control group. For the evaluation of chromosome damage, chromosome and chromatid aberrations were scored.

STATISTICS
Data of each type of study we carried out have been analyzed by the one tailed t-student probability test.

RESULTS

CONVENTIONAL CYTOGENETIC
Results obtained by the conventional cytogenetic and the WBC measures are given in table 1.
As a general trend, data show that contaminated and impacted children exhibit higher frequencies of chromosomal aberrations than the control group. Statistic reveals a significant difference for the total chromosomal aberrations between the control and the contaminated children ($p<0.05$). While no significant difference has been found for the impacted group.

Table I - Conventional cytogenetic results

Group	Number of subjects	Number of metaphases	Aberration/100 cells			
			Ace	Dic	Trl	Total
Contaminated (WBC<100)	41	22,463	0.37	0.08	0.12	0.57*
Impacted (WBC 400-32,343)	31	23,864	0.02	0.03	0.04	0.28
Control (WBC <70)	11	6301	0,22	0,04	0,06	0,33

Ace: acentric fragments; Dic: dicentrics; Trl: translocations
*One tailed t-student probability test : statistically significant ($p<0,05$) compared to control group.

CHROMOSOME PAINTING
Chromosome painting results are shown in table 2. It is evident that most of the subjects shows a high yield of translocations.
Because of the small number of samples we analyzed, it was not possible to perform a reliable statistic test. So, in this pilot study, as far as the FISH is concerned the aim is to point out the advantage of chromosome painting analyses when stable markers of radiation damage have to be investigated long time after the exposure.

Table II - Chromosome painting and cytogenetic results

Groups	Conventional cytogenetic			Chromosome painting		
	Cells scored	Trl/1000cells	Trl/cell	Cells scored	Trl/1000 cells	Fg
Contaminated	2,300	1.08	0.0018	4,087	0.92	0.0035
Impacted	3,244	1.36	0.0013	5,293	1.96	0.0056
Control	1,850	0.5	0.0005	2,921	0.59	0.0023

Trl: translocation
Fg: genomic frequency of translocation/cell calculated as in Materials and Methods section

GPA
The results of the FCM GPA A assay are given in table 3, no statistically significant differences have been found between the contaminated and the Smolensk control group.

Table III - Glycophorin A			
	N/O frequency	N/N frequency	Total variant cell frequency
Exposed	3.38 ± 3.31	8.52 ± 5.42	8.52 ± 5.41
Control	3.74 ± 2.68	3.06 ± 2,22	6.81 ± 4.39

ADAPTIVE RESPONSE

Data are shown in table 4, the results show that in the present instance no statistically significant effect of the Chernobyl accident on these end-points can be demonstrated.

The challenge treatment with gamma-rays does not yield a statistically significant difference between control and contaminated children. The trend of the data is in the direction of a higher in vitro radiation effect for the samples from contaminated individuals. Similarly, 3AB does not affect the radiation response.

Table IV - Adaptive response					
treatment	Cell scored	% Damaged Cell	%Chromosome aberrations	% Chromatid aberrations	% Total
Controls: 4 subjects, ground contamination 0,(WBC<40 Bq)					
None	800	1	0	1.7	1.7
γ-Rays	400	21.5	0.5	23	23.5
3AB	400	1.7	0.3	1.7	2.0
γ-Rays + 3AB	400	21.7	0.3	26.2	26.5
Contaminated subjects: 13 individuals, 12-30 Ci/Km^2 (4.4-11.1x10^{11} Bq/Kme2) (WBC range: 664-26617)					
None	2600	3	0.3	3	3.3
γ-Rays	1300	27.5	1.2	31	32.2
3AB	1300	4.5	0.6	4.3	4.9
γ-Rays + 3AB	1300	27	0.8	32.7	33.5

DISCUSSION

CONVENTIONAL CYTOGENETIC

Our data show a very low frequency of chromosome rearrangements related to a damage continuously inflicted by ionizing radiation and a relatively elevated frequency of acentric fragments compared to dicentrics and translocations. Acentric fragments are known to be induced by ionizing radiation but they should not be persistent aberrations, however some studies indicate that more acentrics than dicentrics are induced at very low dose range [4]; furthermore a longer half time of disappearance of lymphocytes containing acentric fragments in excess that lymphocytes with dicentrics and centric rings has also been reported [8]; our study is in line with previous report and confirm that the frequency of acentric fragments could be related with the continuous exposure to very low doses.

Even if the frequency of aberrations is very low, the cytogenetic picture is not back to normal, and this abnormal situation is clearly related to the effects of the Chernobyl accident.

Not clear relation has been revealed between the WBC evaluated internal contamination and the frequency of radio induced aberrations. This is not surprising considering that it is not possible to evaluate the pattern of the internal contamination value for the elapsed time from the accident.

Moreover deserve specific comments that our data show an elevated abnormal frequency of aberrations in unexposed Russian subjects used as control, this is not easy to explain and suggest further investigations.

CHROMOSOME PAINTING

Even if the number of the subjects studied is to small to see a statistical difference the data indicate an increased translocation frequency in both contaminated and impacted groups compared to the controls. Our study confirms the advantage of chromosome painting analysis but it should be noted that because the number of translocation for the whole genome is deduced from the number of observed translocations detected with chromosome-specific probes, the reliability of extrapolated results is low when translocations are not found.

GPA

The GPA A test results do not evidence statistically significant differences, indicating that within the limits of the assay the total accumulated radiation dose has not produced a relevant number of mutated cells in the bone marrow. The variant cell frequency is remarkably within the range of values reported in literature for control groups even though this is the only group with such a young average age.

ADAPTIVE RESPONSE

The result of the present work show that an effect, , on circulating lymphocytes, that could be described as an adaptive response cannot be observed in children exposed to very small doses of ionizing radiation (using as end point chromosome and chromatid aberrations). Our observation is not in agreement as far as ionizing radiation is concerned , with previous studies carried out on sample pre-exposed in vivo and challenge with in vitro treatment [9,10,11], however it must be pointed out that the exposure modality and the end-points investigated were different. Furthermore some in vitro studies [6] report that the adaptive response cannot be induced in the G_0 phase of the cell cycle, while, in vivo, the exposure of the most of the circulating lymphocytes take place just in the G_0 phase.
More generally, the detection and even the occurrence of the adaptive response appear to depend upon a variety of factors such as the radiation, the condition, the end-points, the cell cycle phase, the dose and the dose rate etc.

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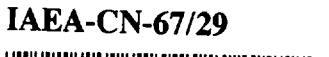

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THYROID TUMOURS FOLLOWING FRACTIONATED IRRADIATION IN CHILDHOOD

F. DE VATHAIRE, E. GRIMAUD, I. DIALLO, A. SHAMSALDIN
Institut Gustave Roussy,
Villejuif, France

Abstract

Results of a cohort study designed to evaluate the long term risk of thyroid tumours after fractionated high doses of external beam radiotherapy received by the thyroid are reported. In this cohort study, doses have been estimated for each child.

INTRODUCTION

Thyroid tissue is one of the more radiosensitive organs of the human body *(1)*. After irradiation, the excess of relative risk (ERR) of thyroid tumour per dose unit decreases with increasing age at time of irradiation *(1,2)*. During the first decades, following a dose of 1 Gy delivered during childhood in one or a very few number of fractions, both the risk of differentiated carcinoma and that of adenoma was found to range between 5 and 10 *(2-4)*. After 20 years following the irradiation, the ERR decreases with time since irradiation *(2,3,5)*. At the opposite, the absolute excess of risk (AER) increases during at least 40 years *(2,3,5)* following irradiation. The dose-response relationship is essentially linear for dose up to a few Gy *(2,4)*. Very few studies have been published concerning thyroid tumours occurring among patients who received external radiotherapy for a cancer in childhood *(6,7)*, although they constitute one of the population at higher risk of thyroid cancer in western countries. In the absence of available cohort of children who received high dose radio-iodine *(6)*, the study of thyroid tumour after first cancer in childhood is the only way to improve the epidemiological knowledge about thyroid tumours occurrence after high radiation dose to thyroid in childhood. As Chernobyl disaster showed, such a knowledge could be an important issue in radioprotection *(8)*. We report here the results of a cohort study designed to evaluate the long term risk of thyroid tumours after fractionated high doses of external beam radiotherapy received by the thyroid. In this cohort study, doses to have been estimated for each child.

PATIENTS

A retrospective cohort of 4096, of which 2827 received external beam radiotherapy, children treated in 8 centres in France and in the UK was established comprising patients who were alive 3 years after the first cancer, diagnosed before the age of 15 and before 1986. The diagnoses of first and second thyroid tumours were confirmed by histology. Only clinical thyroid tumour that needed surgery were taken into account.

RADIATION DOSIMETRY

For each of the 2827 patients who received radiotherapy, the radiation doses were estimated at the middle of the 2 lobes and at the isthmus of the thyroid. A computer program called "Dos_EG" has been developed for these calculations *(9)*. The mean radiation thyroid dose received by the 2827 patients who received external radiotherapy was 7.0 Gy (range : <0.001 to 75).

STATISTICAL METHODS

In the absence of available reference rate, we analyse thyroid adenoma incidence using patients who did not received radiotherapy as the reference category.

Both the Standardised Incidence Ratio (SIR) of thyroid cancer and the Relative Risk (RR) of thyroid adenoma was modelled assuming that the number of thyroid cancers followed a Poisson

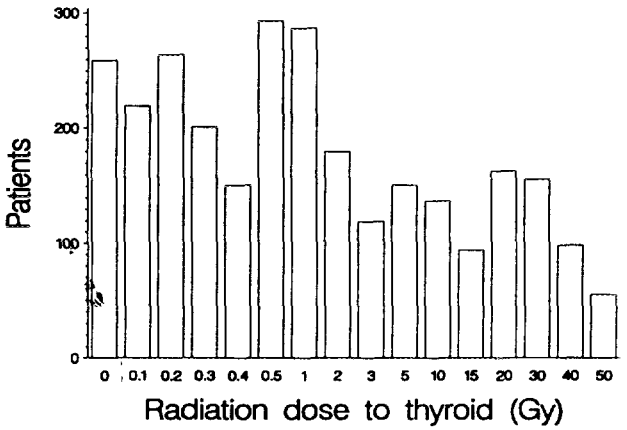

Figure : Radiation dose thyroid in a cohort of 2827
children treated by external radiotherapy for a cancer in childhood

distribution. Statistical tests were performed by comparing the deviance of nested models *(11)*. We modelled the variation of the thyroid tumour risk with time since irradiation, as a power function of the time since irradiation, as done by previous authors *(5)*.

RESULTS

From 3 to 29 years after 1st cancer, 58 patients developed a clinical thyroid tumour, which needed surgery, 44 adenomas and 14 differentiated carcinomas. All these patients but one had received radiotherapy. The cumulative incidence of differentiated thyroid carcinoma 30 years after radiotherapy was 1.5%, with a standard deviation (sd) equal to 0.5%, and that of thyroid adenoma was 5.4% (sd=1.1%).

Overall, the 2827 patients who received radiotherapy had a 88-fold higher risk (95%CI : 50-143) of developing a thyroid carcinoma than expected from the general population.

No thyroid cancer and only one thyroid adenoma occurred between 3 and 5 years after Rx. The temporal pattern of occurrence of adenomas was similar to that of carcinomas (table I). No significant decrease of the excess of SIR of c per Gy nor in the annual incidence of thyroid adenoma par Gy was shown.

The In our cohort, radiation dose to thyroid increased with age at radiotherapy, because of the increasing proportion of CNS and Hodgkin's disease as a first cancer, with increasing age. Both the excess of SIR of thyroid cancer per Gy and the annual incidence of adenoma per Gy strongly decreased with age at radiotherapy (table II).

No decrease of thyroid tumour risk for doses higher than 10 Gy was shown (table III). According to the adjustments, the SIR of thyroid carcinoma and the Relative risk of thyroid adenoma was found to range between 5 and 10 for 1 Gy. As compared to a purely linear model, the addition of a negative exponential term for cell killing due to high doses to thyroid improves the fit of the model (χ^2 = 4.3, df=1, p=0.04 for the carcinoma, and χ^2 = 4.8, df=1, p=0.03 for the adenomas). No modification of effect of the total dose to thyroid according to the number of fractions was found.

DISCUSSION

Based on a cohort of 2827 3-year survivors of a cancer in childhood who received fractionated external radiotherapy (mean number of fractions = 27) leading to a very large range in the dose to thyroid (from 0.05 to 50 Gy), we found the dose-response relationship between the dose to thyroid and the risk of thyroid tumour (adenoma and carcinoma) was linear up to a few Gy. Our estimation of the relative risk of thyroid cancer for a dose of 1 Gy (5 to 10 according to the adjustments) was similar to that observed after irradiation in one or a few number of fractions *(1-4)*. For higher doses, the risk increased, but slower.

Table I - Thyroid tumours occurrence according to time since radiotherapy in a cohort of 2827 patients which received external radiotherapy during childhood.

Years after Rt	Patients still followed	Differentiated thyroid carcinomas				Thyroid adenomas	
		n	Annual incidence x 10^5	Annual excess* of incidence x 10^5	SIR*	n	Annual incidence x 10^5
3-9	2827	2	12	11	55	3	17
10-14	2001	3	36	36	80	15	181
15-19		6	120	119	179	15	229
≥ 20	746	3	63	61	56	10	206
≥ 3	2827	14	39	39	88	43	121

** as compared to general population*
Rt : Radiotherapy
SIR : Standardised Incidence Ratio

Table II - Thyroid tumours according to age at radiotherapy in a cohort of 2827 patients which received external radiotherapy during childhood.

Age at Rt in years	Patients	Differentiated thyroid carcinomas				Thyroid adenomas	
		n	Annual incidence x 10^5	Annual excess* of incidence x 10^5	SIR*	n	Annual incidence x 10^5
0-1	642	4	42	42	159	13	137
2-4	673	3	34	34	92	13	149
5-9	781	3	33	33	77	12	132
≥ 10	731	4	49	49	69	5	63

SIR : Standardized Incidence Ratio
* as compared to general population

Table III - Thyroid tumours according to the radiation dose to thyroid in a cohort of 2827 patients which received external radiotherapy during childhood.

	Dose to thyroid (Gy)					
	No Ct	< 0.24	0.25 to 0.99	1 to 9.9	10 to 29	>= 30
N subjects	1269	743	773	680	411	216
Rx dose to thyroid (Gy)	0	0.11	0.52	3.5	19	40
Adenomas	1	2	5	13	13	10
RR*	1+	2.2	4.7	20	54	94
Carcinomas	0	1	3	5	3	2
SIR	-	11	63	129	151	169
Adjusted SIR *	-	1+	4.0	11	11	23

a : Excluding the first 3 years of follow-up.
** stratified for first cancer type, age at 1st trt, sex, country and follow-up*
+ reference category

Although our study deal with a relatively low number of irradiated patients (2827), the range of the doses available for investigation of dose-response relationship was very large : 20% of patients received less than 0.2 Gy and the 10% higher received more than 26 Gy. No other published study deals with such a range of radiation dose to thyroid. The only other study concerning thyroid tumours after radiotherapy for a 1st cancer, a case-control study in which the lowest dose received by a case of thyroid cancer was 1 Gy, was enable to investigate the shape of the dose-response relationship for doses lower than 2 Gy *(7)*. In the three other large studies concerning thyroid tumours after irradiation in childhood, the problem was inverse, i.e. it was difficult to investigate the shape of dose-response relationship for doses higher than a few Grays : amongst the 2650 children irradiated for thymus enlargement in USA, only 55 children had received more than 5 Gy *(4)*. In the same way, the highest dose received to thyroid by any of the 10834 children in the Israeli study on tinea capitis was 0.5 Gy *(10)*. Only very few of the 14351 infants who received radiotherapy for skin hemangioma in the Swedish study had received more than 5 Gy to thyroid *(3)*

We found a increase of the risk by a factor 3.8 for children aged under 2 years of age at time of irradiation as compared to those more than 5 years. This role of age is also in agreement with the findings of all the other studies on thyroid irradiation effects *(7)*.

We were not able to find a significant quadratic term in the dose-response relationship between dose to thyroid and the ERR of thyroid adenoma. This result agrees with that of Ron *(4)*, but not with those of Shore who has found a significantly supra linear dose-response relationship for adenomas *(3)*. All the studies on thyroid carcinomas after irradiation in childhood, also failed to show evidence of a significant non linear term *(7)*.

Despite the large range of number of fractions per patient (2 to 97) in our study, we failed to demonstrate a clear effect of the dose fractionation.

CONCLUSION

The pattern of the risk for thyroid cancer after fractionated external radiotherapy for a cancer in childhood was found to be similar to that observed by other authors after irradiation delivered during one or a few fractions. This failed to show any evidence for reduction of the risk of thyroid tumour with the fractionation of the dose.

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ROLE OF THE REGULATORY BODY IN CONTROLLING RADIATION DOSES AT NUCLEAR MEDICINE CENTERS IN EGYPT

M. SALAMA*, A. HELMY
National Centre for Nuclear Safety and Radiation Control,
Atomic Energy Authority,
Cairo, Egypt

Abstract :
The motivation of the present paper under taken to discuss was the safety regulation aspects of diagnostic and therapeutic uses of unsealed radioactive material in Egypt. The regulatory matters adupted by the National Centre for Nuclear Safety and radiation Control (NCNSRC) in controlling the radiation doses at nuclear medicine centers in were presented the basic elements of the national regulatory program are highlighted .

1- Introduction :

The use of unsealed or dispersible radioactive substances which are administered to human subject for diagnosis, treatment or research are widespread throughout Egypt .Egypt has a population density of about 60 millions about 40 medical centers equipped with gamma cameras used for diagnostic tests on patients and about 100 laboratories use radio pharma ceuticals for invitro tests mode for the purpose of clinical diagnosis , for biological and biochemical studies . Moreover radioactive materials are used also to test and calibrate the equipment used in these facilities .

The standard of radiation protection adopted in the country by the national center for nuclear safety and radiation control (NCNSRC) is based mainly on the international basic safety standards for protection against ionizing radiation and for the safety of radiation sources (safety Series No 115) .

The fundamental principles of radiation protection adopted in the country were :

- Justification of practices
- Optimization of protection and safety
- Compliance with dose limits

In this paper we are going to discuss, how these principles are going to be implemented by the (NCNSRC).

2- Responsibilities :

Protection of the workers and the public and safety for the dourness are the responsibility of the registrant or licensee who are obliged to set up and implement the technical and organizational measures needed .

Any modifications to any practice or source for which the registrant and licensee are authorized should be notified to the "NCNSRC" .

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* Regulations of Nuclear Emergency Division, National Centre for Nuclear Safety and Radiation Control, P.O. Box 7551 rth Sector Nasr City 11762 Cairo, Egypt.

The role of the NCNSRC regulatory program in controlling radiation doses consists of four basic elements :

- Regulations
- Licensing , Registration, Notification
- Inspection
- Training

2.1 Regulations :

These regulations are considered the milestone of the Egyptian regulatory program which define the basic requirements that must be followed by users, registrants and licensees, as well as the measures and the resources needed to achieve the protection and the safety objectives .

They define such matters as :

- Principles of the optimization of protection
- Compliance with dose limits
- Classification of working areas
- Categorization of workers
- Monitoring requirements
- Actions to be taken routinely and in the emergency situations
- Conditions under which licensing , registration a notification are required .

2.2 Licensing :

The legal person responsible for the use of radioactive material should apply to NCNSRC for a license .

The application should include :

- The owner`s name, address , phone number
- The radiation protection officer , name , address, phone number
- Engineering drawings to illustrate the location of the premises in the floor and its surroundings as well as the nature of the activities in the surroundings .
- Engineering drawing to show the location of the building containing the radioactive material and the surrounding buildings and the access to this building .
- The nature of the floor and the working surfaces
- The presence of ventilation , fume hood , fire fighting equipment . International radiation symbol
- The name, radioactivity , material , its nature quantity , half life and the purpose of use.
- Information about area , contamination monitors and their calibration
- Personal dosimetry devices used .
- Information about nature , quantity of waste produced and the way of storage and disposal
- information about workers; their names, job, experience, training
- The presence of record for each for :
- Personal dosimetry
- Radioactive material, source and inventory
- Area and surface monitoring
- waste storage and disposal

2.3 Registration :

From practices that we have :

- Safety is largely ensured by Designe and quality of used equipment

- Simple appearing procedures
- History of few problems with safety in operations registration is not often used in Egypt .

2.4 Notification :

Any modifications of license conditions concerning use, processing , designe, manufacture , construction , importing, exporting, sitting, locating , commissioning , operation, distributing, loaning, selling, maintaining , repairing , hiring, transferring, decommissioning, disassembling, transporting, storing, disposal shall be notified to "NCNSRC" .

2.5 Inspection :

In Egypt inspection provides the most positive assurance that radiation protection and safety requirements are being met or provides the opportunity to enforce correction actions . The licensees must permit authorized representatives of the "NCNSRC" to carry out inspection of their authorized activities to assess compliance and safety . The "NCNSRC" provides inspectors with a very good knowledge of radiation protection principles and practices as well as a good understanding of the radioisotope operation being inspected . They carryout three inspections per year, one declared inspection and another non declared one. The third one is carriedout at the time of renewal of the license .

2.8 Training :

The NCNSRC at Egypt offers two main types of training programs for users , radiation protection officers, inspectors and technicians . The first type is designated to graduated personnel in order to obtain user license and is held 3 times per year, the second one is for technicians and is held twicely per year . The training program includes :

- Basic physics and introduction to radiation
- Interaction of radiation with matter
- Detection and instrumentation
- Dosimetry
- Biological effects of radiation
- Radio isotopes application in medicine , industry research ... etc .
- Safe transport of radioactive material
- Emergency planning and preparedness
- Regulatory aspects and organization

3- Conclusions :

The Egyptian regulatory authority ensures the protection of workers and the safety of radiation sources by submitting priorities to a system of authorization enforced by periodic inspection to verify compliance with the international regulations and standards .

However there are some kind of shortage in the devlopment of notification and registration systems and updating in the national radiation protection law no 159 issued in 1960 .

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HEALTH RISK IN NUCLEAR POWER PLANTS

V. Bliznakov

National Centre of Radiobiology and Radiation Protection
132 Kliment Ohridski Blvd., 1756 Sofia, Bulgaria

Abstract. Worked out are the health risk indices for NPP personnel that could be used in normal operation and in case of accident. These indices concern temporary incapacity for work, invalidity, lethality, cancer, etc. Risk estimation is based on produced energy in NPP or on the collective dose of personnel exposure. Assessed are the specific risk values for NPP "Kozloduy", which show that the risk in normal operation is significantly low (of the order of $2.3 \div 7.2 \times 10^{-4}$ for invalidity, lethality and cancer). Health risk indices can be used when comparing various alternative energy sources, as well as for determination of the power strategy of a country.

The concept of "risk" is quantitatively expressed with the probability that a certain health effect is manifested after an individual has been exposed to a certain "level" of danger. "Risk" is also the probability of an event occurring, for example disease or death of a certain individual, in a certain period of time, or at a certain age.

Many studies concerning the risk in the operation of various energy sources, have been carried out during the recent years [1, 2, 3, 4, 5, 6]. The risk in NPP can be assessed in two aspects: risk assessment for personnel and for population. The aim of these assessments is to compare NPP with other energy sources (TPP, WPP and others), as well as to answer the question: which of the stages of nuclear fuel cycle is the most dangerous one?

Ionizing radiation can cause two types of health effects:

- nonfatal effects - injures or diseases in which there is no direct relationship with the cause of death.
- fatal effects - injures or diseases which are directly related to the cause of death.

The risk indicators for NPP workers should be organised in 4 groups:

1. Cases of death.
2. Lost calendar days due to temporary incapacity for work.
3. Cases of durable invalidity.
4. Cases of malignant neoplasms.

The methods for risk assessment of NPP personnel in a normal operation can be based on the indicators and on the means of their assessment as presented in Table 1 [1, 7, 8, 9, 10].

TABLE 1. Indicators for risk assessment in a normal operation in NPP

1. Indicator of temporary incapacity for work:

$$\frac{\text{number of lost calendar days due to a disease with temporary incapacity for work}}{\text{produced power } (GWt_{(e)}) \text{ for the same period}}$$

2. Idicator of invalidity:

$$\frac{\text{number of cases with durable invalidity for 1 year}}{\text{produced power } (GWt_{(e)}) \text{ for the same period}}$$

3. Lethality indicator:

$$\frac{\text{number of death cases of workers for 1 year}}{\text{produced power } (GWt_{(e)}) \text{ for the same period}}$$

4. Indicator of cancer cases:

a) $$\frac{\text{cancer cases for 1 year}}{\text{produced power } (GWt_{(e)}) \text{ for the same period}}$$

b) $$\frac{\text{cancer cases for 1 year}}{\text{received collective exposure dose for the same period}}$$

The risk assessment in NPP production accidents is presented in Table 2 [2, 8, 10].

TABLE 2. Risk indicators in NPP production accidents

1. Indicator of "total" lethality

$$\frac{\text{Number of all death cases of NPP workers for 1 year}}{\text{number of labour (including radiation) accidents for 1 year}}$$

2. Indicator of "accident" lethality

$$\frac{\text{Number of death cases in NPP for 1 year}}{\text{number of produced power } (GWt_{(e)}) \text{ for 1 year}}$$

3. Indicator of "production" lethality

$$\frac{\text{Number of death cases in labour incidents at NPP for 1 year}}{\text{number of labour incidents in NPP for 1 year}}$$

This methodology can be used for the health risk assessment of NPP "Kozloduy" personnel, as well as for comparison with other nuclear power plants.

Using these methods, we have made an assessment of health risk in NPP both in normal operation and in production accidents (Tables 3 and 4).

TABLE 3. Assessment of the health risk in NPP "Kozloduy" in normal operation

Indicator	Year	Risk value
1.Temporary incapacity for work	1993	2.62
(related to produced energy)	1994	2.27
	1995	2.39
2. Invalidity	1993	0
(related to produced energy)	1994	6.5×10^{-5}
	1995	0
3. Lethality	1993	3.6×10^{-4}
(related to produced energy)	1994	3.2×10^{-4}
	1995	2.3×10^{-4}
4. Cancer	1993	7.2×10^{-4}
a) related to produced energy	1994	5.2×10^{-4}
	1995	4.6×10^{-4}
b) related to collective exposure dose	1993	0.77
	1994	0.54
	1995	0.67

TABLE 4. Assessment of the health risk in NPP "Kozloduy" in labour accidents

Indicator	Year	Risk value
1. "Total" lethality	1993	3.6×10^{-4}
(related to produced energy)	1994	3.2×10^{-4}
	1995	2.3×10^{-4}
2. "Accident" lethality	1993	0.12
(related to production accidents incidents)	1994	0.11
	1995	0.28
3. "Production" lethality	1993	0.06
(related to labour incidents)	1994	0
	1995	0

We have analysed three successive years: 1993, 1994 and 1995. The risk values have been assessed on the basis of produced energy and collective exposure dose. The lethality indicator includes all cases of death among workers (death due to all causes - production and non-production ones).

In a broader sense, the concept of "risk" is estimated as a possibility that something unfavourable happens or as a probability that a certain unwanted event happens during a definite period of time or as a result of a particular situation.

Some authors [11] present certain groups of diseases (infectious, malignant, diseases of the cardio-vascular, respiratory, digestive systems, etc.) as aggregated health risk indices. Such approach is, however, closely related to the quality of medical aid, as well as to the living standard, and the preliminary choice of personnel in the power plant. Thus, there could be risk assessment results that are not directly connected with the power plant operation.

For estimation of the potential risk for workers could be used the results from cytogenetic studies as well, with unifying the criteria for quantitative assessment of such effects.

The creation of a unified approach when determining the health risk in NPP and in other energy sources, is extremely important for the optimization of the medical radiological protection, as well as for the developing of a national strategy in the sphere of energy policy.

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CYTOGENETIC EFFECT OF LOW DOSE RADIATION AND CONTRAST AGENT

V.Hadjidekova, M.Bulanova, V.Hadjidekov+
National Centre of Radiobiology and Radiation Protection, Sofia 1576
+Department of Radiology, University Hospital Alexandrovska, Sofia 1431

ABSTRACT
The effect of the X-ray contrast medium Amidotrizoate on radiation-induced chromosomal damage was investigated in peripheral human lymphocytes, in vitro. The blood undergoes treatment in one of three ways: 1) Amidotrizoate alone at concentrations 1, 3 and 5 % ; 2) X-irradiation alone at dose 0,2 Gy ; 3) X-irradiation in the presence of the contrast medium. Given alone Amidotrisoate was not effective in producing chromosomal aberrations. The cytogenetic effect of 0,2 Gy X-ray was statisticaly significant. The presence of Amidotrisoate during irradiation potentiates radiation-induced chromosomal damage depending on the concentration used.

Significant increase in the frequency of lymphocyte chromosomal aberrations after diagnostic angiography have been reported [1, 2, 3]. This increase is greater than the yield expected from the exposure dose X-rays received. In vitro results show that this increase is due to the presence of the contrast medium, which can induce chromosomal damage by itself [1, 2, 3] and can increase the absorbed radiation dose [1, 2, 4].
The aim of this work is to investigate the combined in vitro cytogenetic effect of contrast material Amidotrizoate in different concentrations and 0,2 Gy X rays in human peripheral lymphocytes.

MATERIAL AND METHOD

Peripheral blood from five healthy donors was used. The blood was processed in vitro in three different ways: 1).treated with Amidotrizoate alone; 2).irradiated with X rays only; 3).irradiated in the presence of Amidotrizoate.
Amidotrizoate consisted of 75% solution of Na-amidotrizoate and N-methylglucamin amidotrizoate,iodine content - 370 mg/ml, ionic, dimeric was used as a contrast medium. It was applied in blood concentrations of 1, 3 and 5 %, roughly equal to those in vivo.
The X-irradiation was carried out with therapeutical equipment "MULLER T-250" at 100 kV, 20 mA, 3 mmAl, at dose 0,2 Gy, 1,06 Gy/min.
The lymphocyte cultures were prepared by the method of Evans [5]. "t" - criterion of Student and method $Y = arc.sin.\sqrt{P}$ were used for statistical significance of the results.

RESULT AND DISCUSSION

The frequency of cells with chromosomal aberrations after separate and combined action of different concentrations of Amidotrizoate and 0,2 Gy X-rays are shown in Table I.
Amidotrizoate alone in applied concentrations does not enhance the spontaneous frequency of cells with aberrations ($P>0,05$). X-irradiation with a dose of 0,2 Gy causes a statistically significant enhancement of the frequency of cells with aberrations both compared to control ($P<0,05$) and to Amidotrizoate alone ($P<0,05$). The presence of the contrast material at the time of irradiation leads to more expressive enhancement of the yield of abberant cells. There are significant differences from irradiated control for all combinations used (at the limit of significance; $P<0,01$ $P<0,001$)
Our results show that amidotrizoate alone is not effective in producing chromosomal aberrations, but significantly enhances the frequency of X-radiation-induced chromosomal aberrations in human peripheral lymphocytes.

Table I.

CHROMOSOMAL ABERRATIONS IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES AFTER EXPOSURE TO DIFFERENT CONCENTRATIONS OF AMIDOTRIZOATE (A) AND 0,2 Gy X-RAYS

Groups A (%)	Cells scored	Aberrant cells, %	Structural Chromos. aberrations, %			
			Chromatid fragm	Chromosomal		
				fragm.	dic+ring	min+sym.tr.
Control	500	1,8	1,2	0,6		
0,2 Gy	500	4,0	1,4	2,0	0,6	
A-1	500	1,8	0,8	1,0		
A-1+0,2Gy	500	6,6	1,4	4,0	1,4	
A-3	500	2,0	1,0	1,0		
A-3+0,2Gy	500	7,6	2,2	3,8	1,6	0,2
A-5	500	2,0	1,0	1,0		
A-5+0,2Gy	500	9,2	1,8	5,2	2,8	0,4

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LOW DOSE IRRADIATION AND RISK OF LEUKAEMIA: A CASE-CONTROL STUDY

N. Chobanova, A. Bayrakova
National Centre of Radiobiology and Radiation Protection
132 Kliment Ohridski Blvd., 1756 Sofia, Bulgaria

Abstract. The effect of low dose irradiation (medical X-ray diagnostic) on the developing of leukaemias in adults is investigated. The influence of non-radiation agents (occupational exposure to chemical carcinogens, past viral infections, family aggregations) to leukaemias are considered also. During this retrospective study 228 patients have been examined with the following disgnosis: acute myeloid leukaemia, chronic myelogenous leukaemias, myelodisplastic syndrome and non-Hodgkin lymphoma (diagnosed between 1991 - 1993). Each case has been matched with two controls. Statistically significant increase has been found in the risk of developing leukaemias after X-ray diagnostic irradiation (OR=1.98, 95% CI=1.14 ÷ 3.46). Exposure to chemical agents is also associated with significant increase in the risk (OR=1.98, 95% CI=1.25 ÷ 2.86).

The medical X-ray diagnostics is the dominant "man-made" source of radiation exposure to the Bulgarian population [1]. The aim of this study is to evaluate the relationship between exposure to medical X-ray diagnostic procedures and leukaemias.

1. MATERIALS AND METHODS

The study is of a case control type. The cases, 228, have been recruited from hospital patients, most of them being from the National Centre of Haematology and Transfusion, and the rest - from the Haematology Clinic at the University Hospital and from the Military Medical Academy. All cases are diagnosed during the period 1991 - 1993. The distribution of cases by diagnosis is as follows: acute myeloid leukaemia (AML) - 54; chronic myelogenous leukaemia (CML) - 38; myelodisplastic syndrome (MDS) -34, and non-Hodgkin lymphoma (NHL) - 102. The controls are patients without a malignant disease, matched by sex and age (± 2 years). The interviews are carried out by a special questionnaire and they deal with subjects or with their close relatives if the subjects are too ill to be interviewed.

The data about the medical radiation are for a whole person's life excluding the last year before the diagnosis or before the interview. The dose of each medical procedure has been taken from the Actualized Methodological Instruction for Determination of Doses Received by Patients from Medical X-rays and Radioisotope Diagnostics [2]. The cumulative equivalent dose to the red marrow and the dose to the whole body are estimated. Using the method of percentile, the patients are distributed into four groups (separately for whole body and red marrow). The patients are distributed into two groups as well, the first one - without any medical procedures, and the second one - with some medical procedures.

The contact with chemical carcinogens is considered according to the occupational route of all patients. As chemical carcinogens are analysed benzene [3] and other petrol products [4], coal tar [5] and magnetic field too [6]. The estimation is not quantitative.

The predisposition factors include hereditary predisposition and viral diseases. The hereditary factors are estimated according to the presence of malignant disease in the family: parents, sisters and brothers [7]. With regard to the viral aetiology, analysed are herpes simplex and herpes zoster [8, 9].

2. STATISTICAL ANALYSIS

The risk of developing leukaemias is estimated as odds ratio (OR) and is presented with a 95% confidence interval (CI). The frequencies of all risk factors under study are calculated for both cases and controls, as well as for each diagnosis. The results are presented in Tables 1 and 2.

3. ANALYSIS

No statistically significant association has been recorded when examining the risk of leukaemias by the method of percentile (the table not seen). The odds ratio for all groups is above 1.0 with the exception of the group with the highest exposure, the significant differences, however, are very wide. There is a significant difference between cases and controls when patients are distributed into two groups (Table 1). The odds ratio suggests high risk for those patients who have received any medical procedures.

The results for non-radiation factors are given in Table 2. The odds ratio suggests an association between chemical agents and leukaemias. The odds ratio for each dagnosis is over 1.0 but the 95% CI for each one is wide.

The risk estimation for leukaemia has shown no association with past viral diseases and hereditary predisposition. OR is over 1.0, excluding AML, but the corresponding 95% CI includes 1.0.

4. DISCUSSION

The results of the study must be interpreted in the context of potential limitations of the study design. The small number of cases for each diagnosis which makes necessary the analysing of four diagnoses simultaneously probably affects the results. Another limitation arises from the choice of the control group. May be this is due to the chosen patients with chronic diseases. The cases, by comparison, are often patients without a disease before cancer being diagnosed. There is no Register for Punctual Medical Diagnostic Procedures in Bulgaria. They are registered in the relevant hospital but the filling in of the individual card is not always exact. No dose response analysis can be persuasive in view of the difficulties regarding the control selection.

The none - versus - some medical exposure is likely to be more reliable than the amount of medical exposure, since it is easier to remember if you have ever been exposed to X-rays than to remember how many X-rays you have had, where and when. The results of other studies are controversial [9, 10]. In the present study a statistically significant

leukaemia risk is observed only when patients are distributed into two groups. This means that the effect of recall bias is not likely to be as great as in the none - versus - some medical exposure.

The results of this study confirm the relationship between risk of leukaemias and occupational chemical carcinogens [3, 8]. Retroviruses have long been suspected as a cause of human leukaemias [8, 11]. The case-control studies show the role of family aggregation in the aetiology of leukaemias [7, 8]. The present study, on the contrary, does not show such relationships.

TABLE 1. OR with 95% CI for selected leukaemias regarding medical X-ray diagnostic procedures

	AML		CML		MDS		NHL		ALL	
	Co	Ca	Co	Ca	Co	Ca	Co	Ca	Co	Ca
no	28	9	11	0	7	2	27	9	73	20
yes	80	45	65	38	61	32	177	93	383	208
total	108	54	76	38	68	34	204	102	456	228
OR	1.75		-		1.13		1.58		1.98	
95% CI	0.7 ÷ 4.4		-		0.3 ÷ 4.0		0.7 ÷ 3.8		1.1 ÷ 3.5	

TABLE 2. OR with 95% CI for selected leukaemias regarding non-radiation agents

	AML	CML	MDS	NHL	ALL
Chemical agents					
OR	1.60	3.92	3.58	1.32	1.89
95% CI	0.6 ÷ 4.5	1.3 ÷ 12.2	1.2 ÷ 11.0	0.8 ÷ 2.4	1.2 ÷ 2.9
Viral disease					
OR	0.61	0.54	0.39	1.03	0.71
95% CI	0.2 ÷ 1.6	0.2 ÷ 1.5	0.11 ÷ 1.3	0.6 ÷ 1.9	0.5 ÷ 1.1
Hereditary predisposition					
OR	0.58	2.19	1.87	1.26	1.30
95% CI	0.1 ÷ 2.4	0.6 ÷ 8.5	0.5 ÷ 7.0	0.6 ÷ 2.5	0.7 ÷ 2.1

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A COHORT STUDY OF LUNG CANCER MORTALITY OF URANIUM MINERS IN SOUTHERN BULGARIA (TOWN OF BANSKO)

D.Apostolova
Medical University, Center of Occupational diseases, Sofia, Bulgaria

ABSTRACT

This study examines the mortality among uranium workers, residents of the town of Bansko, located in Southern Bulgaria. Case-control and historical cohort studies were initiated in 1985 among workers of the uranium mines and residents of the town of Bansko, located adjacent to mine operations, in order to estimate the patterns of risk more precisely. The investigation period continued till 1996.

A preliminary case-control study of 17 lung cancer mortality cases of uranium miners between 48 and 70 years (average age 57,2) and age-matched controls were carried out among a group of 152 workers of under- and overground mines, residents of Bansko, exposed to Rn-222 and its decay products.

Radon exposure was also estimated in working level months, based on the work histories and available radiation hygiene data. The average exposure for uranium miners was 1250 WLM. The examination carried out among uranium workers have clearly shown that the risk of lung cancer increases with the radon-222 and it's decay products exposure. The absolute risk of lung cancer among uranium workers was $1,1.10^{-1}$, and $7,7.10^{-6}$ person-years . WLM^{-1}.

Among 152 uranium workers 17 cases of lung cancer were observed (R1=0,11) against 0,0081 expected (R2) in the period 1985-1996. The observed to the expected cases ratio was 3,8 (OR=R1|R2).

Key terms: cohort study, radon daughters, lung cancer mortality, risk estimate.

INTRODUCTION

Uranium mining and milling development in Bulgaria started in the 50's early. This industry was operational till 1991, and is presently in a process of closing. Studies of under and overground uranium miners have clearly shown that the risk of lung cancer increases with exposure to Rn-222 and its short level decay products (1,2).

In 1995 the Centre of Occupational diseases, Sofia, Bulgaria, initiated a series of epidemiological studies including a large case-control study of cases of lung cancer mortality among uranium miners. The population subject to this study was under observation for the period 1985-1996.

MATERIALS AND METHODS

Case-control and historical cohort studies were initiated among uranium workers and male residents of the town of Bansko (Blagoevgrad province) located adjacent to uranium mine operations, in order to estimate patterns of risk precisely (3). In the town of Bansko an ecologically pure area - the male population was 4800 persons. In addition there were 152 native residents uranium workers and 58% of them addicted to tobacco. The criteria for inclusion in the cohort study were as follow: resident of Bansko, availability of personal and work description data, under or overground work for 5 years or more. To identify diagnosed lung cancer cases among cohort members for the period of this study, the National residential

registry and the local registry of death of the town of Bansko were used. For all cases of lung cancer mortality a detailed work history has been created, including work area, work unit , initial and final data of work, tobacco use (3,4).

Exposure to radon was measured in units of working level months (WLM) . For each uranium worker , WLM exposure was estimated taking into consideration occupational history (years of work in the mine), working level (WL) concentration , duration and period of work. For "working months"calculation we assumed that workers were directly exposed to radon 6h/d for 285 d/y or 170h/mo. Dose-exposure conversion factor is 3.9 mGy\WLM (2).

To calculate the statistical data and estimate the risk we used the methods, described in (5,6).

RESULTS

The average WLM exposure received by the uranium miners, during work is 1250 WLM (7). WLM was estimated with substantial error due to inaccurate or missing records, incomplete measurement data for WL, and problems in extrapolation and interpolation of WL to unmeasured areas and times. The total number of mortality cancer cases in the town of Bansko for the period 1985-1996 was 162 persons. The observed lung cancer death cases among 4800 male residents of Bansko for the same period was 39. The annual mortality probability of lung cancer cases among male residents in Bulgaria and in Bansko during the period 1985-1996 was nearly - $1,3 . 10^{-3}$. The annual mortality probability of lung cancer cases among uranium miners (town of Bansko) during the period 1985-1996 was $5,5.10^{-2}$. The observed number of lung cancer deaths of uranium workers from Bansko for the same period was 17 of 152 (table 1).

Table 1. Estimation of lung cancer mortality risk among uranium miners and native male population of Bansko, during the last 12 years (1985-1996)

	uranium workers	male population (non uranium workers)	total
number of lung cancer deaths	17 (A)	39 (B)	59 (A+B)
survive	135 (C)	4800 (D)	4935 (C+D)
total	152 (A+C)	2839 (B+D)	4991
person-years	1757	16520	

R1 -Lung cancer mortality risk among uranium miners.
R2-Lung cancer mortality risk among non uranium miners.
R1=A/A+C=17/152=0,11
R2=B/B+D=39/4839=0.0081
OR=R1/R2=0,11/0,0081=13,8
Wr-Annual probability of death from lung cancer per WLM^{-1}.
The average exposure for uranium miners was 1250WLM.
Wr=Person-years . 1250 WLM= 1757 . 1250 = 2196250 per . WLM
$Wr=17/2196250=7,7 . 10^{-6}$ WLM^{-1}.

Table 1 shows the increase in lung cancer mortality risk among uranium miners in comparison with the lung cancer mortality risk among non uranium miners (male population of

Bansko). The expected number of lung cancer cases in the examined group , based on the risk among the average male population (non uranium miners)in the town of Bansko, was 0,0081 cases. The relation risk (OR) observed to expected cases of overall mortality ratio among uranium miners was 13,8. The probability of lung cancer death per WLM was $7,7 . 10^{-6}$ person-years per WLM^{-1}.

CONCLUSIONS

Similar to the conclusions in some of the other studies(8,9), the results of the epidemiological study of lung cancer in Southern Bulgaria show a very high mortality among uranium miners. The average absorbed dose is 4875 mGy (1250 WLM . 3,9 mGy\WLM =4875mGy). The relation risk (OR) of lung cancer mortality among uranium miners was 13,8, and the probability of lung cancer death per WLM was $7,7.10^{-6}$ person-years per WLM^{-1}.

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LOW DOSES - A REAL PROBLEM FOR RADIATION PROTECTION AND RADIOBIOLOGY OR A SEMANTIC CROSSWORD

G. Vasilev, A. Bayrakova, T. Hadjieva, K. Ingilizova, I. Roupova

National Centre of Radiobiology and Radiation Protection
132 Kliment Ohridski Blvd., 1756 Sofia, Bulgaria

Abstract. The ranges of small doses should be more accurately defined and differentiated. The linear nonthreshold conception is of an ethical character. Collective doses should not be used for assessment and limiting of risk without restrictions in the case of minimal doses. Recording of all kind of exposures is important, not just the occupational one. The hormesis and mutagenesis in small doses range do not exclude each other. They are parallel effects.

Low doses mean dreams of roses in Radiobiology. For Radiation Protection they are consider as black clouds. Low doses are essential problem for Human Radiobiology . It, however, forces the radiation protection to ask itself too often whom to protect and how much to protect. During the last decades this problem has gradually lost its purely scientific outline in spite of increasing information. It is becoming to a high degree an ethical problem. Here we are trying to analyse only some of aspects of the problem "biological effects from low doses and dose rates of ionizing radiation". This is an area where still many questions could be asked. Probably it is time to learn asking such questions that can afford right answers.

1. Let us begin with the point, that every scientific research should determine its subject clearly. As to the problem "low doses and biological effect", we are immediately facing at least two vague definitions.

A. Which dose is low dose? Many definitions are presented, no one is generally accepted. Let us consider one of the most frequently cited values: low doses are the ones below 0,2 Gy absorbed dose or below 0,2 Sv equivalent dose. It should be noted that doses from natural radiation background, e.g. about 0,3 mSv/a, vary within a very wide range: from 0,3 mSv to 200 mSv. The ratio is nearly 1:1000! Regarding the "big doses", the ratio is only 1:10. Distinctive somatic determinate effects are manifested from about 1 Gy to about 10 Gy going to the man lethal dose . The general vagueness became extremely wide if we add the time indetermination during that "small dose" is accumulated. How can we compare man exposure of 0,3 mSv per anum with that of 200 mSv per week?

B. How does we interpret "biological effect"? The living organism, even the simplest one, is a multistage hierarchical system. Consider the carcinogenesis, distances from a primary chromosome break to an individual death of cancer are comparable to those from a quark in the Earth centre to the black hollow in "Swan" star constellation.

Both in A and B cases, an exact definition of doses' subranges and areas of effects are necessary.

2. Radiobiology proposes to Radiation Protection for somatic effects in small doses range the linear nonthreshold conception. In the light of all available experimental, epidemiological, theoretical, etc. data, we should admit that this is an ethical hypothesis rather than a scientific one. It could neither be proved nor disproved by biological and medical argument. We should not be afraid assuming that. As the Austrian mathematician K. Gödel already stated during the thirties, such statements can be formulated in any logically completed system of concepts. In this way, the linear nonthreshold conception does not describe the biological effect of small doses. It just postulates them, and nothing can be neither added nor taken out. The essential point is not whether such conception is true or not. The question goes to limits Radiation Protection should apply this hypothesis.

Except the ethics, there is at least one very important consideration. It is accepted, radiation risk assessment to be based on committed collective dose (CCD). The limitation of risk means a limitation of CCD. The cost of 1 man-Sv, however, sharply increases when the doses get lower and close to natural background. So is the cost of control, which should simply specify the extent of this exposure. A generally acceptable and reasonable limit has to be found. It should be accepted, backed with arguments and made public with consensus. H. Rossy warned about the risk lying in the unlimited application of CCD 25 years ago. After 1986, a public sensitivity was growing towards exposure of any kind . For an ordinary person, risk to benefit constellation is far no convincing. The principles of radiation protection harmonisation , even ALARA, should be formulated more accurately and firmly. We need to establish an inferior limit, where no protection is needed even from the ethical point of view.This is a difficult question, not because an answer is lacking, but because there are many solutions. Their choice and acceptance are one of the most important tasks of Radiobiology and Radiation Protection. The time of amorphous formulations might be over.

3. Currently, occupational exposure is more and more approaching the public exposure level from natural radiation background. A special attention is needed to following:

A. In case occupational exposure is recording, exposure from natural radiation background should be determined as well.

B. Medical exposure should be registered by a separately created system.

C. More serious attentions need to be paid to exposure recording from radon and its daughters. The problem of radon is one of the most essential problems of Radiation Protection nowadays. From theoretical point of view there are variety unsolved questions concerning carcinogenesis for instance.

D. It is high time to think over the problem of standardising the radiation impact, taking into account all exposure sources, not just the occupational one.

4. Stochastic genetic (hereditary) effects are a specific item in Radiobiology. Up to now such effects have not been proved in man, including the progeny of the Japanese atomic bombs' survivors. The use of man radiation risk coefficients extrapolated by experimental data on mouse and plant seems to a manifestation of conservatism.

5. For decades Radiobiology seems to be afraid of the concept "Hormesis". It has nothing to do with the principles of radiation protection, but simply with a number of recorded effects of stimulating and accumulating action of small doses. It is true that the mechanisms of these effects are not clarified, but same could be stated for mutagenesis as well. These mechanisms and effects do not exclude each other, they might exist in parallel.

REGULATORY CONTROL OF NATURAL IONIZING SOURCES IN LITHUANIA EXPERIENCE BASED ON INDOOR RADON MONITORING

Albinas Mastauskas, Gendrutis Morkunas
Radiation Protection Centre
Kalvariju 153, Vilnius , LT-2042, Lithuania

Abstract

The situation in legislation of protection against risks from natural sources of ionizing radiation in Lithuania is described The requirements of new standards came into conflict with the real situation which has not been evaluated before implementation of these standards On the basis of recommendations of ICRP Publication 60 and results of indoor radon survey new action levels are being established

Lithuania is establishing its radiation protection legislation based on recommendations of ICRP Publication 60 For long years Lithuania has been using standards and regulations of Soviet Union After re-establishing independence Soviet radiation protection standards remained in force Lack of knowledge and experience in creation of legislation in radiation protection was the main reason for it On the other hand, according to ICRP Publication 60 the new legislation based on new principles of radiation protection was to be created It was not possible to implement practically until the Basic Safety Standards [1] were published Now creation of Lithuanian Law of Radiation Protection and Basic Radiation Protection Standards is under way It is planned to have the Radiation Protection Law in the middle of 1998 and Basic Radiation Protection Standards in the end of 1997

Some standards regarding special fields of radiation protection have been created and approved earlier These standards are the most important in limitation of exposure both of public and personnel and they were implemented before approval of the above mentioned Law and Standards One of standards of such kind is HN40-1994 "Limits of Population Exposure to Natural Ionizing Radiation Sources", approved in 1994 [2] The aim of this standard is to minimise exposure of humans inside buildings

Two types of levels have been established by this standard maximum permissible concentrations of natural radionuclides (Ra-226. Th-232 and K-40) in building materials and maximum permissible concentrations of indoor radon

Indoor radon situation in Lithuania was entirely unknown in 1994 The measurements of indoor radon concentrations have not been started then because necessary equipment was not available in any research or regulatory institution When determining maximum permissible concentrations of indoor radon the results from similar in geological conditions countries have been used Since it was decided that indoor radon concentrations in Lithuania should be rather low the appropriate regulatory levels have been established and approved 100 Bq/m^3 for existing buildings and 50 Bq/m^3 for new ones These levels are very low in comparison with other countries and action levels recommended by [1]

The program of indoor radon survey started in 1995 This program is performed with the technical and methodical help of the Swedish Radiation Protection Institute (SSI) The aim of this program is to clear up the general indoor radon situation in Lithuania and to find out the radon prone areas according to ICRP Publication 65 [3]

The measurements for determination of indoor radon situation are performed in randomly selected detached houses during heating season The E-Perm electrets by Rad Elec Inc are used as

monitoring devices The measurements are carried out in two used rooms nearest to the soil (Survey of building materials used and manufactured in Lithuania proved that building materials is not an important source of indoor radon) Duration of one measurement- more than 3 weeks Multi-storeyed (block) houses have been excluded from survey because indoor radon concentrations in such houses tend to be lower

Some regions of special interest have been selected in co-operation with the Lithuanian Geological Survey The indoor radon concentrations in these regions are expected to be higher than average ones for Lithuania One of the most interesting region is located in the northern Lithuania where karst phenomena take place

The detailed results of measurements in randomly selected houses are described in [4]

The arithmetic mean value of indoor radon concentrations in 350 randomly selected houses and 30 specially selected houses (in karst region) are 55 and 125 Bq/m^3 The maximum permissible concentration of indoor radon in existing houses established by [2] is exceeded in 16 % randomly selected houses and in 48 % of houses in karst region In such case remedial actions ought to be taken in more than 70,000 detached houses all around Lithuania This number for a country with 3 8 million of population and more than 50 % of population living in multi-storeyed (block) houses is extensively high

The minimum action level for indoor radon recommended by [1] is 200 Bq/m^3 Percentage of randomly selected houses and ones in karst region with indoor radon concentrations exceeding this level is 4 4 and 25 %. appropriately Remedial actions should be taken in approximately 19,000 detached houses After discussions it was decided to establish single action level both for existing and constructed houses- 300 Bq/m^3 In such case 11,000 detached houses will need remedial actions This number is rather high, social and economic factors taking into account However, the Basic Radiation Protection Standard is being created with the idea that it will be in force in future. then social and economical factors will be modified in Lithuania

According to estimations based on the results of the above-mentioned survey and [3], the average annual effective dose caused by indoor radon in Lithuanian detached houses is equal to 0 83 mSv The newly established action level will cause the annual effective dose of 4 5 mSv Even in the first case indoor radon as a dose-causing factor is of the same importance as medical procedures In order to be aware about situation connected with medical exposure dose the measurements of patients undergoing x-ray examinations have been started Probably, modified recommended levels of doses of medical exposure will be suggested for inclusion into the above-mentioned standards

It is only one example of problems any country implementing new requirements and recommendations of radiation protection can encounter

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The Regulatory Aspects of the Control of Low Level Radiation in NPP Supervised Areas

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V. Kuts, L. Litvinsky
The State Scientific and Engineering Center of Control Systems and Emergency Response (SSEC CSER), Kiev, Ukraine

V. Belousov, Yu. Roschin
Goscomatom of Ukraine, Kiev, Ukraine

Abstract

The authors are discussed some aspects of the elaborated Ukrainian standard "Automated Radiation Monitoring Systems of the Environment for Nuclear Power Plants. Basic Principles". The systems are applied for automated continuous monitoring of radiological situation in NPP supervised areas and early warning of any significant increase of radioactivity in ambient air or stack gas. The scope of measuring data to be established by the standard depends directly on the current approach to the health effects of low doses of ionizing radiation.

Main sources of global public exposure are natural radioactivity (radon, external natural gamma exposure, cosmic radiation) and medical treatment. The contribution to a public dose of global radioactive precipitations and emissions of the nuclear enterprises does not commonly exceed 1 %. However, in the NPP vicinity the radiological situation can be formed by radioactive releases into the environment. For this reason the international and regional radiation safety norms and regulations provide for continuous radiological monitoring in such zones. The Sanitary Regulations for Design and Operation of NPP (SP AS-88) [1] currently used in Ukraine establish a dose limit caused by radioactive releases of NPP as a 5 % part of the public dose limit of 5 mSv/year (i.e. 0.25 mSv/year as a result of all possible exposures to radioactive releases of NPP on the critical group of population from the nearest locality). Individual dosimetry of population can not provide surveillance of public exposure because of the difficulties in practical realization. Records of the doses are also less important than the insurance that the exposure is not higher than the dose limit. Therefore, SP AS-88 has established the emission limitations of effluents into the environment (gaseous and liquids) based upon the dose limit of 0.25 mSv/year for population as follows:

- radioactive noble gases: $1.8 \cdot 10^{13}$ Bq/(day·1000MW);
- iodine (gaseous and aerosols): $3.7 \cdot 10^{8}$ Bq/(day·1000MW);
- aerosols (mixture): $5.5 \cdot 10^{8}$ Bq/(day·1000MW).

Moreover, SP AS-88 requires the environmental control in the 30 km zone by means of the automated monitoring network for the first time in practice of the former USSR and CIS. In near future these networks should be implemented in every Ukrainian NPP as a component of radiation monitoring systems. In addition, after the introduction of the new "Norms of Radiation Safety of Ukraine" in 1997 (with the population dose limit of 1 mSv/year) the changes of other regulations are planned.

In Ukraine there are 14 nuclear power reactors in operation and the construction of two additional power units will be completed in the nearest years. Influence of a NPP in the normal state to the radiological situation can be illustrated with the amount of radioactive releases of Rovno NPP [2] in 1996 (2 WWER-440 reactors and 1 WWER-1000 unit are in operation) shown in table I.

Table I. Radioactive releases of Rovno NPP in 1996.

Parameter controlled	Average release, Bq/day		Total radioactivity, MBq/y		
	1&2 units	3 unit	1&2 units	3 unit	RNPP
Noble gases	$1.7 \cdot 10^{11}$	$8.4 \cdot 10^{10}$	$6.2 \cdot 10^{7}$	$3.1 \cdot 10^{7}$	$9.3 \cdot 10^{7}$
Iodine (^{131}I)	$1.9 \cdot 10^{6}$	$2.5 \cdot 10^{6}$	683	919	$1.6 \cdot 10^{3}$
Aerosols	$2.2 \cdot 10^{5}$	$1.3 \cdot 10^{5}$	81	48	$1.3 \cdot 10^{2}$

Estimated dose caused by RNPP radioactive releases is about 0.002 mSv in 1996 for member of the public in supervised area.

The authors have elaborated the project of the Ukrainian standard "Automated Radiation Monitoring Systems of the Environment for Nuclear Power Plants. Basic Principles". The standard establishes application and objectives, the main functions, structure of the system, scope of measuring data and general technical specifications of the equipment to be used. The system is intended to provide continuous measurements of meteorological and radiological parameters (gamma background, volumetric activity of iodine and aerosols in air and ventilation ducts). The requirements establishing controlled radiation parameters, quantity and locations of the monitors, measurement ranges are closely connected with the regulatory aspects of the control of low doses.

The norms and regulations that are currently in force in Ukraine define the minimum requirements to the scope of radiation monitoring in supervised areas. According to SP AS-88, OPB-88 [3], the automated system should provide the continuous monitoring of gamma background of the environment. GOST 27452 [4] requires measurement of volumetric activity of iodine (^{131}I) in the accident and post accident states. The monitoring scope should also provide a sufficient amount of the input data for models and algorithms of near-range atmospheric dispersion and the evaluation of radioactivity of the accident release. The radionuclide composition of the environmental samples (flora, soil and water) should be controlled with the laboratory equipment. The IAEA Safety Guide No. 50-SG-D9 [5] recommends also the continuous monitoring of radioactive aerosols and iodine (^{131}I) in the environmental samples. Compliance of national norms to the international regulations is considered as an important aspect of regulatory activity.

To sum up the requirements to the environmental monitoring by means of the automated system it should be noted that the Norms comprise only general principles. The Standard elaborated should specify more detailed requirements to the location and quantity of the monitors, their types and measurement ranges. The document intends the use of about 30 gamma monitors in 30 km zone around NPP, 8 fixed stations equipped with aerosol and iodine monitors and a mobile laboratory. The equipment should have independent power supplies, sampling instruments and reliable data transmission channels

to a remote control panel. Sensitivity of the system to detect small changes of radiological situation is to be in compliance with the possible detrimental health effects caused by low doses of ionizing radiation.

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XA9745577

HORMONE REGULATION SYSTEM AND CYCLIC NUCLEOTIDS IN THE CHERNOBYL ACCIDENT LIQUIDATORS WITH DOSES ABSORBED LESS THEN 1 GY

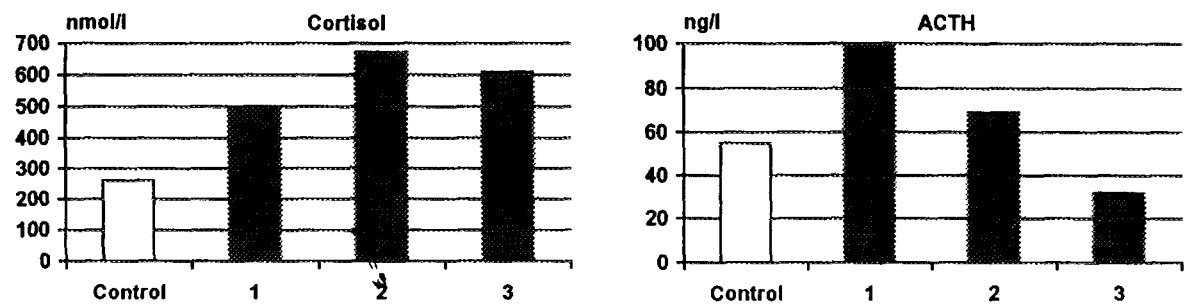
Kovalenko A.N.
Scientific Centre of Radiation Medicine, Kiev, Ukraine

Abstract. During 6 years after the accident (1987-1992) a functional state of endocrine system that regulate the adaptation, reproduction, metabolism, vessels tonicity and water-electrolyte balance were investigated in 249 liquidators with doses absorbed less then 1 Gy. The changes of these systems activity in state of basal secretion and peculiarities of their reactions under influence of perturbation (adrenaline, insulin) were revealed. Post-radiation endocrinopathy was characterised and its role in decrease of the organism's adaptation and in mechanism of sanogenesis and pathogenesis was found.

An organism's cells, tissues, organs and systems response on irradiation is not isolated. It has a co-operative (systemic) character and depends on quantitative and qualitative peculiarities of internal secretion glands' reaction which parenchyma belongs to slow renewal tissues. The reaction quality, as increase or decrease of hormone secretion, and it quantitative character determines by phenomenology of radiobiological effects among which a hormesis, adaptive response, radiation reaction and acute radiation syndrome of different severity are exist. These effects are conditioned by doses absorbed. Therefor it is supposed that endocrine changes are equal during every radiation phenomena would take place.

In the present article the data the hormonal system activity and circle nucleotid concentration in the Chernobyl accident liquidators' plasma are submitted. The liquidators worked at the Chernobyl NPP in 1986, their age was 22-43 years old and dose range was less then 1 Gy. No one liquidator had any sign of bone marrow syndrome. Doses range pointed in special documents laid from 20 till 96 cSv. This fact allows to characterise primary biological effects in these persons as a radiation reaction and this group as a homogenous. A clinical examination of 249 liquidators had been done in three following stages: 1987-1988, 1989-1990 and 1991-1992. Before the accident all persons were healthy. During or after the work at the NPP the original complex of symptoms was developing. It was characterised by multiple neurovegatative disorders which are known as vegetative dystonia. A control group consists of healthy men the same age as liquidators and that had no contact with radiation.

Hypophisis-corticoadrenal system. At the stage 1987-1988 an increased activity of central and peripheral links of this system (hypercorticotropinemia and hypercortisolism) is revealed. In following times a level of adrenocorticotropic hormone (ACTH) basal secretion decreased while glucocorticoids suprarenal activity increased (Fig. 1). Steady hypercortisolism on a background of decreased adrenocorticotropic hormone concentration in plasma (out of central stimulation) we can regard as a forming and consolidating regulation disorders that limits an irradiated organism's adaptation potential. The activation of hypophisis-corticoadrenal system in distant period after an irradiation are caused by the increased organism's needs in glucocorticoids which as J. Baxter said: "... are almost ubiquitous as physiological regulators" [1].



Stage of examination (in this and following figures): 1 - 1987-1988; 2 - 1989-1990; 3 - 1991-1992

Fig. 1. Cortisol and ACTH blood plasma concentration in liquidators with doses absorbed less then 1 Gy

Hypophisis-gonads system. An increased sexual hormone productive function (hypotestosteronemia) was revealed on the stage of 1987-1989. In following times a normalisation of this hormone secretion basal level took place (Fig. 2). At the same time there was found an increase of estradiol blood concentration and expressed tendency to decrease luteinizing hormone (LH) basal level that achieved a reliability in 1991-1992. A blood concentration of follicle-stimulating hormone (FSH) and prolactin didn't change essentially. In a mechanism of temporary hypotestosteronemia we can't exclude following factors:

- direct radiation damage of Leidig cells;
- inhibition of Leidig cells physiological activity by high concentration of cortisol;
- an absence of stimulation from the side of gonadotropic hypophisis function. In other words there is the absence of necessary condition to realise intersystem mechanism of back connection because an essential diencephalon component took place in pathogenesis of sexual dysfunction in these people. An increased concentration of non specific sexual hormone estradiol in peripheral blood of young irradiated men could be connected with weakened processes of estrogens decompose in liver by hydroxylase. The last is a "typical organ of late effect after an irradiation" despite of high regenerative possibilities of this organ [2]. One of the possible reason of blood testosterone concentration decrease and the increased level of estradiol can be an increase peripheral (out of sexual gland) testosterone conversion to estrogens.

Renin-angiotensin-aldosterone system and antidiuretic hormone. In liquidators an "isolated" hyperangiotensinemia II with normal level of plasma renin activity and aldosterone concentration was found (Table I). This phenomenon we explained by acceleration of angiotensin formation from angiotensinogen produced by liver. Angiotensinogen accelerated production caused by glucocorticoids (cortisol) abundance [3]. The cells of zone glomerulosa of suprarenal cortex, that produce of aldosterone, have a sensitivity to stimulating action of angiotensin II only in condition of decreased natrium plasma concentration but examined people had no change in electrolyte balance.

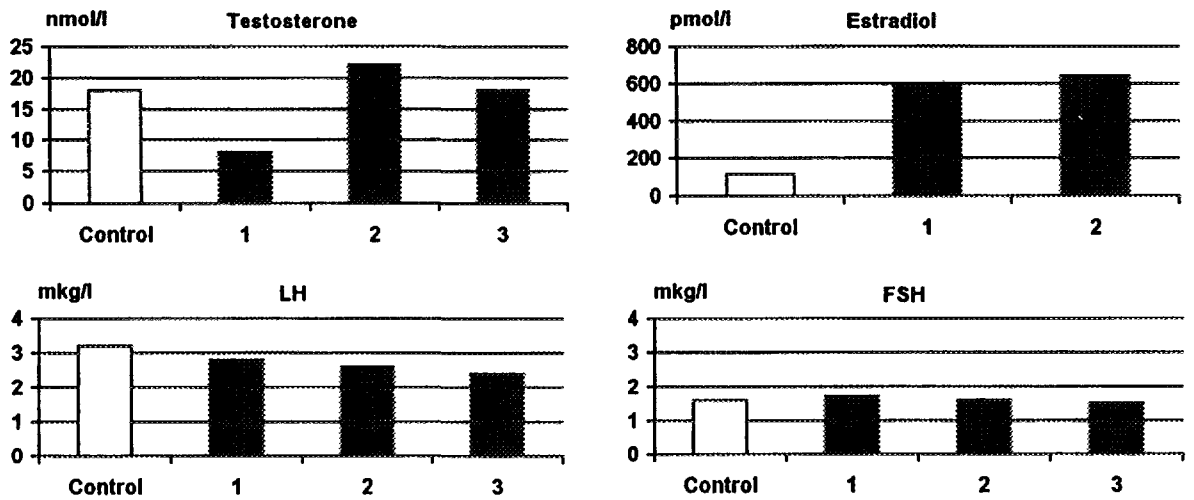


Fig. 2. Blood plasma concentration of sexual and gonadotropic hormones in liquidators with doses absorbed less then 1 Gy

Table I. Healthy men (control group) and liquidators blood plasma basal concentration of hormones that regulate water-electrolyte balance and vessels tonicity (M±m)

Hormones	Control	Liquidators	P
Plasma renin activity, ng/ml/h	1.51±0.12 (20)	1.48±0.21 (24)	> 0.05
Angiotensin II, ng/l	20.5±2.96 (18)	62.5±9.7 (36)	< 0.001
Aldosterone, ng/l	121.5±12.1 (20)	146.7±15.4 (44)	> 0.05
Antidiuretic hormone, ng/l	2.57±0.07 (44)	2.63±0.12 (75)	> 0.05

Note (in this and following tables): P - reliability of difference in comparison with control; in the brackets - number of persons examined

The level of antidiuretic hormone basal secretion didn't change. It is caused by absence of change out cells liquid osmosis and these volumes.

System of hormonal regulation of metabolism. In the liquidators the insulin basal concentration was twice higher than in the control. Hyperinsulinemia combines with reliable somatotoropic hormone (STH) and C-peptid secretion increase. A glucagon level has no essential difference from the control group (Table II).

Table II. Healthy men (control group) and liquidators blood plasma basal concentration of hormones that regulate metabolism (M±m)

Hormones	Control	Liquidators	P
Insulin, pmol/l	63.2±14.3 (25)	128.6±8.7 (72)	< 0.001
Glucagon, ng/l	140.1±12.0 (28)	119.9±15.9 (24)	> 0.05
STH, mkg/l	0.76±0.07 (31)	2.0±0.25 (62)	< 0.01
C-peptid, mkg/l	0.88±0.02 (29)	2.36±0.54 (24)	<0.01

This changes were observed in first four years after the accident. Progressive increase of insulin blood concentration was replaced by it essential decrease on the stage of 1991-1992. The STH concentration was high increased in 1989-1990 and reduced in 1991-1992 (Fig. 3). The changes of these hormones basal secretion shows that the most intensive period in hormonal regulation of metabolism was the 3rd and the 4th years after the taking part in a liquidation of the accident. This shows an expressed activation of reparative processes.

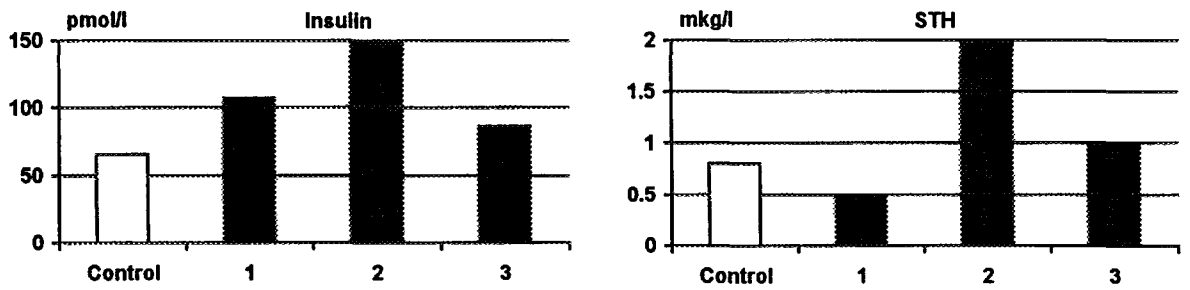


Fig. 3. Blood plasma concentration of insulin and STH in liquidators with doses absorbed less then 1 Gy

Cyclic nucleotids. An increased basal concentration of cyclic nucleotids in blood plasma was found in the liquidators. Cyclic adenosinemonophosphate (cAMP) and cyclic guanosinemonophosphate (cGMP) was increased on 53% and 83%, respectively (Table III). During years after the accident the increase of whole pool of cAMP and cGMP was observed (Fig. 4). In comparison with control group at the stage of 1989-1990 the cAMP concentration was increased in 1.76 times and cGMP in 2.82. So the nucleotid index (ratio cAMP/cGMP) was reduced.

Table III. Healthy men (control group) and liquidators blood plasma basal concentration of cyclic nucleotids (M±m)

Nucleotids	Control	Liquidators	P
cAMP, nmol/l	16.5±2.65 (17)	25.2±2.00 (64)	< 0.02
cGMP, nmol/l	140.1±12.0 (28)	16.8±1.92 (60)	< 0.01

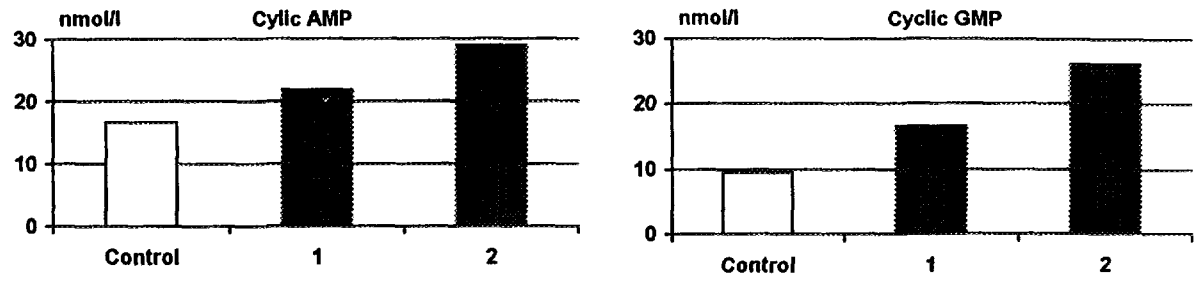


Fig. 4. Blood plasma concentration of cyclic nucleotids in liquidators with doses absorbed less then 1 Gy

According to the getting results the activity of the secondary messengers system in long term period after the accident was increased. It reflects the total effort of adrenergic (connected with cyclic AMP) and cholinergic (connected with GMP) processes. During a time the role of cholinergic influences intensifies that leads to nucleotid index reduced. Hence, our data adds the H. Langendorf and M. Langendorf ideas [4] that the increase the cyclic nucleotids concentration in cells, tissues and bioenvironments can reflect an intensity of an organism's radioprotective potential in connection with a preceding irradiation.

So in the liquidators with doses absorbed less then 1 Gy the non specific polyfactors changes in endocrine homeostasis were revealed. In spite of their pre-clinical character its can be, in complex with neurovegetative disorders, the reflection of the system non-stability and the causes of many structural or functional and metabolic changes on all levels of the organism's integration.

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XA9745578

Spatial Structure of Food Contamination with ^{137}Cs and Estimation of Long-term Internal Dose Loads on Population of Belarus

Konstantin Krivoruchko
International Sakharov Institute of Radioecology, Dolgobrodskaya 23, Minsk, Belarus

Abstract

An analysis of 53,207 records of ^{137}Cs contents in 83 types of food products obtained in 1993 in Belarus was carried out. Internal exposure by eight selected food components has been estimated. To map the non-uniformly distributed data, different types of geostatistical approaches are used. The results of spatial analysis of long term internal dose loads on populations under high radiation risk could be used in decision making.

Introduction

The Chernobyl accident affected Belarus more than any other country. The analysis and visualization of environmental and epidemiological data, therefore, are critical for predicting public health outcomes. Many interpretations of the affects from the Chernobyl accident appeared in post-Chernobyl years. The after effects of radiation 11 years following the accident, however, are yet to be explored and are, therefore, poorly understood. The situation has been exacerbated by a lack of experience in using modern statistical interpolation methods together with a GIS. Such techniques can reveal the interrelations between spatial distributions of radioactive contamination and disease incidence rates.

During the first weeks after the Chernobyl accident the main dose loads on the population were from external radiation by short-lived radionuclides. Levels of the territory contaminated by short-lived radionuclides, in particular ^{131}I, were so high that the corresponding exposure of millions of people was qualified as "iodine shock." In the first days after the accident residents of Belarus received the majority of their doses of radiation on their thyroid gland. This will result in long term health problems for these populations. The epidemic of childhood thyroid cancer is the first indisputable health after-effect of the accident. Reconstruction of dose loads on the population in the initial period of the Chernobyl accident and estimation of thyroid cancer risk in Belarus have been investigated in [1-3].

At present (and over the next decades), the main hazard comes from ^{137}Cs and ^{90}Sr. Today, internal exposure from human intake of ^{137}Cs contaminated food contributes to approximately half of the population income of the inhabitants of villages in Belarus affords these populations no access to "clean" (non-contaminated) food. They, therefore, consume vegetables, potatoes and milk cultivated on their own personal properties as well as mushrooms and berries from nearby forests.

This current investigation is based on more than 50,000 measurements of ^{137}Cs contents in the main types of food, which were carried out in the Byelorussian Institute of Radiation Safety in 1993. The cases of ^{137}Cs content in food exceeding the upper permissible level (UPL) were included in the information bulletins [4], which allow one to carry out the address help to the families under high radiation risk.

For decision making on the regional scale, however, the use of modern methods of spatial analysis is needed. This report brings the results of processing data on ^{137}Cs food contamination into the framework of a geostatistical approach. All databases were processed and visualized using the GIS MapStudio [5,6].

^{137}Cs food contamination in Belarus in 1993

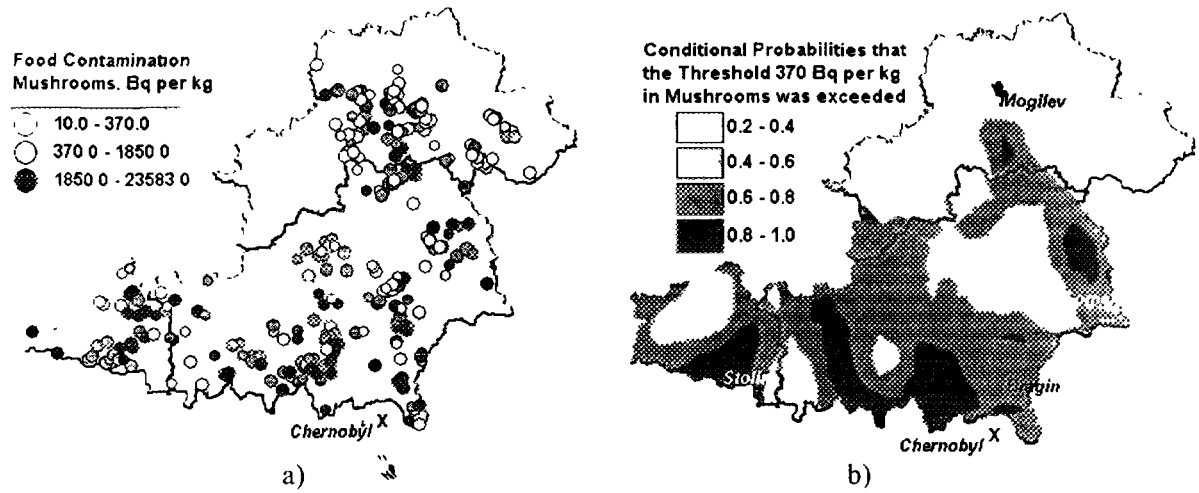
At present, the main sources of radiation hazard for the population living in contaminated regions are internal exposure from food and external exposure from gamma dose rate in the air. The official data of internal and external doses for more than three thousand Byelorussian settlements were published in 1992 [7]. In this investigation internal exposures have been estimated, based on measurements of ^{137}Cs and ^{90}Sr in milk and potatoes, taking into account the average consumption of these types of food for the whole Belarussian population. Unfortunately, maps of exposures have not been published until now.

Our investigation demonstrates that the consideration of additional products leads to an increase in estimation of internal exposure by two-three folds in comparison with [7]. The initial database contains 53,207 records of food contamination in 83 types of food, which are distributed very non-uniformly both as geographical locations and as type of food, see table I.

Table I. Exceeding UPL in food in rural settlements of Mogilev, Gomel and Brest provinces in 1993.

Food	UPL, Bq/kg	Number of settlements	Number of Measurements	Exceeding UPL, %
Cranberry	185	100	429	62,70
Bilberry	185	317	1383	61,03
Mushrooms	370	292	1123	56,0
Milk	111	675	19111	14,85
Pork	185	229	234	14,10
Sour cream	111	83	242	12,81
Cottage cheese	111	103	344	11,63
Well water	18,5	243	2141	8,78
Carrots	185	252	1439	5,84
Cabbage	185	182	590	4,41
Potatoes	370	472	4996	1,64

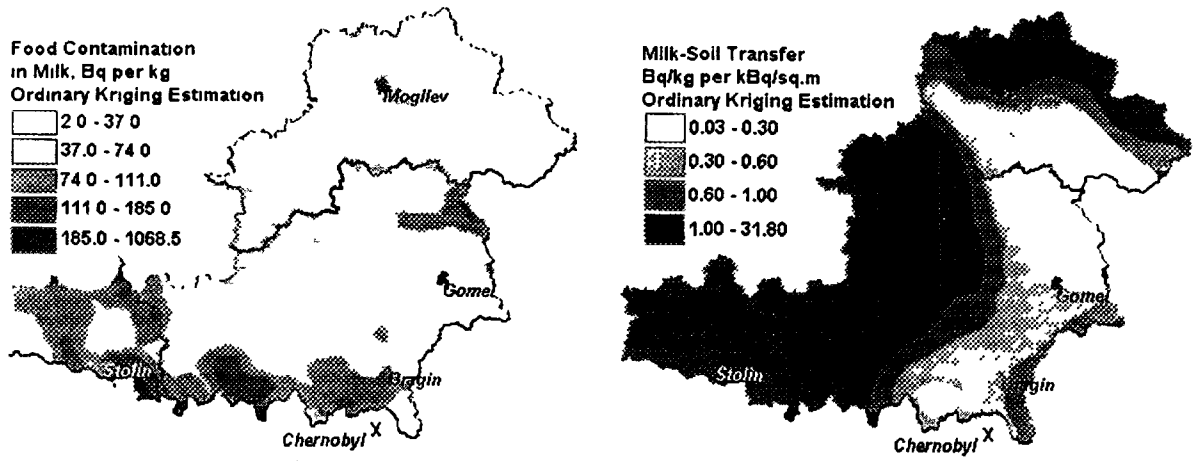
For decision making it is interesting to find regions in which it is dangerous to consume each type of food. We have prepared probability maps for each type of food based on indicator kriging approach. Figure 1 presents data samples of food contamination in mushrooms and a map of conditional probabilities that the UPL for mushrooms was exceeded.



a) b)

Figure 1. a) Food contamination in mushrooms, Bq/kg. b) Conditional probabilities that upper permissible level for mushrooms was exceeded, indicator kriging estimation.

A number of factors influence the uptake of radionuclides from soil to plant, including the level of soil contamination, the soil type, and the type and extent of countermeasures. We have analyzed the spatial correlation between ^{137}Cs in the food and in the soil and found that this dependence is very complicated. Figure 2 presents the results for food contamination in milk and milk-soil transfer



a) b)

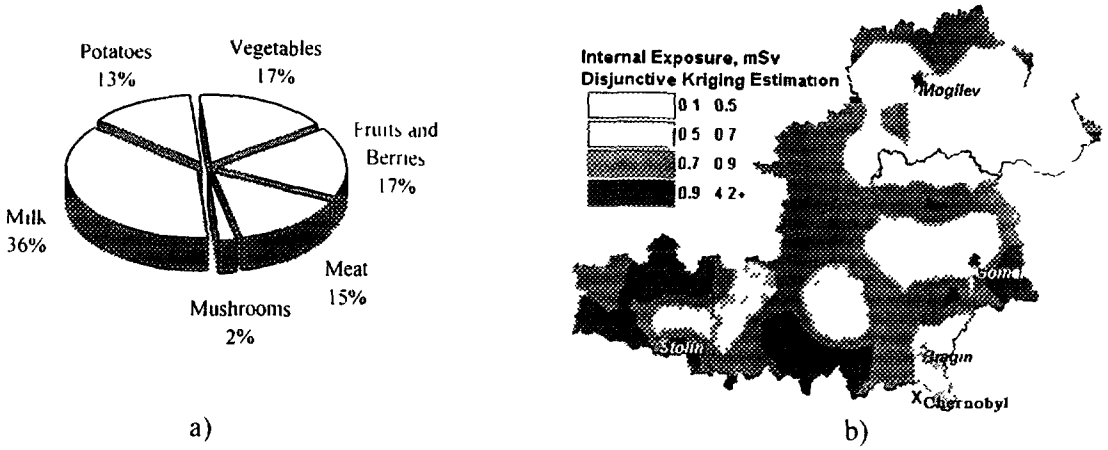
Figure 2. a) Food contamination in milk, Bq/kg. b) Milk-soil transfer, ordinary kriging estimations, Bq/l per kBq/sq m.

Maps presented in Figures 1 and 2 are different from the map of ^{137}Cs soil contamination, especially in relation to the western passage of radioactive cloud in the very first days after the Chernobyl accident

An estimation of internal dose on the Belarus population in 1993

The estimation of the internal exposure was made based on the following components of food milk, potatoes, vegetables, fruit and berries, meat, mushrooms, fish and bread. We had enough information for 120 rural settlements We used the dietary habits of the adult rural population of Belarus and information about diet of children from the Chernobyl zone [4].

Figure 3a presents the structure of the internal dose loads from food for the adult population in 1993 based on information for 120 rural settlements for which we have at least 50 measurements



a) b)

Figure 3. a) The structure of the internal dose loads from food for the adult population in the 1993 b) Spatial structure of the internal exposure, mSv, disjunctive kriging estimation

The result of dose estimation shows that the contribution to total dose from consumption of milk and potatoes is about one half of the whole body dose received by the population. This finding discredits the common practice of utilizing only milk and potato consumption data to estimate internal dose [7,8]. It should be noted that rural citizens who live near forests potentially consume contaminated "forest gifts" - berries and mushrooms - than reflected by average values commonly used in calculations.

The population under high radiation risk extends throughout most of the southern part of Belarus. As was mentioned in [4], practically all children in this area have problems with health.

In the near future we are planning to extend this investigation to take into account additional environmental and epidemiological information.

Acknowledgments

I thank Prof. V.Nesterenko for giving me the data on food contamination and Mr. A.Makeichic for help in the data processing.

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XA9745579

AN EXPLANATION FOR THE MULTIPLICATIVE AND THE ADDITIVE DOSE-EFFECT RELATIONSHIP WITH THE SINGLE-HIT MODEL

Markus M. Kottbauer*, Carl M. Fleck*, Helmut Schöllnberger#
*Atomic Institute of the Austrian Universities, Stadionallee 2, A-1020 Vienna
#University of North Carolina, Chapel Hill, NC 27599-1105

Abstract

For solid tumors and for leukemia the excess cancer rate after a single radiation dose D is different. The multiplicative model describes the excess solid tumor probability rate which is proportional to the background rate of cancer and dependent on dose D. The additive model describes the excess probability rate for leukemia which is proportional to the dose D but unrelated to the spontaneous rate of cancer. A second great difference between the two models is the duration of the increased cancer probability rate. The multiplicative model predicts that the additional cancer risk persist the whole lifetime after exposure and the additive model predicts an excess risk over a period of time. With the Single-hit model (SHM) which is a multistage cancer model both dose-response relationships can be described. It will be shown that only small differences in the derivation will lead to the different relationships. We then analyze the incidence data of leukemia (1950-1987) and of all solid tumors (1958-1987) of the atomic bomb survivors.

1. THE MODEL FOR THE SPONTANEOUS CANCER RATE

The basis of both models is the multistage process of carcinogeneses which was already formulated by Armitage and Doll [1] and later in advanced form by Fleck et.al. [2]. This multistage cancer model supposes that at age t an individual has a population of $M_0(t)$ completely normal cells. In each of these cells are several DNA regions which are sensitive to the induction of cancer. These are for example the proto-oncogenes, tumor-suppressor genes, or normal cellular genes. B_i (i=0,1,...) is the number of these critical DNA bases (nucleotides) in critical codons of all tumor associated genes per cell which has undergone the i-th transformation. The healthy ($M_0(t)$) cells acquire one mutation at a rate $B_0M_0(t)P_S$. P_S is the mean spontaneous probability for a mutation per base. The generation and in consequence the number of existing cells with one mutation is also dependent on the mutation-rate of cells of the following stage $M_1(t)$. The cells with one mutation acquire a second mutation at a rate $B_1M_1(t)P_S$, and so on until full malignancy is reached.

$$\frac{dM_1(t)}{dt} = \left[B_0 M_0(t) - B_1 M_1(t)\right] P_s \tag{1}$$

Regarding the huge number of human cells and the fact that the probability of mutation is very low (otherwise all human would die soon after birth on cancer), we may assume that M_1 is several orders of magnitude smaller than M_0. In consequence the sink in Eq. (1) is negligible and $M_0(t)$ is constant. We get a model which predicts the spontaneous tumor incidence rate per 10^5 persons and per year proportional to t^{n-1}, where n is the number of mutations to become fully malignant [3]:

$$\boxed{c_1(t) = {}_1P_{sn}{}^n t^{n-1}} \tag{2}$$

with

$${}_1P_{Sn} = \left(10^5 \lambda_1 \frac{B_0 B_1 B_2 B_3 \ldots B_{n-1} M_0}{(n-1)!}\right)^{\frac{1}{n}} P_S \tag{3}$$

We consider the activity of the immune system with λ_1. This is the probability that a cell is not eliminated by the immuno surveillance ($\lambda_1 << 1$). For our calculations we assume a constant immune system activity over lifetime.

2. THE SINGLE-HIT MODEL FOR THE CANCER RISK AFTER A SINGLE RADIATION DOSE

At a certain age t_x, $M_{1be}(t_x)$[1] cells are in the 1st transformation step, $M_{2be}(t_x)$ cells are in the 2nd transformation step and so on. The radiation dose D leads to the transformation of ΔM_{01} cells from the 0th step into the 1st step. ΔM_{12} cells transforme from the 1st step into the 2nd step and so on. In theory cells can be transformed from each transformation step into the next or in one of the following steps.

$$M_{1be}(t_x) \xrightarrow{\text{exposure}} M_{1ae}(D,t_x) = M_{1be}(t_x) + \Delta M_{01}(D) = M_{1be}(t_x) + B_0 M_0 P_D \tag{4}$$

$$M_{2be}(t_x) \xrightarrow{\text{exposure}} M_{2ae}(D,t_x) = M_{2be}(t_x) + \Delta M_{12}(D,t_x) + \Delta M_{02}(D,t_x) \tag{5}$$

$$\text{with} \quad \Delta M_{12}(D,t_x) = B_1 M_{1be}(t_x) P_D = B_0 B_1 M_0 P_S P_D t_x \tag{6}$$

$$\Delta M_{02}(D,t_x) = B_0 B_1 M_0 P_D^2 \tag{7}$$

and so on.

The probability P_D that cells transform from a stage into the next one can be written as a linear quadratic dependence from dose D [3]:

$$P_D = \ell D + q D^2 \tag{8}$$

Previous research indicates that a single radiation dose of the magnitude of a few Grays causes only one mutation [3]. So we will only take into account the ΔM_{ij} transformed cells, where j:=i+1. After an exposure the generation rate of cells that reach the 1st transformation step is defined as:

$$\frac{dM_{1ae}(t)}{dt} = B_0 P_S M_0 - B_1 P_S^* \left(M_{1be}(t) + \Delta M_{01}(D) \right) \tag{9}$$

P_S^* is the mean spontaneous probability for a mutation per base after the first mutation. We assume the initial condition $M_{1be}(0)=0$. The condition of $M_{1ae}(t_x)$ is given in Eq. (4). The ΔM_{01} cells change the size of the sink in the differential equation. Provided that the sink of Eq. (9) ($B_1 P_S^* (M_{1be}(t)+\Delta M_{01}(D))$) *is nevertheless negligible* and $P_S \sim P_S^*$ we get:

$$\frac{dM_{nae}(t)}{dt} = B_0 \ldots B_{n-1} M_0 P_S{}^n \frac{t^{n-1}}{(n-1)!} + \Delta M_{01} B_1 \ldots B_{n-1} P_S{}^{n-1} \frac{(t-t_x)^{n-2}}{(n-2)!} + \\ + \Delta M_{12} B_2 \ldots B_{n-1} P_S{}^{n-2} \frac{(t-t_x)^{n-3}}{(n-3)!} + \ldots \tag{10}$$

In Eq. (10) is considered that the remaining transformations till full malignancy is reached, will be caused by the spontaneous mutation probability P_S. As it needs some time for the occurence of the remaining mutations there is a latency period between the time of exposure and the appearance of the excess probability rate. For the cancer incidence rate after exposure $c_{1\,ae}$ we get [3]:

$$\boxed{c_{1\,ae}(D,t) = c_1(t) + ec_1(D,t) = {}_1P_{sn}{}^n t^{n-1} + (n-1)\,{}_1P_{sn}{}^{n-1}\,{}_1P_{Dn}\,t^{n-2}} \tag{11}$$

$$\text{with} \quad {}_1P_{Dn} = \left(\frac{10^5 \lambda_1 B_0 \ldots B_{n-1} M_0}{(n-1)!} \right)^{\frac{1}{n}} P_D = {}_1\ell_n D + {}_1q_n D^2 \tag{12}$$

ec_1 is the excess cancer incidence rate. Note, that no age at time of exposure t_x occurs in Eq. (11), all terms that include t_x have been reduced. This relationship has validity for the **solid tumor rate following a single hit of radiation exposure** and it is called **Single-hit model for solid tumors**

[1] The index **be** means before exposure, **ae** means after exposure and t_x is the age at exposure.

(SHM-S). Eq. (11) is similiar to the multiplicative dose-effect relationship. The excess cancer rate ec_i contains the mutation probability $_iP_{sn}$ and the age t of the spontaneous cancer rate c_i just with reduced exponent. The proportional constants are the factor (n-1) and the dose-dependent mutation probability $_iP_{Dn}$. If we derived the SHM-S only with the consideration of ΔM_{01} cells and without ΔM_{12}, ΔM_{23} and so on, we would have to exchange t^{n-2} in Eq. (11) with $(t-t_x)^{n-2}$ and the similarity to the multiplicative model would be lost.

If $P_S^* >> P_S$, the sink of Eq. (9) is not negligible. In consequence the additional cancer rate after exposure again decreases after some time and we get an additive dose-effect relationship. Since $P_S^* >> P_S$ there are always only very few cells in higher transformation stages. This means ΔM_{12}, ΔM_{23} and so on are very small and we therefore assume that they are negligible. The dose-effect relationship for the **leukemia rate following a single hit of radiation exposure** becomes to:

$$\boxed{c_{i\,ae}(D,t,t_x) = c_i(t) + ec_i(D,t,t_x) = {}_iP_{sn}{}^n\, t^{n-1} + {}_iP_{Dn}\,(t-t_x)^{n-2}\, e^{-\nu(t-t_x)}} \qquad (13)$$

$$\text{with} \qquad {}_iP_{Dn} = \left(10^5 \lambda_i \frac{B_0 B_1 B_2 \ldots B_{n-1} M_0}{(n-2)!}\right)\left(P_s^*\right)^{n-1}\left(\ell D + q D^2\right) = {}_i\ell_n D + {}_iq_n D^2 \qquad (14)$$

Eq. (13) is called **Single-hit model for leukemia** (SHM-L) [4]. ν is a mean constant which takes into account that the total collective of additional cells in intermediate stages (caused by the radiation) will be decreased by the cells that reach the n-th transformation step and rendered harmless by the immuno surveillance. The constant ν is dependent by $B_0 \ldots B_{n-1}$ and P_S^*.

3. APPLICATION TO THE INCIDENCE DATA OF THE ATOMIC BOMB SURVIVORS

We restrict our analysis to age at exposure $t_x<60$ years and age $t<75$ years to avoid some of the uncertainties of diagnosis. In addition we only use classes with shielded kerma < 4 Gy. The spontaneous solid cancer incidence data [5] are stratified in 6 ATB (age at exposure) cohorts and 7 calendar-time cohorts. The dose-related solid cancer incidence data are stratified in 4 ATB cohorts, 5 calendar-time cohorts and 8 dose classes. The spontaneous leukemia incidence data [6] are stratified in 3 ATB cohorts and 5 calendar-time cohorts. The dose-related leukemia incidence data are stratified in 3 ATB cohorts, 5 calendar-time cohorts and 5 dose classes [4].

The solid cancer incidence data are related to the person-year weighted colon dose. The leukemia incidence data are related to the person-year weighted bone marrow dose. The fit of the spontaneous solid cancer incidence rate resulted in a mean number of 5 occuring mutations. The fit of the leukemia incidence rate yields in only 3 transmutation stages. The fit of the SHM-S to the dose related solid cancer incidence data was done with the values for n and $_iP_{Sn}$ from fit 2 and resulted in a best fit with an assumed linear-quadratic dose dependence (fit3). However, the fit with fixed $_iq_5:=0$ results in only a little larger sum of squared deviations. The fit of the SHM-L to the dose related leukemia incidence data was done with the values for n and $_iP_{Sn}$ from fit 6 and resulted in a best fit with an assumed linear-quadratic dose dependence (fit7). However, the fit with fixed $_i\ell_3:=0$ also yields a little larger sum of squared deviations. Fig. 1 and Fig. 2 show some fitted curves in relation to the observed cancer data.

Tab. 1 Best estimates, 95% confidence interval and the sum of squared deviations of the fits of the two models SHM-S and SHM-L to the atomic bomb survivor data. The regression analysis were done with Nonlin © which uses a combination of Gauss-Newton and Levenberg-Marquardt methods.

fit	tumor	equation	fit parameter	best fit	95% confidence interval	sum of squared deviations
1	spontaneous solid cancer	(2)	${}_iP_{Sn}$ n	0.151 a^{-1} 4.79	0.14 - 0.17 a^{-1} 4.57 - 5.00	49384
2	spontaneous solid cancer	(2)	${}_iP_{S5}$ n	0.137 a^{-1} 5	0.136 - 0.137 a^{-1} fix	55432
3	solid cancer	(11)	${}_i\ell_5$ ${}_iq_5$	1.150 Sv^{-1} 0.088 Sv^{-2}	0.30 - 2.00 Sv^{-1} -0.45 - 0.63 Sv^{-2}	7384815
4	solid cancer	(11)	${}_i\ell_5$	1.283 Sv^{-1}	1.06 - 1.50 Sv^{-1}	7392956
5	spontaneous leukemia	(2)	${}_iP_{Sn}$ n	0.178 a^{-1} 2.699	0.02 - 0.34 a^{-1} 1.64 - 3.76	76
6	spontaneous leukemia	(2)	${}_iP_{S3}$ n	0.140 a^{-1} 3	0.13 - 0.15 a^{-1} fix	79
7	leukemia	(13)	${}_i\ell_3$ ${}_iq_3$ ν	5.514 Sv^{-1} 27.15 Sv^{-2} 0.212 a^{-1}	-28 - 39 Sv^{-1} 11 - 44 Sv^{-2} 0.17 - 0.25 a^{-1}	76792
8	leukemia	(13)	${}_1q_3$ ν	29.47 Sv^{-2} 0.212 a^{-1}	18 - 41 Sv^{-2} 0.17 - 0.25 a^{-1}	76959

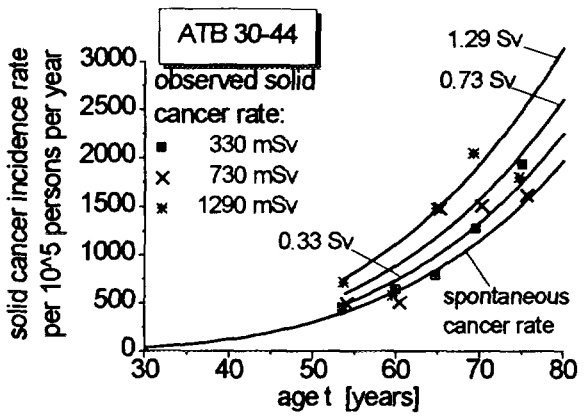

Fig.1 Observed and fitted solid cancer inc. rate of the bomb survivors with parameters from fit 3

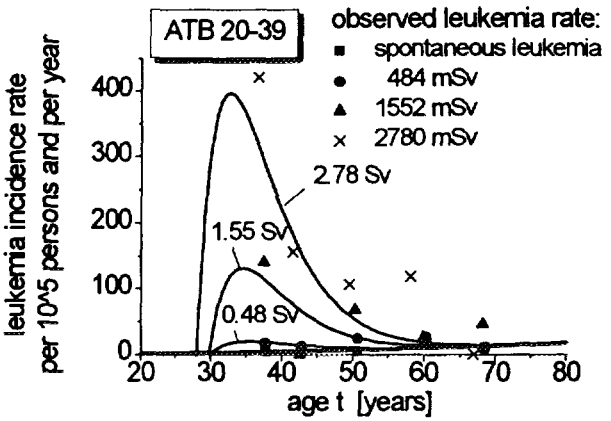

Fig.2 Observed and fitted leukemia incidence rate of the bomb survivors with parameters from fit 7

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MODULATION OF LOW DOSE RADIATION EFFECT ON PENTOSE PHOSPHATE PATHWAY ENZYMES BY B-MULTIVITAMIN DEFICIENCY

T.I Zimatkina, L K Lashak, A G Moiseenok
Institute of Biochemistry, National Academy of Sciences, Grodno 230017, Belarus

Abstract - Blood, liver, thymus and spleen of albino rats injected subcutaneously with antivitamins (othythiamine and methotrexate) and subjected to prolonged γ-irradiation in the overall dose of 0 75 Gy were assayed for transketolase and glucose-6-phosphate dehydrogenase after 12h, 1, 2, 5 and 40 days from the last radiation dose High transketolase sensitivity was found both to radiation (activation) and the combined effects of vitamin deficiency and radiation (potentiation of antivitamin inhibitory action) in all the tissues studied The activity of glucose-6-phosphate dehydrogenase was little changed under the given experimental manipulations, but the combined effect of the factors considerably inhibited the enzyme activities in the organs of the immune system Consequently, in B-multivitamin deficiency the effect of low radiation doses was subjected to a considerable modulation resulting in profound inhibition of the oxidative and nonoxidative branches of the pentose phosphate pathway

Alongside with intensification of different biochemical and physiological processes activation of reparative systems plays an important role in the structure of the adaptive response of cells and the whole organism to the action of low doses of ionizing radiation [1-3] The reparative systems are closely related to the production of pentoses required for synthesis of nucleic acids and nucleotides as well as reduced NADP forms utilized in biosynthetic reactions Only individual studies are available which do not enable us to evaluate the roles of the key enzymes of the pentose phosphate pathway in the formation of the adaptive response to the effect of low radiation doses combined with the accompanying multivitamin deficiency[4] The present paper describes the changes in the activities of glucose-6-phosphate dehydrogenase and transketolase in different organs and tissues of experimental animals subjected to long-term low-dose γ-irradiation in combination with vitamin deficiency producing factors Therefore the real situation of the Chernobyl accident regions was simulated [5]

Materials and Methods

In our experiments male albino rats weighing 160±10g were used which were subjected to long-term irradiation by γ-quanta of ^{60}Co (for 3 weeks, once a week, 0 25 Gy) combined with B-multivitamin deficiency induced by 3-fold administration of a devitaminizing agent containing oxythiamine and methotrexate The proportion of these antivitamins in the single dose of this agent was 200 and 1mg/kg (Agent 1) or 100 and 0 5 mg/kg, respectively (Agent 2) The results of our previous studies indicate that the application of this antivitamin combination enables to simulate not only deficiencies of thiamine and folic acid but also of other B group vitamins, in particular nicotinic and pantothenic acids deficiencies [6] Rats were decapitated after 12h, 1, 2, 5 and 40 days following the last irradiation dose Blood, liver, thymus and spleen were assayed for glucose-6-phosphate dehydrogenase [7] and transketolase [8]

The investigation of organ and tissue glucose-6-phosphate dehydrogenase, the basic enzyme of the pentose phosphate pathway oxidative branch, enabled us to reveal the presence of significant compared to control changes in enzyme activity (inhibition) only in the case of the combined effect of radiation and multivitamin deficiency on the body. The long persistence of the changes and their occurrence only in immune organs (Table 1) and rather low sensitivity of the enzyme to the effect of ionizing radiation and, especially, multivitamin deficiency should be noted. The radiation effect may be enhanced and considerable changes in glucose-6-phosphate dehydrogenase may occur under the action of low radiation doses combined with B group vitamin deficiency, which should be especially emphasized.

Table 1. Effect of low-dose irradiation and (or) multivitamin deficiency on the activities of glucose-6-phosphate dehydrogenase (nmole $NADPH_2$/mg tissue/min)in thymus and spleen of rats (Mean±SEM, n=6)

Experimental groups	Time after the last irradiation dose				
	12 hours	1 day	2 days	5 days	40 days
Thymus					
Control	3,6±0,2	3,6±0,2	3,7±0,3	3,7±0,2	3,6±0,1
Irradiation	3,8±0,2	3,6±0,5	3,8±0,2	3,8±0,2	2,7±0,2*
Agent 1	3,4±0,1	3,6±0,6	3,5±0,2	3,5±0,2	3,3±0,6
Agent 2	3,5±0,2	3,8±0,2	3,7±0,4	3,5±0,1	3,6±0,4
Irrad.+Agent 1	2,9±0,2*	3,3±0,2	2,8±0,3*	3,1±0,1*	2,9±0,1*
Irrad.+Agent 2	3,1±0,1*	3,2±0,2	2,8±0,1*	3,4±0,1	3,2±0,3
Spleen					
Control	13,2±0,8	13,2±0,8	13,9±0,8	13,5±1,3	13,7±0,9
Irradiation	13,6±0,5	14,0±0,5	15,9±1,1	13,7±0,9	11,0±0,8
Agent 1	12,1±0,5	14,9±0,7	16,0±0,9	12,7±1,2	11,6±0,7
Agent 2	12,3±0,4	16,0±1,7	16,6±0,9*	13,9±0,4	11,8±1,1
Irrad.+Agent 1	10,1±0,5*	14,1±0,6	15,2±1,1	9,5±0,9*	11,3±1,3
Irrad.+Agent 2	11,0±0,8*	14,9±0,6	15,4±0,7	10,9±0,5*	12,1±1,0

Note: coefficient of significance of differences ($P<0.05$) compared to control. No statistically significant changes were found in blood and liver.

The transketolase reaction is related to functioning of the nonoxidative branch of the carbohydrate conversion pentose phosphate pathway. The literature data indicate high sensitivity of this enzyme not only to thiamine deficiency but also to ionizing radiation [6, 9]. In this connection of special interest was to study the transketolase response to the combined effect of radiation and vitamin deficiency. Table 2 shows the dynamics of the changes in the activities of this enzyme in different animal organs and tissues. Attention is drawn to the principal and very significant differences in the responses of transketolase to the action of each of the factors or their combination studied. In the majority of cases radiation induced significant enzyme activation (Table 2) which was more pronounced in the radiosensitive blood, thymus and spleen compared to the liver. It may be suggested that alongside with glucose-6-phosphate dehydrogenase, the transketolase activation is an adaptive change directed to elimination of radiation consequences in the body. A different picture is characteristic of Agents 1-and 2-induced vitamin deficiency. The administration of these devitaminizing agents to animals strongly and dose dependently decreased the enzyme

activities, especially those in blood and thymus (up to 60%) which was even more pronounced during the combined effects of radiation and vitamin deficiency (Table 2).

Table2. Effect of low-dose irradiation and (or) B-multivitamin deficiency on the activities of transketolase (nmole sedoheptulose-7-phosphate μl blood or mg tissue/min) in thymus, spleen, blood and liver of rats (Mean±SEM, n=6).

Experimental groups	Time after the last irradiation dose				
	12 hours	1 day	2 days	5 days	40 days
Thymus					
Control	2,6±0,1	2,6±0,1	2,4±0,1	2,6±0,1	2,4±0,1
Irradiation	3,8±0,1*	2,9±0,1*	3,6±0,1*	3,1±0,1*	3,0±0,1*
Agent 1	1,3±0,1*	1,2±0,1*	1,5±0,1*	1,5±0,1*	1,9±0,1*
Agent 2	1,6±0,1*	1,6±0,1*	1,8±0,1*	2,0±0,1*	2,5±0,1
Irrad.+Agent 1	1,0±0,1*	1,1±0,1*	1,2±0,1*	1,1±0,1*	1,9±0,1*
Irrad.+Agent 2	1,8±0,1*	1,8±0,1*	1,7±0,1*	1,8±0,1*	2,3±0,1
Spleen					
Control	2,9±0,1	2,9±0,1	2,8±0,1	4,0±0,2	2,7±0,1
Irradiation	3,8±0,1*	3,7±0,2*	3,8±0,1*	3,9±0,1	3,1±0,1
Agent 1	1,8±0,1*	1,9±0,2*	1,9±0,1*	2,3±0,1*	2,5±0,1
Agent 2	2,3±0,1*	1,8±0,1*	2,0±0,1*	2,6±0,1*	2,6±0,1
Irrad.+Agent 1	1,8±0,1*	1,9±0,1*	1,6±0,1*	2,0±0,1*	2,1±0,1*
Irrad.+Agent 2	2,0±0,1*	2,2±0,1*	2,2±0,1*	3,0±0,1*	2,7±0,1
Blood					
Control	0,33±0,01	0,33±0,01	0,33±0,01	0,30±0,01	0,31±0,01
Irradiation	0,35±0,02	0,43±0,02*	0,38±0,01*	0,35±0,01*	0,29±0,01
Agent 1	0,12±0,01*	0,12±0,01*	0,12±0,01*	0,11±0,01*	0,32±0,01
Agent 2	0,18±0,01*	0,14±0,01*	0,11±0,01*	0,17±0,01*	0,29±0,01
Irrad.+Agent 1	0,11±0,01*	0,11±0,01*	0,11±0,01*	0,17±0,01*	0,31±0,01
Irrad.+Agent 2	0,19±0,01*	0,12±0,01*	0,11±0,01*	0,19±0,01*	0,30±0,01
Liver					
Control	4,8±0,2	4,8±0,2	6,0±0,2	5,9±0,1	5,9±0,2
Irradiation	5,0±0,2	8,6±0,3*	7,8±0,3	6,6±0,1*	5,6±0,2
Agent 1	3,3±0,2*	3,2±0,2*	3,0±0,1*	3,9±0,1	5,0±0,2
Agent 2	4,2±0,2	4,0±0,3	3,5±0,1*	4,0±0,2*	5,6±0,2
Irrad.+Agent 1	3,2±0,2*	3,0±0,2*	2,9±0,1*	3,6±0,2*	4,0±0,1*
Irrad.+Agent 2	3,7±0,1*	4,3±0,2*	3,9±0,1*	4,2±0,1*	5,5±0,1

Note: coefficient of significance of differences ($P<0,05$) compared to control.

The data presented show that transketolase manifested much more pronounced sensitivity to the effect of low radiation doses compared to glucose-6-phosphate dehydrogenase. The latter exerted the opposite in comparison with multivitamin deficiency effects on this enzyme. During the combined effect the vitamin deficiency very significantly changed the influence of radiation on transketolase. These alterations confirm the suggestion about the principal and very essential features of the body's response to the radiation effect whose character very much depends on the vitamin status of the body. The transketolase and glucose-6-phosphate dehydrogenase activities increased by low radiation doses suggest activation of the oxidative and nonoxidative branches of the pentose phosphate pathway and pronounced inhibition of its functioning in the case of multivitamin deficiency and combined

effect. Taking into consideration the exceptionally important role of glucose-6-phosphate dehydrogenase and transketolase as the pentose phosphate pathway key enzymes in the repair of radiation injuries, the marked inhibition of their activities after the combined effects of radiation and multivitamin deficiency should be considered as a very unfavorable factor for the body. Consequently, in estimating the nature of the radiation-related nonspecific adaptive response of biochemical systems one should proceed from the possibility of a strong modeling effect of B-multivitamin deficiency on the changes in the activities of the pentose phosphate pathway key enzymes.

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THE CONGENITAL DEVELOPMENTS IN DESCENDANTS OF LIQUDATORS AFTER 10 YEARS CHERNOBYL ACCIDENT

E.P. Guskov*, S.B. Berezhanskaya, , S.S. Amelina, M.Yu. Krynochkina, I..Spivak
Biological Research Institute of Rostov State University, Stachki 194/1, Russia,344090*; Obstetric & Pediatric Research Institute, Russian Federation, Ministry of Health Rostov-on-Don, Russia

Abstract

Despite much progress made in areas such as genetic toxicology or mutagenic epidemiology, much difficulty in biomedical sciences still remains to be overcome. Considerations needed and factors to be taken into account are addressed. Findings of investigations relating to liquidators and parameters to be analyzed are described.

During last decade of effort of the genetisists were directed on creation of methodological base of the analysis of influence of the various factors of an environment on genome somatical and germinal of tissues of the person and development of complex measures on protection of the genetic apparatus against mutagenic influence. In these years such sections of a science as genetic toxicology, toxicological of the genetisist, mutagenic epidemiology and etc. were created. However and on today's day the decision of delivered problems collides with problems, about which spoke J. Neel, 15 years ago specifying on almost insuperable difficulties for biomedical sciences and - first of all, on necessity of a correct estimation of influence on people of the radiating and chemical factors at drawing up epidemiological of the forecasts [1].

The certain successes, achieved for this time, have caused the whole number(line) of new problems, which today require development of the new methodological approaches to their sanction. In result of long-term researches as the conclusions the most essential to genetic epidemiology it is possible to consider following:

1. Majority of the physical and chemical factors in extreme dozes influencing on organism, are not in itself the agents, cooperating with a genetic material of cells. Their mutagenic properties, as a rule, will be realised through metabolism of cells and tissues of the organism.

2. There is the wide disorder inside populations on degree of individual stability to individual and complex influence of the factors of environment with potential mutagenic activity, which is determined, on the one hand, variety generically of determined peculiarities of metabolism, with other, ecological conditions, in particular(personally), specific character of a food ration.

3. The data, received in the "pure"("clean") experiments in vitro or on inbred animals, usually pursue the purpose to study gears of action of mutagen, and they cannot correctly be used for epidemiological of estimations of mutagenic The Chernobyl tragedy has highlighted one more important, for specialists in genetics and doctors epidemiological factor, the necessity of research of which today becomes dominant, for its consequences' while hard to predict and the gears of action are not so clear. The speech goes about psychotropic influence of radiophobia on the person, in particular on the level of somatical and germinal cells. The long - term monitoring of health of the participants of liquidation of consequences of breakdown at the Chernobyl nuclear power station ("Chernobyl liquidates"), has revealed no true radiation - induced diseases. At the same time nearly 90% of liquidators suffer

which were represented ,mainly, are submitted chromatids and chromosomes by breaks. A lot of data have been accumulated in literature evidencing that an emotional stress may be a powerful source of genome destabilisation. It has been shown that stress affect such parameters of genetic systems as change of frequency of chromosome recombination's, the level of reparation synthesis of DNA; and the stress will inhibit as replicative and reparative synthesis, increasing the rate of replication errors. Stress induces changes in the gormonal status of the organism which also results in mutagenous effects [2,3,4]. In view of all these facts throwing more light on aggravation of the consequences of the Chernobyl breakdown the focus of analysis must apparently be transferred from external to internal factors which require methodological approaches that would differ those that have been, and are still, used for estimating the genetic effects' of the 1986 catastrophe.

In 1995 at the Rostov Obstetric & Pediatric Research Institute preliminary information has been collected on the structure of congenital morfogenesis defects (CMDs) in the families of Chernobyl liquidators. Examination of 196 children from the liquidators' families has revealed high CMDs occurrence - about 37.7% . Although even in the control group CMDs occurrence significantly exceeded the data in literature for the human population on the average (12.6%), differences between our two groups are highly reliable. In both groups the leaders were CMDs of multifactorial etiology, however, in the examined group the proportion of CMDs of hereditary and nuclear etiology was substantially higher than in the control group. Among CMDs of hereditary etiology there were 2 cases for which there were good reasons to suspect appearance of a new mutation. With respect to localisation of CMDs in the organism, most frequent are CNS defects (27.9% us 5.8% in the control group), lesions of skin and skin appendages (20.9% and 5.8% respectively), and disturbances in the cardio-vascular system (16.2% us 14.7%). The fact may be purely coincidental yet the authors would like to point out that the largest number of CMDs were related with ontogenetic realisation of ectoderm which may be explained either by its polyvalent differentiation or by its high sensitivity to environmental influences.

It should be noted that mother's contribution to CMDs formation is rather high. Depending upon the obstetrico-gynecologic history, the families under study were split into three groups families' in which the obstetrico-gynecological histories were aggravated both before and after the husband's participation in Chernobyl breakdown liquidation works (30); those with aggravated histories only after the husband's work in the Chernobyl zone (19); and with no aggravations (147). We regret that the psychoemotional status of each mother was not estimated quantitatively, yet the influence of stress factors on occurrences of CMDs in children cannot be denied. Nevertheless, nearly twenty per cent of families with no aggravations in the obstetrico-gynecological histories (including gestosis) had children with CMDs' which permits to reveal the father-related hazard factor.

In the majority (156) of examined families husband suffered from chronic diseases after having worked in the Chernobyl zone. In this groups CMDs were found in 62 children, 10 of them having multiple CMDs. In 19 families husbands had microanomalies and microcharacters of hereditary diseases, in 8 of these 19 families there were indication that other relatives had CMDs. In the presence of CMDs in fathers occurrence of CMDs in children reached 84.2% which indicates a familial predisposition to CMDs.

These preliminary data give rise to the question, what is the cause of CMDs in liquidators' children? According to official in formation, the majority of them did not from aggravated forms of vegetovascular distonia, neurotic disorders, and somatic

receive radiation doses large enough to induce impairment of generative cells. Besides children born in a year or more after their fathers' return from the Chernobyl zone similarly have CMDs, and proportion of such children in liquidators ' families reliably does not decrease with time.

A number facts point at the leading role of internal mutagenous factors resulting from stress conditions in impairing the genetic system of generative cells. Immobilisation stress in mice of A/He and DD/J lines increases the rate of genic mutations in spermatogones' and embrionic death rate [5]. Emotional stress in mice induced by " open field" conditioning leads in males of the C57BL/6 line to higher rate of mutations in early spermatids lethal mutations. However, according to the data of the same authors the BALB/c line of mice has show remarkable resistance to this influence, which directly indicates the role of genetic control over the response of the nervous system to stress.

All this indicates that liquidators, even those who had worked in relatively "uncontaminated" zones, experienced stress which was no weaker than artificially modelled "open field" or immobilisation stress types. For this reason the mutation-forming process in them (if its presence will be demonstrated) must principally differ from the radiation-induced one. In this connection it is necessary to select criteria of individual resistance to emotional stress, which would allow to predict appearance of CDD-stricken descendants and to take preventive psychological and medicine measures.

It seems reasonable to delineate three main blocks of the following parameters:

- type of the nervous system;
- dominant cerebral hemisphere (and also right- or left- handiness)
- characteristics of EEG rhythms.

The second block - biochemical which includes analysis of the following parameters using non-invasive methods:

- lipids peroxidation level;
- level of enzymes providing antioxidation protection: SOD, catalase, peroxidase;
- total antioxidative status of the organism.

The third block - medico-genetic including analysis of:

- resistance of the genome to oxidants (e.g. hyperbaric oxygenation)
- congenital developmental defects.

This simplistic scheme requires further development yet it may prove useful as an initial method of selecting individuals capable of coping with extreme conditions with the least damage to their health and to the health of their descendants.

diseases of psychogenic etiology. The majority of examined patients; 8-9 year after their work in the breakdown area, had a high level of chromosome aberration

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Optimisation of Staff Protection

K Faulkner
NW Marshall
DJ Rawlings
Regional Medical Physics Department
Newcastle General Hospital
Newcastle upon Tyne, United Kingdom

ABSTRACT It is important to minimise the radiation dose received by staff, but it is particularly important in interventional radiology. Staff doses may be reduced by minimising the fluoroscopic screening time and number of images, compatible with the clinical objective of the procedure. Staff may also move to different positions in the room in an attempt to reduce doses Finally, staff should wear appropriate protective clothing to reduce their occupational doses. This paper will concentrate on the optimisation of personal shielding in interventional radiology. The effect of changing the lead equivalence of various protective devices on effective dose to staff has been studied by modeling the exposure of staff to realistic scattered radiation Both overcouch x-ray tube/undercouch image intensifier and overcouch image intensifier/undercouch x-ray tube geometries were simulated. It was deduced from this simulation that increasing the lead apron thickness from 0.35mm lead to 0.5mm lead had only a small reducing effect. By contrast, wearing a lead rubber thyroid shield or face mask is a superior means of reducing the effective dose to staff. Standing back from the couch when the x-ray tube is emitting radiation is another good method of reducing doses, being better than exchanging a 0 35mm lead apron for a 0 5mm apron In summary, it is always preferable to shield more organs than to increase the thickness of the lead apron.

1.0 Introduction

It is always important to minimise radiation dose levels received by members of staff working in radiology departments. Staff dose minimisation is particularly important in interventional radiology as these procedures generally involve higher radiation doses to both patients and staff than general radiography or fluoroscopy. These higher doses arise, in the main, from the extended fluoroscopy times and greater number of radiographic images acquired during these procedures. Recently, there have been several cases of patients receiving deterministic effects, such as radiation burns and ulcers, reported in the published literature (1,2).

In recent years interventional radiology has become more prevalent, as the improvements in health care associated with these procedures have become widely appreciated. Moreover, developments in interventional radiology continue a pace, with more complicated procedures being investigated at the present time. There is increasing concern about radiation doses to staff. This concern relates to the risk of both deterministic and non deterministic effects The annual review of radiation doses received by classified radiation workers in the United Kingdom reveals that only one individual received a whole body dose in excess of 15mSv, somewhat less than the annual dose limit (3).

Another group of staff working in radiology departments whose radiation dose is of concern is pregnant staff. The recommendation by the International Commission on Radiological

Protection (4) that the foetus should be protected by a supplementary dose limit of 2mSv to the surface of the abdomen once pregnancy has been declared results in both a monitoring and operational problem. Accurately monitoring dose levels as low as those implied by the limit in diagnostic radiology. There are two principal operational problems. First, in certain circumstances the dose limit could be exceeded even for relatively low interventional radiology workloads. Second, both the film badge and thermoluminescent dosemeters do not give an instantaneous indication of dose received. Thus the wearer of the dosemeter may not realise that the limit has been exceeded until sometime after they have received the dose.

2.0 Reduction of staff doses

In interventional radiology it is necessary for the interventionalist to be able to manipulate catheters and other devices. This requirement means that the interventionalist must stand at the couchside during interventional procedures and have unimpeded access to the patient. It is therefore impractical to attach lead rubber protection from the image intensifier as a means of reducing occupational exposures as would be the norm on equipment designed for barium studies. As a consequence scattered dose rates at the couch side are higher than on fluoroscopy equipment designed for barium studies. Thus not only do interventional procedures involve longer fluoroscopy times, scattered dose rates in the vicinity of the couch are higher for the same technique factors. The combination of long fluoroscopy times and the lack of shielding attached to the fluoroscopy equipment leads to higher occupational doses in interventional radiology.

Moreover patients undergoing interventional radiology procedures tend to require more staff in the room for clinical support. Thus other doctors such as anaesthetists and nursing staff may also be present during a procedure. In the main these staff groups are unaware of radiation protection measures and have to be taught the basic principles of radiation protection.

In view of the high occupational dose levels it is important to ensure that staff are monitored adequately. Interventionalists and others who stand at the couchside should be provided with one or more dosemeters to wear. One dosemeter, generally worn at the waist level under a lead apron, will be issued to monitor whole body or effective dose. In some countries whole body dose is monitored using a dosemeter at collar level worn above the lead apron. Staff may also be issued with additional dosemeters to assess the equivalent dose to critical organs such as the eyes or hands. Hand dose may be monitored using small thermoluminescent dosemeters worn under rubber gloves.

Unfortunately, wearing a single dosemeter does not give a good indication of effective dose(5). A combination of two dosemeter readings, one above the apron and one below will yield an improved estimate of effective dose (6,7).

Local action levels are a useful means of limiting staff doses in interventional radiology. Dosemeter readings in excess of the values given in table 1 would be investigated. The reason for the higher than usual dosemeter reading should be established and action taken to minimize the individual's dose. As may be deduced from table 1, these action levels are set some way below the levels at which the individual would be classified. These action levels serve to identify individuals who may receive higher than normal doses and enable the radiation protection service to implement an action plan to reduce staff doses. This action plan could involve staff training or a review of protective measures. The use of local action levels serves as a constraint on occupational exposures. They are not dose constraints in the true meaning of the definition given by ICRP (4).

Scattered radiation dose-rates at the couchside during fluoroscopy procedures can be quite high (8). However, dose-rates decrease rapidly with increasing distance away from the couch, approximately obeying an inverse square law with the reference point being the centre of the field on the patient. Taking one step back from the couch can have a dramatic effect on the radiation dose to the individual.

Radiation doses to staff working with fluoroscopy equipment have been simulated for both undercouch x-ray tube/ overcouch image intensifier and overcouch x-ray tube/undercouch image intensifier equipment configurations (9). In this study, a patient equivalent phantom was placed on the couch and irradiated using x-ray beams generated at tube potentials of 70, 90 and 110 kV to produce scattered radiation. An anthropomorphic phantom loaded with lithium fluoride thermoluminescent dosemeters was placed adjacent to the couch at the position where the radiologist stands during fluoroscopy. Organ doses in the phantom were measured, from which effective dose was calculated. Transmission data (10) were used to deduce the effect of a lead apron on effective dose. In addition, the effect of a thyroid collar and face mask was simulated.

The impact of wearing a lead apron, a lead apron and thyroid shield and a lead apron and face mask is summarised elsewhere (9). Effective dose decreases with increasing lead apron thickness reaching an asymptote near 0.35mm lead. Wearing extra protection in the form of a face mask or a thyroid shield always reduces the effective dose to an individual wearing a 0.35mm lead apron by a greater amount than exchanging a 0.35mm lead apron for a 0.5mm one.

3.0 Conclusions

Patient and staff doses from interventional procedures can be quite high. It is important that these potentially high radiation doses are minimized. Both patient and staff may be at risk of both deterministic and non-deterministic effects. Staff doses can be reduced by a number of relatively simple methods. It is worth noting that, in general, most of the methods of reducing patient doses will also reduce staff doses. Interventionalists are recommended to consider applying these dose reduction measures in their clinical practice. They will thereby significantly reduce their radiation dose and the dose received by their colleagues.

Table 1 Suggested action levels for staff dosimetry results (10)

Monitor Position	Period worn (weeks)	Action level (mSv)
Body	4	0.5
Eyes	4	5
Extremities	4	15

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The Impact of Regulatory Control on Monitoring of Pregnant Hospital Staff In Diagnostic Radiology

K Faulkner
DJ Rawlings
NW Marshall

Regional Medical Physics Department
Newcastle General Hospital
Newcastle upon Tyne NE4 6BE
United Kingdom

Abstract

In 1990, the International Commission on Radiological Protection recommended the introduction of a supplementary dose limit for pregnant staff so that the foetus was adequately protected. This dose limit was framed in terms of an abdomen surface dose of 2 mSv for the duration of the pregnancy, once it had been declared. The philosophical basis underlying this supplementary dose limit was the desire to treat the foetus as a member of the public in respect of the occupational exposure of the mother. In the Basic Safety Standards, the International Atomic Energy Agency endorsed the need to limit the foetal dose, but in this document the dose limit refers to the foetus. The introduction of dose limits for foetal exposure to radiation has significant implications for hospitals as many workers are women of child bearing age. The practical implications of this dose limit will be discussed as well as suggested monitoring arrangements.

1. Introduction

In report 60, the International Commission on Radiological Protection (1) recommended the introduction of a supplementary dose limit to protect the foetus of pregnant workers. The recommended dose limit was 2 mSv to the surface of the abdomen for the remainder of the pregnancy, once pregnancy has been declared. The intention of this supplementary dose limit is to treat the foetus as a member of the public and to limit the dose accordingly.

In the Basic Safety Standards (2), the International Atomic Energy Agency endorsed the need to limit the dose to the foetus of pregnant staff.

Many occupationally exposed members of hospital staff are women of child bearing age. The implications of new supplementary dose limits for pregnant staff has been the subject of some scientific articles (3), however many of the practical applications have not been discussed. The objectives of this paper are to:-

1) review dose levels to occupationally exposed staff
2) to assess the practical implications
3) to suggest appropriate monitoring arrangements

2. Exposures In Diagnostic Radiology

In general, radiation dose levels received by members of staff who are occupationally exposed are relatively low, typically being in the range 0-3 mSv (4) in diagnostic radiology.

These relatively low levels of radiation dose reflect good radiation protection practices. However, there are a group of procedures in interventional radiology in which it is possible to approach the supplementary dose limits for pregnant staff for a realistic number of patient studies. Thus there is a potential monitoring problem for radiologists, radiographers, nurses and clinical staff associated with high dose interventional procedures.

3. Materials and Methods

Scattered radiation conditions typical of those encountered in fluoroscopy were simulated for primary x-ray beams generated at 70,90 and 110 kV. In abdomen phantom (3M, Minnesota, USA) was placed on a patient couch and irradiated with a primary beam. The field size of the primary beam was 20 x 20 cm measured on the entrance surface. A focus skin distance (FSD) of 1m was used for the simulation of an overcouch x-ray tube/undercouch image intensifier geometry, whilst an FSD of 0.45 m was used for an undercouch x-ray tube/overcouch image intensifier geometry.

A staff member standing at the couch side was represented by a Rando anthropomorphic phantom (Alderson Research Laboratories, Stamford, USA). Seventeen lithium fluoride thermoluminescent dosemeter chips were used to measure uterus dose. A further 20 dosemeters were used for background and calibration purposes. The equivalent dose to the uterus was determined from the mean of the dosemeter readings, after applying an energy dependent correction factor and subtracting the background reading.

Film badges supplied by the Regional Medical Physics Department's Approved Dosimetry Laboratory were attached to the Rando phantom at waist level. For each irradiation condition two dosemeters (left and right) were used. The waist level film badge dosemeter reading was the mean of the two individual results.

Extended fluoroscopy times were used to irradiate the anthropomorphic phantom loaded with thermoluminescent dosemeters. This ensured that the dosemeter readings were above background.

Uterus dose and film badge dosemeter readings when a lead apron is worn were estimated from the unshielded results. A transmission factor for the attenuation of scattered radiation through lead was applied. The transmission factor was deduced from previously published data (5).

Direct irradiation of staff in diagnostic radiology was also simulated. The Rando phantom leaded with lithium fluoride dosemeters was irradiated in a primary beam. Three tube potentials were investigated (70,90, 110 kV). Protective aprons, either 0.25 mm or 0.33 mm lead equivalent were used to shield the phantom. The unshielded case was also simulated.

4. Results

Table 1 gives the ratio of uterus equivalent dose to waist level film badge dosemeter reading at three tube potentials for scattered radiation from both an overcouch x-ray tube/undercouch image intensifier and an overcouch image intensifier/undercouch x-ray tube geometry. Table 2 summarises the results for direct irradiation in diagnostic radiology.

5. Discussion

It may be deduced from table 1 that the ratio of uterus equivalent dose to film badge dosemeter reading are dependent on irradiation conditions. However, in all instances studied this ratio is 0.3 or lower. This implies that the uterus dose is less than or equal to 30% of the dose monitored by the film badge. This accumulating a dose of 2 mSv on a film badge dosemeter, would equate to a dose of 0.6 mSv at most to the foetus. The application of a 2 mSv

abdomen dose limit will therefore adequately protect the foetus from scattered radiation in diagnostic radiology.

For primary radiation the ratio of uterus dose to film badge dosemeter reading lie in the range 0.2 - 0.55. This implies that for some irradiation conditions, the foetus could receive a dose greater than 1 mSv, for an accumulated dosemeter reading of 2mSv. The direct irradiation of staff in diagnostic radiology should only occur as a result of an accidental exposure. Fortunately, this is relatively unlikely to occur.

In interventional radiology, it is possible to exceed the abdomen dose limit for a relatively low number of procedures. Extrapolating from previous work (7), indicates that a cardiologist need only perform 22 cardiac catheterisations to exceed the limit, and a nurse only 66.

Suggested Monitoring Scheme

1) Staff working in diagnostic radiology, particularly interventional radiology, should a dosemeter at waist level. This dosemeter overestimates foetal dose, so ensuring that the accumulated dosemeter reading does not exceed 2 mSv will ensure that the foetal dose does not exceed 7 mSv.
2) Use of electronic dosemeters to monitor stuff in interventional radiology is recommended.

Table 1

Ratio of the Uterus Equivalent Dose to Waist Level Dosemeter Reading (film Badge) at three Tube Potentials (70,90,110 kv) for scattered radiation from an Undercouch X-ray Tube/ Overcouch Image Intensifier and Overcouch X-ray tube/Undercouch Image Intensifier Equipment.

		Lead Apron Thickness (mm lead)		
	Tube Potential	0	0.2	0.3
Overcouch	70	0.08	0.08	0.08
x-ray tube	90	0.14	0.14	0.14
	110	0.18	0.18	0.18
Undercouch	70	0.18	0.18	0.18
x-ray tube	90	0.29	0.29	0.29
	110	0.30	0.30	0.30

Table 2

Ratio of Uterus Equivalent Dose to Waist Level Dosemeter Reading (film badge) for Primary Irradiation

	Lead Apron Thickness (mm lead)		
Tube Potential	0	0.25	0.33
70	0.25	0.50	0.55
90	0.21	0.46	0.53
110	0.20	0.43	0.47

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An Assessment of Effective Dose to Staff in External Beam Radiotherapy

DJ Rawlings, and L Nicholson, Regional Medical Physics Department, Newcastle General Hospital, Westgate Road, Newcastle-upon-Tyne, NE4 6BE

Abstract

Radiation safety in external beam radiotherapy is governed by national legislation. Annual doses recorded by radiographers and others associated with external beam radiotherapy are typically much lower than the relevant dose limit. However, it is posssible that larger doses might be received as a result of an accidental irradiation. In the event of a significant exposure resulting in a dose at or near a relevant dose limit, an accurate conversion has to be made from the dose meter reading to the limiting quantity. A method was devised to demonstrate ratios of effective dose to personal dose equivalent which might be anticipated in the event of an individual other than the patient being irradiated within a radiotherapy treatment room consisting of a linear accelerator. The variation of ratios obtained under different conditions is discussed.

Introduction

Radiation safety in external beam radiotherapy, as in other practices involving ionising radiation is governed by national legislation which is largely derived from publication 26 of the International Commission on Radiological Protection (ICRP)[1]. In the UK, this resulted in the publication of The Ionising Radiations Regulations 1985 (IRR85)[2] and the associated Guidance Notes[3] and Approved Code of Practice[4] Since then, ICRP have introduced publication 60[5]. Although not yet fully translated into UK law, aspects of this are largely observed.

The Guidance Notes[3] specify that external beam radiotherapy must be carried out in a room with structural shielding providing adequate protection to all persons outside the room. The doors to the treatment room are then normally designated as the boundary to the radiation controlled area. The Approved Code of Practice[4] specifies that no person may enter a controlled area unless that individual is a classified person or is operating under a suitable system of work. All individuals, other than the patient, entering a radiotherapy treatment room are in general subject to personal monitoring, often through integrating dosemeters.

It is further specified[3] that all persons except the patient should normally be outside the room during a treatment, but that very occasionally and for compelling clinical reasons it may be necessary for a further person to be within the room during the time the beam operates. Such a person should wear a direct reading personal dosemeter.

It has been shown[6] that annual doses recorded by radiographers and others associated with external beam radiotherapy are typically much lower than the relevant dose limit. However, it is possible that larger doses might be received, perhaps as a result of an accidental irradiation of an individual remaining in the room with the beam having been switched on.

While any personal dosemeter should be calibrated to indicate the quantity personal dose equivalent[7], a personal dosimetry service is required to report a 'reasonable estimate' of the

relevant limiting quantity, either effective dose, effective dose equivalent or organ dose equivalent[2]. In the event of a significant exposure resulting in a dose at or near a relevant dose limit, the service would have to make an accurate conversion from the dose meter reading to the limiting quantity. Published conversion factors exist[8], which cover the radiation quantities involved, but it is assumed that the radiation field is isotropic, parallel and monoenergetic. None of these features apply in practice in the case of an individual subject to scatter and leakage radiation from a linear accelerator.

The following was devised, therefore, to demonstrate ratios of effective dose to personal dose equivalent which might be anticipated in the event of an individual other than the patient being irradiated within a radiotherapy treatment room consisting of a linear accelerator.

Method Radiotherapy treatment using a linear accelerator is carried out over a wide range of conditions in a variety of different treatment rooms yielding a large range of conditions for room scatter and head leakage. All such variables will have an influence on the conversion factor to effective dose. The position of the dosemeter on the body will also be an influence factor. In order to simplify the task, a relatively small number of conditions regarded as most likely to occur were selected.

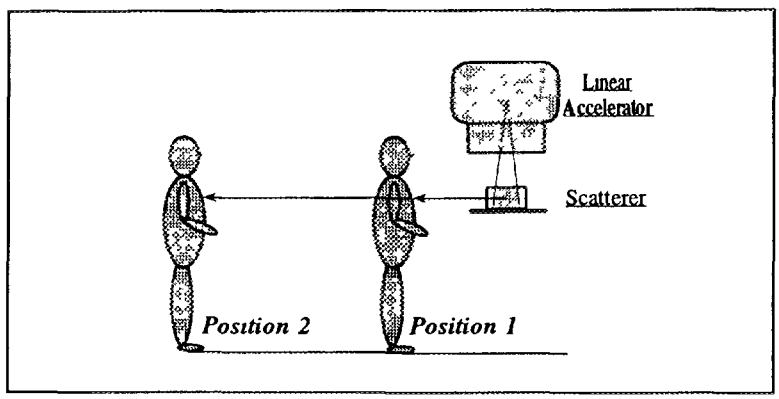

Figure 1

Organ	W_T
Gonads	0.20
Red Bone Marrow	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Oesophagus	0.05
Thyroid	0.05
Skin	0.01
Bone Surfaces	0.01
Remainder	0.05

Figure 2

Two positions within the room were selected to model the irradiation of the individual. One of these, position 1 on figure 1 simulated an individual standing position close to the side of the patient as if performing a patient procedure at the time of the irradiation. The other, position 2 on figure 1 simulated an individual further from the patient, and closer to the entrance maze. In both cases, the primary beam was vertical and the individual was simulated directly facing the patient. Couch height was adjusted such that the source of scatter (ie the simulated patient) was at the same height as the centre of the chest of the anthropomorphic phantom. The standing height of the phantom (both male and female) was 173.5cm. The source of head leakage radiation was approximately 2.5m above the floor. One radiation quality, a generating voltage of 8MV, was selected for modelling, being typical of clinical practice. Field sizes at the simulated patient representing the smallest (0.5x1cm) and largest (20x20cm) possible were selected. These sizes spanned the range of possible combinations of leakage and scatter radiation. Two phantoms were used. One of these simulated the patient and simply consisted of a rectangular block of commercial tissue equivalent material, WT1 (Radiation Physics Department, St Bartholomew's Hospital), 25cm square by 11cm deep set up on the central axis of the machine with an isocentric depth of 5cm and a focal-surface distance of 95cm, according to local procedure. An anthropomorphic phantom was used to

simulate the irradiated member of staff. Both male and female versions were used. The phantoms had been designed to represent ICRP standard man (or woman) in both physical and radiation characteristics. They allow the placement of suitably calibrated thermoluminescent dosemeters (TLD-100, LiF:Mg:Ti) at appropriate positions in order to estimate a range of individual organ doses for the various irradiation conditions. The loading scheme for TLD within the various organs of the male phantom has been described previously[9,10]. The loading scheme for the female phantom was adapted from that of the male by reference to a CT atlas[11]. Doses to skin, red bone marrow and remainder organs were found using a method described by Huda and Sandison[12]. Effective dose was estimated from individual organ dose using organ weighting factors recommended by the ICRP[5] (Figure 2). Bicron-NE[13] whole body personal TLD dosemeters were also attached at appropriate points to the front surfaces of the anthropomorphic phantoms, enabling an estimate of the ratio effective dose to personal dose equivalent to be made.

No	Phantom	Field Type	Isocentre to chest wall (cm)	Shoulder Ratio	Chest Ratio	Waist Ratio
1	Male	Leakage	41	0.193	0.559	1.199
2	Male	Leakage +Scatter	41	2.686	1.591	0.850
3	Female	Leakage +Scatter	41	0.825	0.437	0.394
4	Female	Leakage +Scatter	241	1.286	1.082	0.940

Figure 3

Results Four irradiations were carried out, simulating the conditions selected. In each case the linear accelerator was operated for suitable period such that the radiation dose to the dosemeters on the surface of the anthropomorphic phantom was within the range 10-100mSv. Irradiation conditions are summarised in figure 3. Uncertainties on individual TLD results, estimated according to a method previously described[14], were in the range 6-12% at the 95% confidence interval. Values of the ratio of effective dose to personal dose equivalent were obtained for each irradiation and for each of three positions on the anthropomorphic phantom for placement of the personal monitor. Values of these ratios are shown in figure 3 . A ratio of greater than 1 means that the personal dosemeter is underestimating the effective dose.

Discussion The results show the largest variation in ratio for a personal dosemeter placed at the shoulder. This position is therefore the least reliable for personal monitoring purposes, since it appears to be unrepresentative of organ doses within the trunk. Ratios at position 4, which is some distance from the sources of scatter and leakage are close to unity, particularly at chest and waist positions. This result which is in broad agreement with previous work[8] using isotropic parallel beams, and indicates that for an individual some distance from the patient, but facing the source of scatter at the time of the exposure, a personal monitor when worn at the waist or chest is a good indicator of effective dose. For positions 1-3, ratios are more variable. In this situation, close to the source of both scatter and head leakage, there are considerable variations in dose between different parts of the body. For example, the

waist badge overestimates effective dose when the radiation is dominated by scatter, but underestimates the effective dose when the radiation is predominately leakage which would be directed obliquely downwards. For all irradiation conditions measured, it may be seen that a personal monitor worn at either chest or waist will estimate effective dose to within +/-60%. It may be seen that results for irradiation 2 and 3 differ significantly. The only difference between these two is the gender of the phantom. An analysis of individual organ dose contributions to effective dose indicated that differences between irradiation 2 and irradiation 3 were dominated by gonad and breast components, both of which are relatively superficial organs. It may be postulated, therefore, that despite the penetrating nature of the radiation, some soft components exist within the near leakage and scatter field which may contribute to the dose distribution in an irradiated individual standing close to the treatment couch.

Conclusions

1 For the irradiation conditions studied here, a personal monitor worn at the chest or waist gives a good (+/-10%) indication of effective dose to a person some distance (~2.4m) from a radiotherapy treatment couch irradiated by scatter and leakage radiation.

2 For a person standing close (~41cm) to the source of scatter or leakage at the time of irradiation, the personal monitor is a less reliable indicator of effective dose, and may be in error by +/-60%.

3 In the event of an incident resulting in an apparent dose to a employee or member of the public close to a dose limit, it may be appropriate to measure retrospectively a conversion factor appropriate to the prevailing irradiation conditions.

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CORRECTION OF GLUTATHIONE METABOLISM IN THE LIVER OF ALBINO RATS AFFECTED BY LOW RADIATION DOSES

A.G. Moiseenok, V.S. Slyshenkov, T.I. Khomich, T.I. Zimatkina, N.P. Kanunnikova
Institute of Biochemistry, NAS, 230017, Grodno, Belarus

Abstract - The levels of total glutathione GSH, GSSG and the activities of glutathione reductase and glutathione peroxidase were studied in the liver of adult albino rats subjected to 3-fold external γ-irradiation throughout 2 weeks at the overall dose of 0.75 Gy after 15 h, 2 and 5 days from the last irradiation. Some animals were injected intraperitoneally with the pantothenate containing complex «pankar» 3 times on days 1-3 before the irradiation. The radiation related decrease of GSH, GSH/GSSG and the total glutathione level was prevented by the prophylactic administration of the complex and probably at the expense of the activation of the G-SH biosynthesis and/or transport in the liver by the CoA biosynthetic precursor.

Glutathione-SH (GSH) and its metabolic enzymes play a key role in formation of cell effect under conditions of radiation [1-3]. The significance of this component of protection against free radicals is also evident in irradiating biological objects by low doses. The situation is similar to that observed on the territory of the regions of Belarus suffered from the Chernobyl accident [4]. Search for the ways of the GSH system metabolic correction under conditions of radiation effect is an important element of maintaining homeostasis and prevention of consequences of the radiation factor. In previous works [5-6] we showed that initiation of lipid peroxidation can be prevented by using such nonantioxidative factor as pantothenic acid.

Further studies showed that the biochemical mechanism of the above effect is enhanced CoA biosynthesis and increased GSH intracellular level [6-8]. In the present work we studied the efficiency of the pantothenate-containing complex «pankar» in prevention of disturbances in glutathione metabolism in the liver of albino rats subjected to prolonged effect of γ-irradiation at the overall dose of 0.75 Gy.

Materials and Methods

Albino heterogeneous stock rats weighing 160±10 g were used which were irradiated with γ-quanta at a dose of 0.25 Gy at a power of 0.00792 Gy/sec (overall dose was 0.75 Gy). One group of animals received as intraperitoneal injections the original provitamin complex «pankar» including panthenol (D(-)-panthenol, the substance was a generous gift of Hoffmann-La-Roche, Switzerland). After 15 h, 2 and 5 days following the last injection the liver homogenized in ice-cold sucrose medium (0.25 sucrose in 10 mM Tris buffer and 1 mM EDTA and 0.1% Triton X- 100, pH 7.4) was used. The resulting homogenate was centrifuged at 8000 g for 5 min and applied for the enzyme assay: glutathione peroxidase (GP) and glutathione reductase (GR) were assayed at 37°C. The units of enzyme activity were calculated using a millimolar extinction coefficient of 6.22 $mM^{-1} \cdot cm^{-1}$ for NADPH [9, 10]. GSH and GSSG were assayed enzymatically [11] and by a reaction with dinitrobenzoic acid [12]. The total levels of glutathione and GSH/GSSG ratio were calculated from the data of analytical determination of oxidized and reduced glutathione.

Results and Discussion

The experimental results presented in Table 1 show that the level of liver GSH tended to decrease throughout all the three observation periods following the irradiation of the experimental animals. The most significant decrease of the parameter (by 28.2%) was found by the 15th h following the last irradiation. The GSSG level was simultaneously increased by over 2.5 - fold. The most evident cause for the above effects is radiation-induced formation of free radicals and consumption of GSH for their detoxication [13], which is confirmed by the glutathione peroxidase activation observed. The process of GSH regeneration from GSSG in the glutathione reductase reaction does not provide for homeostasis of the glutathione system under these conditions, moreover, by the 48th h of the experiment the enzyme activity turned out to be decreased by 29.6% (see Table 1). In addition, by the 15th h the total glutathione (GSH+GSSG) level was significantly decreased (by 21.8%), which suggests accompanying disturbance in the processes of biosynthesis or transport of the tripeptide in the cell [14].

The pantothenate-containing complex used by us as a prophylactic turned out to be extremely effective in prevention of all the above changes occurring in the system of liver glutathione during the long-term action of γ-irradiation. The exception was the retaining activity of glutathione peroxidase (see Table 1). The facts of the complete GSH/GSSG ratio reduction throughout the experimental period and the considerable increase of this parameter observed at the crucial period (judging from the decreased glutathione reductase activity) after 48 h following the last irradiation of the experimental animals should be especially emphasized. (see Fig. I). It is within this period that significant increases of both the levels of GSH and the total glutathione above the normal values were found (see Table 1). It may be suggested that the mechanism of realization of the pantothenate-containing complex protective effect was stimulation of GSH biosynthesis and/or transport into hepatocytes.

Table 1. Activities of glutathione reductase (NADPH/min·mg protein), glutathione peroxidase (μmol GSH/min·mg protein) and glutathione level (μmol/g tissue) in the liver of control (1), irradiated (2) and protector complex-treated rats (3)

Parameters, experimental period	1	2	3
	15 hours		
GR	37.98±4.31	39.30±1.18	34.00±2.45
GP	6.07±0.46	8.06±0.11*	8.29±0.17*
GSH	5.05±0.07	3.60±0.108*	4.97±0.11$^{@}$
GSSG	0.20±0.02	0.54±0.05*	0.22±0.03$^{@}$
GSH+GSSG	5.27±0.06	4.12±0.09*	5.20±0.08$^{@}$
	2 days		
GR	31.45±1.21	22.10±1.39*	29.87±0.35$^{@}$
GSH	5.25±0.32	4.36±0.26*	6.63±0.48*$^{@}$
GSSG	0.19±0.01	0.56±0.03*	0.16±0.01$^{@}$
GSH+GSSG	5.47±0.29	4.92±0.28	6.70±0.36*$^{@}$
	5 days		
GR	31.15±1.15	28.03±2.10	31.02±1.44
GSH	5.25±0.32	4.16±0.36*	5.48±0.27$^{@}$
GSSG	0.19±0.01	0.52±0.05*	0.20±0.02$^{@}$
GSH+GSSG	5.47±0.29	4.70±0.30	5.60±0.21

Note: coefficient of significance of differences ($P<0.05$) compared to Group 1*, Group 2 – $^{@}$

As is known in the liver pantothenic acid is rapidly transformed to CoA [15], with 40% of the cellular pool being formed by symmetric and mixed with glutathione disulfide.

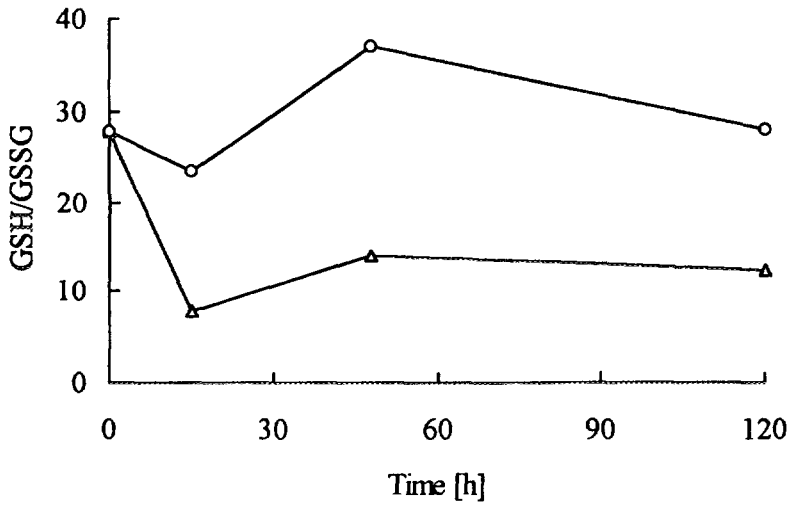

Fig. I. Time course of GSH/GSSG in irradiated (Δ—Δ) and protective complex-treated animals (o—o). GSH/GSSG control ratio – 27.82±1.82

The latter was found in the liver in the amount of 36-41 nmol/g [16] and plays an important role in regulation of the activity of the key enzyme of CoA biosynthesis – pantothenate kinase [17]. This fraction of glutathione disulfides contributes insignificantly to its overall metabolism and realization of the activities of pantothenate-containing compounds during radiation. The effect of pantothenates on the transport system of GSH and its conjugates should be considered to be more realistic, which has already been confirmed by the experimental model of oxidative damage of erythrocyte membranes [18].

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IMPLEMENTACION DE NUEVO REGLAMENTO DE SEGURIDAD RADIOLOGICA EN EL PERU

MEDINA GIRONZINI, Eduardo
Sociedad Peruana de Radioprotección
Instituto Peruano de Energía Nuclear
Casilla Postal 18-0260. Lima, Perú

RESUMEN

Desde su creación en 1975, el Instituto Peruano de Energía Nuclear (IPEN) ha generado 3 reglamentos de alcance nacional donde se establecen las normas de protección contra las radiaciones ionizantes. El primero de ellos, denominado Reglamento de Protección Radiológica (1980) fue aprobado mediante una resolución del IPEN y surgió del trabajo de un Comité Mixto IPEN-Ministerio de Salud. Su implementación generó algunos problemas, por lo que en 1989 se aprueba un nuevo Reglamento de Protección Radiológica mediante un Decreto Supremo.

Tomando en cuenta las nuevas recomendaciones de la Comisión Internacional de Protección Radiológica y las Normas Básicas Internacionales de Seguridad para la protección contra las radiaciones ionizantes y para la seguridad de las fuentes de radiación, se aprueba en mayo de 1997, el Reglamento de Seguridad Radiológica, el cual también considera aspectos desarrollados en el Proyecto ARCAL XVII/OIEA.

Este reglamento abarca diversos temas tales como: exclusiones, requisitos de protección (exposición médica, exposición ocupacional, exposición pública, exposición crónica), requisitos de seguridad de las fuentes, intervenciones y emergencias, control de fuentes y prácticas (exenciones y dispensas, autorizaciones, inspecciones), etc. y su implementación a nivel nacional esta a cargo del IPEN, que es la única autoridad encargada del control de las instalaciones nucleares, radiactivas y de rayos X que existe en la medicina, industria e investigación.

1. INTRODUCCION

Las radiaciones ionizantes se utilizan en el Perú desde hace más de 70 años principalmente en el campo médico y desde 1955 el Estado realiza un control de todas las aplicaciones de las radiaciones mediante instituciones establecidas para este fin.

Como consecuencia del desarrollo alcanzado en el campo nuclear y debido a la experiencia adquirida en protección radiológica, se ha logrado consolidar una sola Autoridad Reguladora, que es el Instituto Peruano de Energía Nuclear (IPEN), el cual se encarga del control de las instalaciones nucleares, radiactivas y de rayos X a nivel nacional. Esta consolidación también ha sido favorecida debido al establecimiento de normas adecuadas tanto de carácter técnico como de tipo legal, como son los Reglamentos de Protección Radiológica.

El recientemente aprobado Reglamento de Seguridad Radiológica, contempla a diferencia de los otros Reglamentos, los aspectos de seguridad de las fuentes de radiación y en su revisión se han contemplado las observaciones de las entidades que utilizan radiaciones ionizantes y las opiniones de las sociedades profesionales que tienen que relación con el tema.

3. EVOLUCION HISTORICA DE LA NORMATIVA

En 1954 se crea la Junta de Control de Sustancias Radioactivas que se encarga de controlar las sustancias radiactivas. En 1955 entra en funciones la Junta de Control de Energía Atómica, encargada de la promoción, investigación y control de las actividades relacionadas con el uso de la energía atómica, la cual hasta 1975 origina normas legales referidas al control de los minerales radiactivos. En esta etapa se empiezan a generar las primeras normas técnicas sobre protección radiológica, las cuales son inicialmente obligatorias para las personas que trabajan en esta institución. Igualmente, se inicia la difusión de las normas emitidas por el Organismo Internacional de Energía Atómica (OIEA) y se emiten recomendaciones para el personal que trabaja con radiaciones ionizantes (dosimetría, contaminación, vigilancia médica, etc.). Se inicia la creación de un Servicio de Protección Radiológica a fin de establecer un sistema de normas y regulaciones para un adecuado control de las radiaciones ionizantes.

En 1975 se crea el Instituto Peruano de Energía Nuclear (IPEN), como institución dependiente del Ministerio de Energía y Minas, con las funciones de promover, coordinar y controlar el desarrollo de la energía nuclear y sus aplicaciones en el país, y a través de su Reglamento de Organización y Funciones y otros dispositivos legales, se va definiendo como la Autoridad Reguladora encargada del control de las radiaciones ionizantes en el campo médico, industrial y de investigación.

En 1977 se aprueba el Reglamento Provisional de Seguridad Nuclear y Protección Radiológica, el cual es de carácter interno. En el mismo año, se aprueba por Resolución de Presidencia del IPEN, las Normas Básicas de Seguridad Nuclear y Protección Radiológica para las personas que utilicen fuentes de radiaciones ionizantes. Prácticamente en esta etapa se inicia el desarrollo de la reglamentación y normativa en protección radiológica, en donde incide favorablemente el tipo de organización que va adoptando el IPEN para realizar estas funciones. Tal es así, que en un determinado momento las actividades de normalización, control, servicios, investigación y desarrollo en protección radiológica recaen en una sola dependencia del IPEN, y en otro momento se crean organismos independientes con las funciones de normalización y control exclusivamente, siendo esta última la condición más favorable, y la que existe actualmente. [1]

El primer Reglamento de Protección Radiológica fue aprobado en 1980 mediante una Resolución de Presidencia del IPEN y su elaboración participó un Comité Mixto IPEN-Ministerio de Salud. Aquí se establece las normas básicas y se reconoce al IPEN como la Autoridad Nacional en energía nuclear, contando con el aval del Ministerio de Salud. El control es para todas las instalaciones de fuentes de radiaciones ionizantes del país.

A fin de darle un mayor reconocimiento legal se expide una versión revisada del Reglamento de Protección Radiológica en 1989 a través de un Decreto Supremo firmado por el Presidente de la República y refrendado por los Ministros de Salud, Trabajo, Industria, Energía y Minas, entre otros.

Este Reglamento reconoce al IPEN, a través de su Presidente, su función de Autoridad Nacional en el ámbito nuclear y trata de los siguientes temas: 1) Límites de Dosis para el personal ocupacionalmente expuesto, para el personal no ocupacionalmente expuesto y para la población, 2) Protección radiológica operacional, 3) Vigilancia radiológica, 4) Requisitos para equipos y fuentes de radiaciones ionizantes, 4) Transporte de material nuclear y radiactivo, 5) Desechos radiactivos, 6) Emergencias radiológicas, 7) Criterios para exposiciones médicas, 8) Exenciones.[2]

Paralelamente se emite un Régimen de Sanciones y se inicia un programa coordinado de elaboración de normas técnicas dirigidas a complementar lo dictaminado por el Reglamento. Este Reglamento permite un mejor control por parte del IPEN, lo cual se ve reflejado en el mejoramiento de las condiciones de protección radiológica en las instalaciones del país.

3. AUTORIDAD REGULADORA

La protección radiológica, en términos generales, ha tenido una evolución bastante importante en los últimos años, debido en parte a una adecuada definición de la Autoridad Reguladora, que lleve a cabo las funciones de control de las radiaciones ionizantes, la cual en el momento actual ejerce el control mediante la emisión de normas, la expedición de autorizaciones y licencias, inspecciones y acciones de coerción en instalaciones nucleares, radiactivas y de rayos X de cualquier aplicación.

El Instituto Peruano de Energía Nuclear a través de la Oficina Técnica de la Autoridad Nacional (OTAN) se encarga desde 1991 de controlar el uso de las radiaciones ionizantes en el campo médico, industrial y de investigación. Tiene a su cargo el control de unos 1200 usuarios de uso médico, 110 instalaciones industriales, 50 dedicadas a la comercialización e investigación y a unas 2500 instalaciones de radiología dental. En el aspecto normativo ha originado mas de 15 normas técnicas y 2 dispositivos legales que son suficientes para ejercer su función de Autoridad Reguladora.[3]

Esta Autoridad ha ido evolucionando mediante el cambio organizacional basado en la premisa de que para desarrollar las funciones reguladoras es necesario contar con una organización claramente definida tal que no se entremezclen los compromisos de usuario y regulador, o al menos se alcance una independencia suficiente.[4]

4. REGLAMENTO DE SEGURIDAD RADIOLOGICA

Las recomendaciones de la Comisión Internacional de Protección Radiológica en su publicación Nro. 60 de 1990, la edición en español de las Normas Básicas Internacionales de Seguridad para la protección contra las radiaciones ionizantes y para la seguridad de las fuentes de radiación en 1996, incidieron fuertemente para culminar de manera formal con el análisis del Reglamento de Protección Radiológica que estaba vigente en el país y con la propuesta de un nuevo Reglamento sobre Seguridad Radiológica.

En esta revisión también se tomó en cuenta la documentación generada por el Proyecto ARCAL XVII del OIEA: "Estructura Normativa y Organización Regulatoria" y en donde participaron 18 países de la región latinoamericana. Estos documentos fueron: Implementación de las Recomendaciones de la CIPR y de las Normas Básicas Internacionales de Seguridad, y el Reglamento genérico de Protección Radiológica.

Los borradores del Reglamento de Seguridad Radiológica fueron revisados por profesionales del IPEN, del Ministerio de Salud, del Ministerio de Trabajo y Promoción Social, del Instituto de Enfermedades Neoplásicas, del Colegio Médico del Perú, de la Sociedad Peruana de Radiología y de la Sociedad Peruana de Radioprotección. Su aprobación fue 20 de mayo de 1997 mediante el Decreto Supremo Nro.009-97-EM y refrendado por los Ministerios de Salud, Trabajo y Promoción Social, Energía y Minas, Defensa e Industria, Turismo, Integración y Negociaciones Comerciales Internacionales.[5]

Los 9 temas del Reglamento son: Disposiciones Generales (Objeto, Finalidad y Alcance, Definiciones, Exclusiones, Partes Responsables, Obligaciones e Interpretaciones), Requisitos de Protección (Criterios Fundamentales, Requisitos de Gestión, Exposición Ocupacional, Exposición Médica, Exposición Pública y Exposición Crónica), Requisitos de Seguridad de las Fuentes, Intervenciones y Emergencias (Criterios Generales, Emergencias), Transporte de Material Radiactivo y Nuclear, Desechos Radiactivos, Control de Fuentes y Prácticas (Autorizaciones, Exenciones y Dispensas, Registros y Reportes, e Inspecciones), Responsabilidad Civil y Sanciones. Además tiene anexos sobre: Límites de Dosis, Radón en viviendas y puestos de trabajo, Exenciones, Concentraciones y cantidades exentas del material radiactivo, entre otros.

Como aspecto importante, el nuevo Reglamento contempla los requisitos de protección contra las radiaciones, los de seguridad de las fuentes y así mismo los requisitos administrativos de control, y de ahí el cambio de denominación de esta regulación. Igualmente, toma en cuenta los nuevos límites de dosis establecidos internacionalmente tanto para los trabajadores expuestos como para el público, para las personas que prestan asistencia voluntaria a pacientes y para niños que visiten pacientes que han incorporado sustancias radiactivas. En cuanto a las exposiciones médicas establece requisitos relativos a la prescripción médica, al personal que administra las exposiciones médicas, a la calibración de haces de radiación, al control de calidad de los equipos, a la obligación de contar con un Físico Médico en toda instalación médica con fines terapeúticos, entre otras consideraciones.

Además establece los niveles de dosis para los que se debe intervenir en caso de exposiciones agudas, de exposiciones crónicas y define los niveles de intervención para la retirada o sustitución de alimentos. Establece las acciones protectoras urgentes así aspectos sobre la reubicación temporal y permanente. Y en cuanto a las exenciones también se consideran las recomendaciones internacionales para declarar exentas fuentes y prácticas en función a la dosis efectiva al público y a la dosis efectiva colectiva comprometida anual, así como las fuentes adscritas a prácticas que son exentas de los requisitos de notificación, registro y licencia. Se agrega una lista de concentraciones y cantidades exentas de material radiactivo.

Se especifica que la violación, infracción o incumplimiento del Reglamento será sancionado por la Autoridad Reguladora conforme a un Régimen de Sanciones que se establezca.

5. CONCLUSIONES

El Reglamento de Seguridad Radiológica es el documento normativo de mayor nivel legal que establece las pautas para continuar con las actividades de control de la Autoridad Reguladora e incrementar sus funciones profundizando el desarrollo de la protección radiológica con normas técnicas específicas y de obligado cumplimiento en todas las personas e instalaciones médicas, industriales y de investigación que utilizan material radiactivo, nuclear y equipos generadores de rayos X en el Perú.

Su implementación se verá facilitada por la actividad que ha venido desarrollando la Autoridad Reguladora, por el reconocimiento como tal por parte de los usuarios de radiaciones ionizantes y por la aceptación de las entidades representativas vinculadas al tema y que han opinado favorablemente en las diferentes etapas de la revisión del Reglamento y en eventos posteriores a su aprobación.

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The Effects of Polyamines on the Cell Survival Against γ-Irradiation in Polyamine Deficient *Escherichia coli*

Tae Jeong Oh, Jeong Ho Lee, Kug Chan Kim, In Gyu Kim

Department of Radiation Biology
Korea Atomic Energy Research Institute
P.O. Box 105, Yusong, Taejon 305-600, Korea

Abstract

We examined the possibility that the polyamine was involved in the survival of cells against γ-irradiation in *E. coli* at low doses using polyamine-deficient mutant strain, KL527. In 40 Gy, 80 Gy and 200 Gy irradiated group, Survival of cells increased by 62%, 44% and 30% respectively by addition of polyamine putrescine (1 mM). When the dose of irradiation was 400 Gy, the survival of cells was 7% in the polyamine supplement condition and the survival colonies were not detected in the polyamine absent condition. Wild type strain MG1655 showed that the survivals of cells were 3.6% and 6.6% in both conditions at a dose of 400 Gy, respectively.

Introduction

The natural polyamines (PAs) including putrescine, spermidine and spermine that are ubiquitous polycationic molecules containing several groups of amines, are widely presented in most living cells such as plants, animals and microorganisms at the levels of mM (1). Not only biosynthetic pathways of PA but also enzymes related to PA-biosynthesis and their regulatory mechanisms have been revealed. There are also many evidences that PAs may be involved in important cellular metabolisms such as DNA replication, transcription, translation and stabilization of membrane structures (2). In addition, it is well known that PAs are required for normal cell growth, cellular proliferation, protection of DNA against radiation damages in many eukaryotic cells (3). Nevertheless, its specific biological functions have not been clearly defined, *in vivo* (1).

The studies about molecular mechanisms accounting for the radioprotective role of PAs were started in recent years (4). It was shown that PAs protected against the radiation-induced loss of transforming activity of DNA mainly scavenging of hydroxyl (OH) radicals in the bulk. Although PAs produced condensation of DNA and chromatin ,

since it might largely be lost in the steps used to prepare nuclei, chromatin and DNA from cells, it has not been clear what role they play in intracellular radioprotection (5).

It was reported that PAs were responsible for the protection of DNA damages against UV-irradiation and singlet oxygens in *E. coli*, but has not been studied about the effects of PAs on the cell survivability against γ-irradiation in PA-depleted mutant type.

In this study, in attempt to investigate the possibility that PAs are involved in the survival of irradiated *E. coli*, we preliminary determined survival ability along the differential radiation doses using PA-depleted mutant type on the media including and depleting PA

Materials and Methods

Bacterial Strains and Culture Conditions

KL527 [Δ (*speA speB*) Δ*speC-glc gyrA*] (6) was used as polyamine-depleted *E. coli* K-12 strain and MG1655 [F^- λ^-] (7) as wild type strain. Cells were grown at 37°C under the aerobic conditions in Luria-Bertani (LB) or M56 minimal salts supplemented with 1% glucose (8). The PA, putrescine was finally supplemented to media at 1 mM.

Irradiation and determination of Survival Curves

Cells were grown in 1 ml of LB at 37°C for overnight. These cells were subcultured to 1 ml of glucose minimal media (initial OD_{600nm} = 0.05) and incubated for 12 hours in order to deplete intracellular polyamines. These PA-depleted cells were inoculated to 1 ml of glucose minimal media with 1mM putrescine and without putrescine, incubated with shaking at 200 rpm for 4 h and reached to active growing log phase. These cells were separated in two parts, one was immediately irradiated with single exposure to a dose of 40, 80, 200 and 400 Gy (Co^{60} γ-ray) and other was not irradiated. These cells were appropriately diluted with 1 ml of M56 minimal salts. Each 100 ul of dilution was spread on the glucose minimal plates with PA supplement and without PA, incubated at 37°C. The number of survival colonies was scored.

Results and Discussion

It has been suggested that PA was essential roles for the cell growth and differentiation, also involved in the protection of cell structures (2). The fact that the intracellular organelles were subjected to damage by irradiation was also reported. We examined the possibility that PA was involved in survival ability against γ-irradiation in PA-deficient *E. coli* strain KL527.

In order to test whether the PA was involved in the survival of E. coli cells against γ-irradiation, wild type strain MG1655 and PA-deficient mutant KL527 were examined. Cells were irradiated after cultured in glucose minimal media with PA supplement (1 mM putrescine) and without PA supplement, these cells were immediately plated on the glucose minimal media with PA and without PA and determine the number of viable cells (Table 1).

Table 1. The effects of polyamine on the survival of cell in KL527(mutant type) and in MG1655 (wild type) after γ-irradiation.

Strains	Dose (Gy)	Irradiated/Not irradiated (% of survival)	
KL527		-PA	+PA
	40	32.9	54.3
	80	41.6	60.1
	200	9.3	12.05
	400	N.D	7.0
MG1655	40	59.4	
	80	59.2	
	200	18.4	
	400	3.6	6.6

N.D; Not detected

Survivability of wild types was higher than that of mutant types after γ-irradiation in the PA condition. Survivals of KL527 grown in PA supplement medium following γ-irradiation to a dose of 40 Gy, 80 Gy and 200 Gy were 62%, 44% and 30% higher than those in PA absent conditions. On the other hands, at a dose of 400 Gy, the survival cells were not found in the PA-absent medium but showed 7% of survival in the case of PA supplement. Over 200 Gy, the degree of survival was rapidly decreased even by addition of PA. In wild type strain MG1655, the survival was very low as 3.6 to 6.6% at a dose of 400 Gy irrespective of PA supplement.

This study shows that significant differences of survival of *E. coli* cells between mutant type in the PA supplement condition and wild type in the PA absent condition were not detected and the PA was involved in survival of cells against irradiation in PA deficient *E. coli* strain. These results suggested the first evidences that PA played role in cell survival of PA-deficient *E. coli* mutant against irradiation.

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ESTUDIO DE LA RESPUESTA ADAPTATIVA EN CELULAS DE HAMSTER CHINO

S.C. MICHELIN, M. DEL R. PÉREZ, D. DUBNER, P.A. GISONE
Autoridad Regulatoria Nuclear, Gerencia de Apoyo Científico,
Buenos Aires, Argentina

Resumen

Durante muchos años se consideró la posibilidad de que las bajas dosis de radiación indujeran cambios en células y organismos permitiendo una adaptación a los efectos mutagénicos de la radiación. Actualmente, numerosos datos experimentales avalan la existencia de una respuesta adaptativa, que se caracteriza por una disminución del daño genético radioinducido.

La comprensión de los mecanismos moleculares involucrados en este fenómeno permitiría estimar los efectos y riesgos de exposiciones a bajas dosis.

En este trabajo se presentan los resultados preliminares tendientes a estudiar la inducción de la respuesta adaptativa en células de mamíferos con distintas dosis condicionantes de radiaciones ionizantes.

Introducción

Existen numerosas evidencias por las cuales las células expuestas a bajas dosis de agentes mutagénicos o clastogénicos, resultan menos sensibles a los efectos de mayores dosis administradas posteriormente.

En los últimos años un gran número de trabajos indican que la administración de bajas dosis de radiación, del orden de mGy, producen cambios en organismos eucariotes y procariotes que le permiten disminuir los efectos de posteriores irradiaciones.

Desde los primeros trabajos de Olivieri et al (1984), (1), numerosas experiencias con radiaciones ionizantes han contribuido a confirmar la existencia de una respuesta adaptativa (RA). Esta respuesta es inducida en células eucariotes por dosis que varian entre 5 y 200 mGy (dosis condicionante) y se caracteriza por una reducción de los niveles esperados de aberraciones cromosómicas, intercambios de cromátidas, formación de micronúcleos y mutaciones, luego de una segunda dosis variable entre 2 y 4 Gy (dosis provocadora).

Se postula que la dosis condicionante induce la activación de genes que participan en la transducción de señales, control del ciclo celular, reparación del ADN, eliminación de radicales libres y apoptosis. La presencia de estas proteínas en concentraciones adecuadas en el momento de la segunda irradiación haria que el daño sea menor

Entre las proteínas propuestas figuran las kinasas y ciclinas que actúan en los puntos de control del ciclo celular, los productos de varios antioncogenes (Rb, p53) que participan en la regulación del ciclo celular, proteínas nucleares, receptores de membrana, etc.

Esta hipótesis es avalada por la observación de que un inhibidor de la síntesis de proteínas como la cicloheximida y la 3 amino-benzamida, un inhibidor de la poly ADPrribosil-sintetasa, bloquean la respuesta adaptativa.

Se ha demostrado que la RA ocurre en células de animales irradiados y algunos trabajos muestran que la sobrevida puede ser incrementada y la incidencia de cáncer puede disminuir por la preexposición de animales a bajas dosis. (2)

Por otra parte, las distintas fases del ciclo celular, la dosis y la tasa de dosis asi como el intervalo de tiempo entre la dosis condicionante y la dosis provocadora, regulan la efectividad de la RA.

Si bien la RA se ha demostrado en animales, e in vitro, en sistemas eucariotes y procariotes, los resultados no pueden ser fácilmente extrapolables a humanos dada la complejidad de un organismo superior que incluye el sistema inmunológico, factores endócrinos, etc que también pueden modificar la respuesta. Por otra parte, las distintas condiciones de exposición a las radiaciones ionizantes y a agentes mutagénicos ambientales podría activar mecanismos diferentes de RA.

La inducción de un mecanismo radioprotector por bajas dosis tendría importantes aplicaciones para la salud humana. Esto sugeriría la posibilidad de una sobreestimación de los riesgos de efectos estocásticos a bajas dosis de radiaciones ionizantes. Sin embargo, aun no existen claras evidencias epidemiológicas de dicho efecto.

Un gran esfuerzo se está realizando para comprender los mecanismos básicos de este fenómeno que permitiría una mejor estimación de los efectos y riesgos de exposiciones a bajas dosis (3)

Objetivos

Los objetivos de este trabajo son:
a) determinar la existencia de la respuesta adaptativa con distintas dosis condicionantes,
b) determinar el tiempo necesario para la inducción del fenómeno y la duración del mismo
c) analizar la influencia de las distintas dosis condicionantes en la expresión de la RA en células de la línea V79 de hamster chino.

Como parámetro de evaluación se utiliza la frecuencia de mutaciones en el gen de la hipoxantina guanina fosforribosil transferasa (HGPRT) y la eficiencia de clonado.

Para las experiencias se utilizan células de la línea V79 de hamster chino, mantenidas en medio F-12 suplementado con 10 % de suero fetal bovino.

Resultados

Se determinó la eficiencia de clonado y la frecuencia de mutaciones espontáneas de esta línea.

La eficiencia de clonado se realizó sembrando en cada experiencia 1000 células por cada 10 cápsulas de petri de 10 cm de diámetro. La eficiencia fue del 62 %.

Para determinar la frecuencia de mutaciones espontáneas en el gen mencionado se ensayaron distintas concentraciones de 6 tioguanina (6-TG), utilizada para seleccionar las mutantes. Se determinó que 2 ug/ml es la más adecuada.

La frecuencia de mutaciones espontaneas se determinó sembrando en cada experiencia 10^6 células por cada 10 cápsulas de petri de 10 cm de diámetro. A los 11 dias de cultivo se determinó la frecuencia de mutaciones espontáneas, siendo de 3,7 mutantes cada 10^5 células viables.

Con el objeto de determinar la inducibilidad de la respuesta adaptativa y la duración de este mecanismo, las células fueron irradiadas con una dosis condicionante de 0,03 Gy con una tasa de dosis de 0,015 Gy/min. A las 18 horas se aplicó la dosis provocadora de 3 Gy con una tasa de dosis de 0.20 Gy/min.

Paralelamente otros cultivos fueron irradiados con 3 Gy solamente. Luego de esta irradiación las células permanecieron en cultivo durante 48 horas.

Para determinar la eficiencia de clonado, se procedió como se describió previamente. Se obtuvo una eficiencia del 41 % para las células irradiadas con 3 Gy y del 46 % para las irradiadas con 0,03 Gy y 3 Gy.

Para determinar la frecuencia de mutaciones, las células permanecieron en cultivo durante 14 días. Las frecuencias de mutaciones fueron de 4,96 mutantes cada 10^5 células para las irradiadas con 3 Gy y 4,42 mutantes cada 10^5 células para las irradiadas con 0,03 Gy y 3 Gy respectivamente.

Estos resultados preliminares no evidencian diferencias estadísticamente significativas que permitan inferir la existencia de una respuesta adaptativa en las condiciones establecidas. Se están realizando nuevas experiencias para confirmar estas observaciones.

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RADIACION, OXIDO NITRICO Y MUERTE CELULAR

D. DUBNER, M. DEL R. PÉREZ, S.C. MICHELIN, P.A. GISONE
Autoridad Regulatoria Nuclear, Gerencia de Apoyo Científico,
Buenos Aires, Argentina

RESUMEN Los mecanismos de la muerte celular radioinducida constituyen un objetivo de investigación desde que los primeros efectos biológicos de las radiaciones fueron observados
La explosión de información producida en los últimos 20 años necesita de un cuidadoso análisis debido a los aparentemente conflictivos datos, que en realidad no son tales ,smo que están en estrecha correlación con el sistema celular estudiado y el rango de dosis usado
Esta revisión, focaliza la atención en el rol de las especies activas del oxígeno ,en particular el Oxido Nitrico , en relacion a su relevancia como potenciales mediadores de la muerte celular radioinducida.

MUERTE CELULAR

La muerte celular inducida por radiación ionizante ha sido extensamente estudiada tanto desde el punto de vista del tejido normal, como de la respuesta tumoral .
Dos formas de muerte celular, genética, bioquímica y morfológicamente diferentes han sido reconocidas la apoptosis y la necrosis, siendo su expresión dependiente no sólo del tipo de celula sino de la dosis de radiación Dosis altas pueden causar la destrucción de células linfoides via necrosis, mientras que dosis bajas inducen apoptosis [1]

La apoptosis o muerte celular programada es una forma genéticamente mediada de muerte celular en la cual la célula diseña y ejecuta el programa de su propia desaparicion, en respuesta a estímulos externos e internos, cuya complejidad se está revelando recientemente La necrosis es el resultado de un daño externo a la celula, que la lleva a un colapso metabólico, cuando la célula no puede mantener ya la homeostasis iónica, siendo un proceso pasivo, catabólico y degenerativo
La capacidad de la radiación para inducir apoptosis ha sido bien documentada entre otras en celulas acinares de la glándula parótida, en timocitos, en celulas de la cripta intestinal y en linfocitos [2].
Debido a que la apoptosis implica un proceso regulado de degradación, ha sido postulado que la señal de inducción de apoptosis luego de la irradiación se origina en el nucleo [3] Estudios que muestran la capacidad de BrdUrd de incrementar la apoptosis radioinducida y al decaimiento del I^{125} en el DNA como inductor de apoptosis en células susceptibles, implican al daño en el DNA como disparador [1]
Sin embargo hay evidencias que el daño en la membrana puede inducir apoptosis Estudios recientes han demostrado que la hidrólisis de la esfingomielina por rayos X lleva a la producción deun segundo mensajero lipídico- la ceramida- que contribuye a la respuesta apoptotica [4]

ESPECIES ACTIVAS DEL OXIGENO

Las especies activas del oxígeno (EAO) con su capacidad de iniciar peroxidación en los lípidos de membrana, oxidación de proteínas, inactivacion de sitios activos y rupturas de simple o doble cadena en la molécula de DNA , se constituyen en moleculas claves en el estudio de la muerte celular, tanto por necrosis como por apoptosis
El stress oxidativo, que describe un desbalance entre la produccion y la remoción de EAO ha sido propuesto como un mediador de apoptosis [5] De hecho, la radiacion ionizante genera por radiólisis del agua uno de las especies mas activas , el radical hidroxilo (OH)

Varias clases de moléculas han sido propuestas como potenciales blancos del stress oxidativo en la apoptosis [6]:

a) Factores de transcripción sensibles al estado redox de la célula podrían contribuir a la regulación de los genes involucrados en la apoptosis (c-myc , bcl-2, p-53) [2]
b) La regulación redox de moléculas involucradas en la homeostasis del calcio pueden llevar al incremento sostenido de calcio intracelular que ha sido asociado con la apoptosis [7]
c) Un stress oxidativo moderado induce un incremento en la proteolisis concordante con la observación de una incrementada proteolisis durante la apoptosis y con los estudios genéticos que ligan a la enzima convertidora interleukina-1- (ICE) de la familia de las cistein-proteasas al mecanismo de apoptosis [8]

OXIDO NITRICO

Entre las EAO, el óxido nítrico (NO), nombrada la molècula del año en 1992 por Science, [9] merece un enfoque especial por su caracter de mensajero biológico involucrado en una variedad de estados fisiológicos y patológicos.

Es producido por una variedad de células, incluyendo endotelio vascular, neuronas, células musculares lisas, macrófagos, neutrófilos, plaquetas y endotelio pulmonar. Es sintetizado por la óxido nitrico sintasa (NOS) a partir del aminoácido L-arginina y se han identificado tres genes NOS. neuronal (n NOS), endotelial (e NOS) e inmunológica o inducible (i NOS), de acuerdo al tejido en el cual fueron primero clonados.

Existen ahora evidencias que demuestran que el $NO^{\cdot}$ causa necrosis o apoptosis en una variedad de tipos celulares La exposición sostenida a bajos niveles de $NO^{\cdot}$ causa apoptosis, mientras que la exposición aguda a concentraciones altas, resulta en la muerte celular por necrosis [10]

Como media el NO sus efectos tóxicos?

Numerosas evidencias sugieren que gran parte del daño inducido por el NO puede deberse a la generación de peroxinitrito ($ONOO^-$), producto de la reacción del NO con el anión superóxido (O_2^-) , generado en varias vías del metabolismo celular [11].

Cuidadosos estudios *in vitro* han demostrado que en algunos sistemas, el peroxinitrito es un potente inhibidor de la actividad de la aconitasa, no así el NO [12]. En forma similar, mientras el NO causa una inhibición reversible de las enzimas mitocondriales, la acción del peroxinitrito causa la inhibición permanente de la función mitocondrial [13].

El daño al DNA puede ser fundamental al efecto citotóxico. El daño por NO y principalmente por peroxinitrito ocurre a través de la deaminación, nitración e hidroxilación de las bases , así como por ruptura de las cadenas [14].

La fragmentación del DNA estimula la actividad de la poli-ADPribosil sintetasa (PARS). Esta enzima cataliza la unión de unidades de ADP-ribosa a proteínas nucleares tales como la histona y a la PARS en sí misma. Por cada molécula de ADP-ribosa transferida, una molécula de NAD es consumida y su subsecuente regeneración consume cuatro moléculas de ATP

Dado que la PARS es una enzima nuclear abundante y que el NO además actúa sobre la cadena mitococondrial de transporte de electrones, su activación lleva a una rápida depleción de los depósitos de energía y a la muerte celular [15].

Clarificar el rol del $NO^{\cdot}$ en la muerte celular radioinducida requiere estudios de la respuesta en los diferentes tipos de células.

En macrófagos peritoneales obtenidos de ratones irradiados con bajas dosis (4 cGy) de radiación gamma, ha sido reportado un aumento de la producción de NO y de la actividad citolitica, aunque bajas dosis de irradiación *in vitro* no los activaban. [16] Los mismos autores, trabajando *in vitro* con dosis altas (6Gy) encontraron que la irradiación gamma aumentó la expresión de la i-NOS y la producción de NO Dado que ha sido descripto un factor de transcripción nuclear (NF-kB) que se une al promotor del gen de la iNOS, cuya expresión y unión es inducida por irradiación con rayos gammas y es bloqueada por antioxidantes, sugieren

que el aumento es atribuible a efectos en el DNA directamente por los rayos gamma e indirectamente a través de la formación de EAO, pero no a la oxidación de la membrana celular [17]

Es bien conocida la radiosensibilidad de las células del sistema nervioso central (SNC) en desarrollo. Horas después de una irradiación total o cefálica con una dosis de 0.25 Gy, a una tasa de dosis de 0.2 Gy/min, ya es posible observar precursores en diferentes estadíos de la muerte por apoptosis [18] Numerosos trabajos demuestran la participacion del NO en la muerte neuronal en diferentes desórdenes neurodegenerativos [19]

Por otra parte en células exquisitamente radiosensibles como son linfocitos y timocitos,que mueren por apoptosis en un periodo de horas luego de una exposición aun a bajas dosis, no se ha demostrado hasta el momento una participación del NO

Siendo el NO por sus características una molécula que estimula nuestra imaginación, su rol en la muerte celular radioinducida, es un desafío más que queda planteado

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EFECTOS RADIOINDUCIDOS SOBRE EL SISTEMA NERVIOSO CENTRAL EN DESARROLLO

P Gisone, D. Dubner, S, Michelin.y M del R Pérez
Autoridad Regulatoria Nuclear, Gerencia de Apoyo Científico, Buenos Aires, Argentina

Resumen

El embrión y el feto humano son particularmente sensibles a las radiaciones ionizantes y esta sensibilidad presenta variaciones cualitativas y cuantitativas en función del estado de desarrollo intrauterino Fuera de la carcinogénesis radioinducida, el daño más grave que puede sobrevenir como consecuencia de una exposición prenatal en la especie humana es el retraso mental severo. El principal cuerpo de datos en humanos sobre efectos radioinducidos en el sistema nervioso central en desarrollo proviene de los estudios epidemiológicos realizados en individuos expuestos "in utero" durante las explosiones atómicas de Hiroshima y Nagasaki. Estas observaciones demostraron la existencia de un momento de máxima radiosensibilidad entre las semanas 8 y 15 de edad gestacional (e g), período en que tiene lugar la proliferación y migración neuronal . En el rango de las bajas dosis, donde adquieren relevancia los aspectos vinculados con la radioprotección y el establecimiento de límites de dosis tanto ocupacionales como del público, resulta particularmente importante poder determinar las características de la relación dosis-respuesta y la eventual existencia de un umbral para los efectos de la radiación sobre el SNC en desarrollo. Se estudió la generación de óxido nítrico (NO) y su relación con la producción de especies activas del oxígeno en cerebros de ratas expuestas "in utero" a dosis de hasta 1 Gy en el momento de máxima radiosensibilidad Se discute su posible rol en el mecanismo de daño radioinducido en SNC en desarrollo

1 INTRODUCCION

El sistema nerviosos central (SNC), que en la vida adulta presenta una radiosensibilidad relativamente baja, resulta particularmente vulnerable a la acción de las radiaciones ionizantes en la vida prenatal. La exposición prenatal a radiaciones ionizantes puede causar una variedad de efectos sobre el sistema nervioso que pueden evidenciarse como microcefalia, retraso mental severo (RMS), disminución del rendimiento en tests de inteligencia, convulsiones y afectación del rendimiento neuromuscular.

La frecuencia de RMS en los individuos expuestos entre las semanas 8 y 15 de e g. en Hiroshima y Nagasaki fue del orden del 40 % por Sv, observándose una frecuencia 4 veces menor en los individuos expuestos entre la semanas 16 y 25 de e g. No hubo evidencias de RMS en los expuestos antes de la semana 8 ni después de la semana 25 de e. g.[1]. Las semanas 8 a 15 de e.g. corresponden al momento de máxima proliferación neuroblástica con un crecimiento de tipo exponencial. La mayor parte de los precursores neuronales culminan su multiplicación hacia el final de este período, iniciando un proceso de diferenciación. En esta etapa tiene lugar la migración neuronal, guiada a través de un tipo especial de células gliales con fibras elongadas: la glia radial. Sólo una variedad especial, las células granulares o microneuronas continúan teniendo actividad proliferativa hasta varios meses después del nacimiento en el cerebelo e hipocampo lo que explica la radiosensibilidad de estos tejidos aún al final de la gestación. Los fenómenos migracionales se combinan con fenómenos de muerte celular programada (apoptosis), esenciales para el normal desarrollo del cerebro y sus anexos. La secuencia de fenómenos debe respetar una adecuada correlación temporoespacial que asegure la posición final de las neuronas maduras, ya que las funciones del SNC dependen de la correcta disposición e interconexión de sus estructuras.

2- SNC EN DESARROLLO Y RADIACION

El efecto de las radiaciones ionizantes sobre el SNC en desarrollo podría explicarse a través de diferentes acciones: pérdida de la capacidad proliferativa de precursores neuronales y gliales, muerte de neuronas post-mitóticas en vías de diferenciación, muerte de las células de la glia radial con alteración de fenómenos migracionales, afectación de células gliales y disturbios en la formación de mielina, alteración del proceso de sinaptogénesis con afectación de las conexiones interneuronales

La limitación de datos en humanos sobre irradiación prenatal ha inducido a la utilización de especies animales de ontogenia comparable en el intento de responder algunos interrogantes vinculados a los mecanismos subyacentes al daño radioinducido y la influencia de distintas variables tales como dosis, tasa de dosis y calidad de radiación.

La relación dosis-efecto para la inducción de RMS en el estudio de Hiroshima y Nagasaki no permite el ajuste de los datos a una función lineal o lineal cuadrática ni determinar la presencia de un umbral desde un punto de vista matemático. La diversidad de los fenómenos concurrentes tales como muerte celular, alteraciones migracionales y sinaptogénicas, que contribuyen a la inducción del RMS, hacen pensar que podría haber múltiples ajustes posibles. Se ha postulado que dosis mínimas del orden de los 0.1 Gy serían necesarias para inducir daño cerebral severo[2]. Estudios experimentales permitieron observar efectos más sutiles con dosis aún más bajas, del orden de los 0.05 Gy (disminución de la tasa de proliferación y diferenciación celular) en cultivos de cerebro de ratón expuestos a radiación beta [3] y hasta de 0.01 Gy (disminución de la masa encefálica) en ratas expuestas a neutrones de 600 keV en el período de máxima radiosensibilidad [4].

3 INJURIA OXIDATIVA Y OXIDO NITRICO

La producción de especies activas del oxígeno constituye el principal mecanismo indirecto de daño radioinducido en sistemas biológicos. La radiólisis de los sistemas acuosos genera un conjunto de moléculas altamente reactivas tales como el anión superóxido ($O^{\cdot}_2$), el peróxido de hidrógeno (H_2O_2) y el radical hidroxilo (HO). El delicado equilibrio oxidativo celular es mantenido por la acción de sistemas de defensa antioxidante enzimáticos y no enzimáticos La alteración del equilibrio oxidativo desencadena una cascada de eventos autosostenidos que pueden llevar a la muerte celular .

Evidencias crecientes sostienen el concepto de que los fenómenos de stress oxidativo están implicados en la patogenia de numerosas enfermedades neurodegenerativas y en el daño radioinducido en el cerebro fetal [5]. En condiciones fisiológicas las estucturas fetales se encuentran sometidas una baja presión parcial de oxígeno. El cerebro fetal contiene niveles relativamente bajos de antioxidantes resultando particularmente vulnerable al daño oxidativo. Por otra parte el alto contenido de lípidos, en particular ácidos grasos poli-insaturados (PUFA), lo hace más susceptible de sufrir procesos de lipoperoxidación. La inducción de apoptosis mediada por injuria oxidativa sobre el ADN constituye uno de los principales mecanismos de daño radioinducido en este sistema.

El óxido nítrico (NO) es un radical libre que cumple funciones de mensajero a nivel del SNC, implicado en procesos fisiológicos vinculados a la transducción de señales y la plasticidad sináptica, que incluyen la memoria y el aprendizaje. La enzima óxido-nítrico sintasa (NOS), que cataliza la síntesis de NO, se encuentra selectivamente distribuida en el 1 al 2 % de las neuronas del cerebro adulto Su concentración es mayor a nivel de las neuronas del cerebelo. Las células gliales, particularmente los astrocitos,son la fuente principal de NO en el SNC. En el cerebro en desarrollo la cantidad y distribución de células que contienen NOS es variable de acuerdo a la edad gestacional Se ha sugerido que el NO podría jugar un rol esencial en el proceso de sinaptogénesis.

El NO opera como un un mensajero retrógrado: una vez producido en la terminal post-sináptica difunde fácilmente a la terminal pre-sináptica, ejerciendo así un control de la neurotransmisión Dependiendo de su concentración y de su estado de óxido-reducción el NO puede ejercer funciones neuroprotectoras o neurotóxicas. Una cascada de señales que involucran al glutamato, uno de los principales neurotransmisores excitatorios del SNC, con la producción de NO, activación de

guanilatociclasa y producción de un segundo mensajero, el guanosisn monofosfato cíclico (GMPc) regula la transmisión sináptica en el cerebro En ciertas condiciones patológicas la excesiva activación de los receptores NMDA mediada por el glutamato conduce a una secuencia de eventos neurotóxicos conocidos como excitotoxicidad. Bajo ciertas condiciones el NO puede reaccionar con el O^{-}_{2} generando un agente oxidante extremadamente tóxico: el peroxinitrito ($ONOO^{-}$) En concentraciones fisiológicas de NO la tasa de formación de $ONOO^{-}$ no es significativa Pero en situaciones en las que hay una producción excesiva de NO con alta disponibilidad de O^{-}_{2}, podría resultar altamente neurotóxico [6]

Los conceptos señalados conducen a la idea de que stress oxidativo y excitotoxicidad son eventos interdependientes que se potencian mutuamente para producir daño neuronal Ambos fenómenos han sido descriptos en desórdenes muy variados como la isquemia cerebral, enfermedad de Parkinson, esclerosis lateral amiotrófica, enfermedad de Alzheimer, epilepsia y otras [7] [8]

4-DESCRIPCION DEL TRABAJO

El objetivo del trabajo se orientó al estudio del rol del NO en el daño radioducido en el SNC en desarrollo y su relación con parámetros de stress oxidativo en un modelo experimental de irradiación prenatal a bajas dosis de radiación gamma.

Se irradiaron lotes de ratas Wistar preñadas el día 17 de e.g. con dosis de 0.4, 0.7 y 1 Gy (fuente de Co 60, tasa de dosis 0.23 Gy/min) Se disecaron los cerebros fetales los días 17 y 18 de e g (1 h, 6 hs y 24 hs post-radiación), y los días 2 y 9 de vida post-natal en lotes irradiados y controles Luego de su homogeneización las muestras fueron centrifugadas y los sobrenadantes conservados para la realización de los distintos ensayos

a) *Enzimas antioxidantes* se midió la actividad de superoxido dismutasa (SOD) por espectrofotometría a 480 nm, a través de la tasa de inhibición de la formación de adrenocromo La actividad de NADPH-diaforasa se determinó espectrofotométricamente a 600 nm con el agregado de NADPH como dador de electrones y DCPIP como aceptor

b) *Enzimas vinculadas con el metabolismo del NO* · se determinó actividad de óxido nítrico sintasa (NOS) a través de la tasa de formación de citrulina a partir de L-[^{3}H]arginina La actividad de guanilatociclasa se determinó midiendo la formación de GMPc a partir de [^{32}P]GTP

c) *Radical ascorbilo* se determinó concentración de radical ascorbilo por resonancia paramagnética electrónica

c) *Lipoperóxidos* Se determinó la concentración de sustancias reactantes al ácido tiobarbitúrico (TBARS)

Se observó aumento de la actividad de las enzimas antioxidantes y del nivel de lipoperóxidos en muestras de 0 7 y 1 Gy respecto de los controles Un incremento en la actividad de enzimas vinculadas al metabolismo del NO se observó solo en las muestras de 1 Gy. No se observaron diferencias significativas en la concentración de radical ascorbilo en los tiempos estudiados

6-DISCUSION

El aumento en la actividad de enzimas antioxidantes en las muestras de cerebro expuestas a dosis más altas revela la implicancia de la especies activas del oxígeno en el sistema estudiado Su correlación con la actividad de enzimas vinculadas al metabolismo del óxido nítrico sugiere una vinculación de ambas vías en el mecanismo de daño radioinducido. El incremento en los niveles de lipoperóxidos, evidenciable en las muestras tomadas más tardíamente, durante la vida postnatal, podría relacionarse con una afectación de las estructuras lipídicas ocurrida como consecuencia de la exposición prenatal. Con el objeto de testear la hipótesis de que el stress oxidativo y la excitotoxicidad podrían ser fenómenos secuenciales e interactivos en la patogenia de la injuria radioinducida en SNC en desarrollo hemos comenzado irradiaciones "in vitro" de cultivos primarios de cerebro que permitirán estudiar los efectos radioinducidos y su relación con un conjunto de

variables tales como respuesta del sistema a la incubación con antioxidantes (ácido lipoico, SOD), bloqueantes de receptores popst-sinápticos (MK-801) , bloqueantes de canales de calcio (nimodipina) e inhibidores de la NOS (L-NAME y gangliósidos). Se estudiará nitración de proteínas mediante técnica de inmunomarcación con anticuerpos antinitrotirosina y concentración de nitrito y nitrato en los sobrenadantes de cultivos .

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Down's Syndrome clusters in Germany in close temporal relationship to the Chernobyl accident

Bernd Grosche, Angela Schoetzau, Werner Burkart
Institute for Radiation Hygiene, Federal Office for Radiation Protection, 85762 Oberschleissheim, Germany

Abstract
In two independent studies using different approaches and covering West Berlin and Bavaria, respectively, highly significant temporal clusters of Down's syndrome were found. Both sharp increases occurred in areas receiving relatively low Chernobyl fallout and concomitant radiation exposures. Only for the Berlin cluster was fallout present at the time of the affected meioses, whereas the Nuremberg cluster preceded the radioactive contamination for one month. Hypotheses on possible causal relationships are compared. Radiation from the Chernobyl accident is an unlikely factor, also, because the associated cumulative dose was so low in comparison with natural background. Given the lack of understanding of what causes Down's syndrome, other than factors associated with increased maternal age, additional research into environmental and infectious risk factors is warranted.

1. Introduction

Down's syndrome (trisomy 21) is a major congenital chromosomal disorder resulting in most cases from nondisjunction during meiosis in oocytes. Although nondisjunction is not thought to show any particular sensitivity to ionizing radiation, two ecological studies of Down's syndrome prevalence in the aftermath of Chernobyl showed statistically significant increases in birth cohorts and in prenatal diagnoses for which conception occurred in the early phase of environmental contamination caused by the reactor accident, i.e. in early May 1986 in Berlin [1] and in fall 1986 to winter 1986/87 in Scotland [2]. Both studies covered areas where maximum exposures due to Chernobyl reached only about 10 % of annual natural exposures to ionizing radiation.

Our institute conducted a large geographical correlation study to generate hypotheses of possible adverse health effects from the Chernobyl accident. An increase of Down's syndrome was found in Northern Bavaria (O=10, E=4.4, O/E=2.27, 95%CI=1.2-4.1) in December 1986 in close temporal relationship to the occurrence of the Berlin cluster [3]. Further analyses revealed that the increase in Northern Bavaria was due mainly to four diagnoses made in the urban area of Nuremberg, Fuerth, and Erlangen (NFE). These three adjacent cities form a metropolitan area of app. 700,000 people and 6,117 life births in 1986. The four cases in this area is 8.9 times what would be expected from the North Bavarian long term average of 0.94 cases in 1,000 live births (O=4, E=0.45, O/E=8.9, 99% CI 1.8-22.6). A causal relationship to Chernobyl radioactivity was excluded because the area received very low contamination and because the peak occurred in December 1986. Since none of the affected infants was premature, the meiotic nondisjunction in the germ cells must have taken place before the onset of fallout from the Chernobyl accident.

2. Characteristics of the Studies, Results

Characteristics of both studies are given in Table I.

2.1 Description of the Berlin cluster

The West Berlin series is based on routine data from prenatal and neonatal diagnostic examinations from all relevant hospitals of the city. Sperling et al. [4] reported a significant increase of cases with trisomy 21 among the children born in January 1987 in West Berlin, where about 2 cases were expected against 12 observed The mother of one child with Down's syndrome had not been in Berlin at the time of conception The cluster contained both preterm and fullterm births

No obvious common cause for the cluster was apparent to the authors except the temporal correlation with Chernobyl fallout They concluded that internal exposure to ionizing radiation, especially ^{131}I was likely responsible for the cluster [1], either directly or indirectly via changed sexual behavior of the mothers due to thyroid dysfunction caused by the low-level ^{131}I exposure [4]

Table I: Main study characteristics, prevalences, peak values of Down's syndrome, and activity concentration in the Bavarian and West Berlin studies

	Bavaria [16]	West Berlin [4]
method	spatio-temporal comparison	time series analysis
case ascertainment	live births, data collection via records from children's hospitals	antenatal diagnosis, stillbirths, live births
study period	1984-1989	1980-1989
mean live births per year	119,000 Bavaria 52,000 North Bavaria 6,400 NFE	19,000
mean prevalence of Down's syndrome	$1.08/10^3$ Bavaria $0.94/10^3$ North Bavaria	$1.56/10^3$
highest value	$2.45/10^3$ North Bavaria in December 1986 ($8.1/10^3$ NFE)	$6.8/10^3$ in January 1987
exposure (time integrated activity concentration in the air for April 28 - May 8, 1986 [23])	^{131}I [Bq*h/m³] N. Bavaria 200-500 S. Bavaria 500-1000 ^{137}Cs [Bq*h/m³] N.&S. Bavaria 200-500	^{131}I [Bq*h/m³] 100-200 ^{137}Cs [Bq*h/m³] 50-100

The highest rate of Down's syndrome during the study period was found in Northern Bavaria one month before the peak occurrence in Berlin, i.e. December 1986. A more detailed analysis of the cases born in December 1986 was conducted to make sure that no preterm births were included, because this would lead to misclassification of conception in terms of pre- or post-Chernobyl exposure. Though the peak in December 1986 was the highest observed in the study, it is only slightly higher than several other peaks, and does not differ significantly from these.

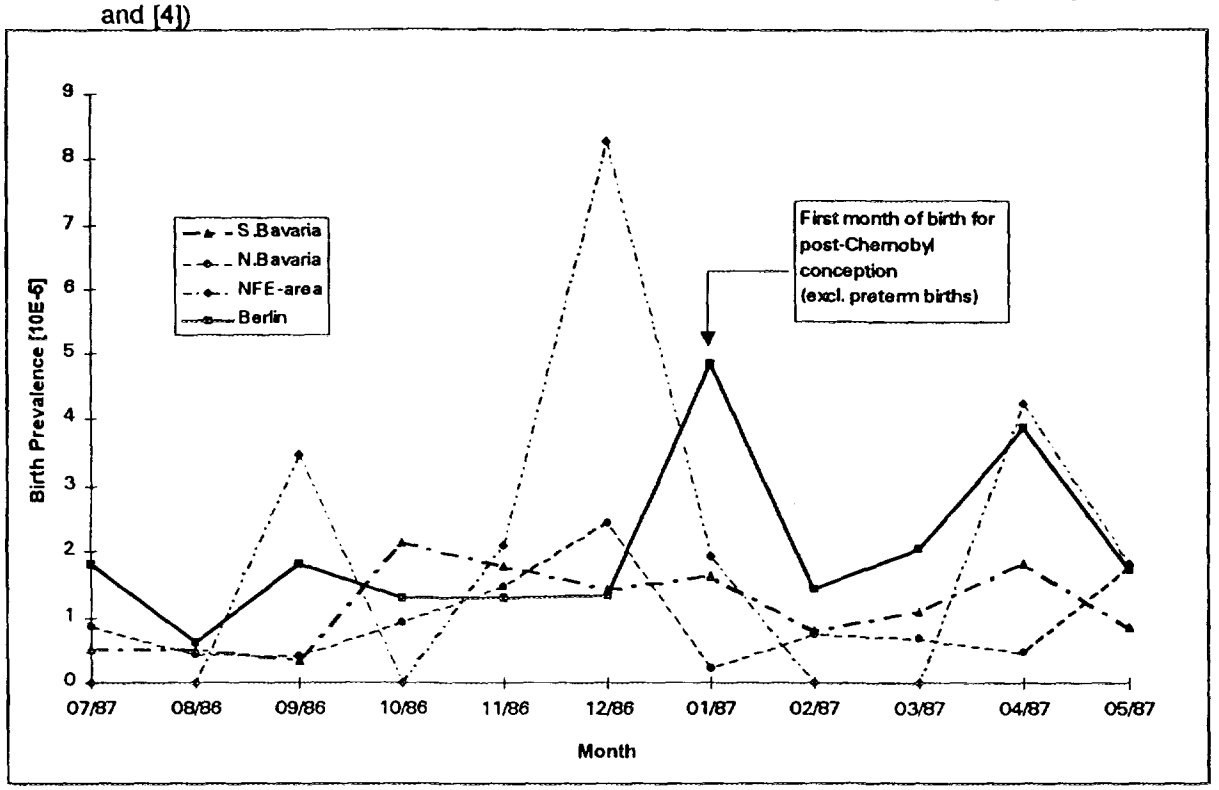
Fig. 1 depicts the prevalence rates of Down's syndrome in West Berlin, Southern Bavaria, Northern Bavaria, and the NFE-region for the time period described in [1]. This figure indicates that the variation within the Bavarian data set is much larger than in the Berlin series, even though the underlying population in Bavaria is larger. Berlin, it should be noted, is more urbanized and more homogeneous than Northern Bavaria in terms of socio-economic status.

3. Dosimetry

In view of the relatively short time period when nondisjunction is assumed to occur, a comparison of maximal exposure rates is also relevant. Therefore, maximal daily exposures are to be considered in exposure situations determined in part by short-lived radionuclides. Although for Southern Bavaria, the increase dose rate in the first day(s) of the Chernobyl fallout is up to ten times higher than natural background, the value for Berlin is in the range of local background, i.e. the dose rate was nearly double the background rate for a few days. Estimated average cumulative organ doses to the thyroid gland were 0.48 mSv and 2 mSv for Berlin and Southern Bavaria, respectively. The dose from iodine to the ovaries is even less by 3-4 orders of magnitude [5].

At the low contamination levels found for Berlin and the national average, microdosimetry concepts are relevant considerations. The energy deposition pattern of gamma and beta radiation from fission products is such that the minimal dose in a cell nucleus hit by one single electron track is in the range of 1 to 3 mSv. Lower macroscopic doses translate into only a fraction of the cell nuclei in the tissue being hit. This means that with the maximal additional daily exposure of 65 μSv for the thyroid and 6 μSv for the ovaries found for Berlin in April/May 1986, fewer than 1 in 200 oocyte nuclei could be directly affected by Chernobyl fallout.

Fig. 1: Birth prevalence of Down's syndrome in Berlin, Southern, Northern Bavaria, and NFE-Region, July 1986 - May 1987 (rates for Berlin were estimated from the figures given in [1] and [4])



As a remote possibility, an indirect mechanism acting via an altered thyroid function is not ruled out by Sperling et al. [4]. Despite some disputed reports that mothers of children with Down's syndrome have a higher prevalence of thyroid antibodies (e.g. [6]), thyroid doses in Berlin after Chernobyl were much too low to cause deterministic effects such as autoimmune reactions. In addition, the time course of such reactions would be difficult to reconcile with the malformation pattern under study.

4. Discussion

The cluster reported by Sperling et al. is statistically highly significant. But additional elements are lacking to suggest a causal relationship between the considered agent "radiation" and the observed health outcome "Down's syndrome". No cluster of Down's syndrome was found in other areas with higher fallout such as Finland [7] and Southern Bavaria. The increase found in Sweden was the only one in higher contaminated areas. It cannot be told from the publication [8], if the overall increase in 1987 was due to an outstanding increase in one single month.

To explain a short-term increase of Down's syndrome cases, radiation would have to act in a very small time window to interfere with chromosome segregation leading to nondisjunction events during meiosis of female germ cells. Such a deterministic effect is extremely unlikely at the low doses and dose rates considered here. Theoretically, bacterial or viral infections with their potential to change body parameters such as temperature and concentrations of cytotoxins such as radicals might increase the risk of nondisjunction but any important contribution from such pathways should show in statistics after major pandemics caused by infectious agents.

In view of the combined findings of Sperling et al. [1] and Irl et al. [3] nonradiogenic hypotheses should be explored to explain the Bavarian cluster and also the Berlin cluster. Even when we concede that geographical correlation studies are of limited value for testing causal relationships, the combined findings and their close temporal - and geographical - relationship (Northern Bavaria was one of only three surface travel gates to Western Berlin in times of the former GDR) should be carefully considered in view of other environmental and infectious agents.

Even when statistical fluctuations and other confounders, which will tend to cluster in time periods showing the largest deviations from long-term means, are taken into account, both the Berlin and the Northern Bavaria peaks in the Down's syndrome incidence remain remarkable. They represent

the highest singular values in both series. Considering the hypothesis that an unknown infectious agent influencing the rate of nondisjunction has passed through the study areas from the South of Germany to the Northeast, an elevated risk in Southern Bavaria has been observed in October 1986, i.e. few weeks before the increased risk in Northern Bavaria. This elevation is significant, too (O=12, O/E=2, 95%CI=1.1-3.4). Still, there is little evidence that maternal infections increase the rate of Down's syndrome. In fact, the only conclusive risk factor is advanced maternal age at conception.

It is obvious that the hypothesis of a non-radioactive external factor is based on unproved theoretical assumptions and has been developed during the analysis of the two series. The reevaluation of the Bavarian data set revealed several significantly increased regional rates, which in two cases even were traced to spatial clusters. Increased rates in Southern Bavaria observed in February and October 1986, respectively, were geographically widespread in one case (October 1986), whereas the increase in February 1986 was due to a cluster occurring in the area of the city of Augsburg (O=4, E=0.43, O/E=9.3, 95%CI=3.0-22.4). The conclusion can be drawn that clusters of Down's syndrome are probably not as uncommon as might be suspected from looking at the Berlin data alone.

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Negative trends for *in utero* Chernobyl exposure and early childhood leukaemia in Western Germany

Burkart, W , Steiner, M , Grosche, B
Institut für Strahlenhygiene, Bundesamt für Strahlenschutz, Postfach 1108,
85758 Oberschleißheim, Germany

Kaletsch, U , Michaelis, J
Institut für Medizinische Statistik und Dokumentation der Johannes-Gutenberg-Universitat Mainz,
55131 Mainz, Germany

Abstract

A recent report in Nature linked increased incidence of early infant leukaemia in Greece with ^{137}Cs fallout density, attributing the effect to an increased *in utero* exposure to ionising radiation from the Chernobyl accident As a validation exercise in a similarly affected region, we performed an analysis based on the data of the Childhood Cancer Registry for Western Germany Using the same definitions as Petridou et al we also observed an increased incidence of infant leukaemia in a cohort of children who were born after the Chernobyl accident More detailed analyses of embryonic/foetal doses regarding areas of different contamination levels and dose rate gradients with time since the accident showed non-significant negative trends with exposure Therefore, we conclude that the observed effect was not caused by exposure to ionising radiation due to the Chernobyl accident Dosimetric considerations per se, based on careful assessments of *in utero* doses in three different exposure categories, show doses much too small relative to natural radiation exposures to account for a significant effect on leukaemia rates

Introduction

Petridou et al [1] reported about infant leukaemia after *in utero* exposure from the Chernobyl accident in April 1986 The authors defined two birth cohorts The first cohort consisted of children who were born in the second half of 1986 and all children born in 1987 These were considered to be exposed and were compared with a combined cohort of children born between January 1980 and December 1985 and of children born between January 1988 and December 1990 The authors found that infants exposed *in utero* by this definition had an increased incidence of leukaemia compared to the „unexposed" children (rate ratio = 2 6, 95%-confidence interval 1 4 to 5 1) In addition, the authors described that children born in regions with increased radioactive contamination had a higher incidence of leukaemia For children diseased at an age of 1 to 4 years no significant results were found Until this publication no increase in incidence or mortality of childhood leukaemia had been reported, neither for areas near Chernobyl nor for other European countries

Due to different regional weather situations in the end of April 1986 in West Germany there was a heterogeneous contamination by the Chernobyl fallout with a south-north gradient About 2 to 50 kBq m^{-2} ^{137}Cs were deposited on the soil with maxima greater than 100 kBq m^{-2} A similar distribution was observed for other radionuclides [2] The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimated an effective dose equivalent of 0 49 mSv due to the Chernobyl accident (1st year) for the population in southern Germany and of 0 33 mSv for the greatest part of Greece [3]

We therefore decided to perform an analysis comparable with that of Petridou et al in order to check whether their observation could be confirmed by an independent study

Material and Methods

Since 1980 the German Childhood Cancer Registry has recorded all malignant diseases for children diagnosed under the age of 15 in West Germany [4] Information on gender, date of birth, date of

diagnosis, type of disease, place of residence at time of diagnosis and a large number of clinical parameters are collected The same birth cohort definitions as Petridou et al were used Children born between 1 July 1986 and 31 December 1987 were considered as being exposed during pregnancy to radiation due to the accident (cohort B) The first cohort (cohort A) and the third cohort (cohort C) covering all children born between 1 January 1980 and 31 December 1986, resp 1 January 1988 to 31 December 1990 were considered as unexposed For further methodological details see Kaletsch et al [5]

For an estimate of the *in utero* exposure of children in the region around Munich, the external gamma radiation due to the ground deposition of radionuclides and the internal radiation originating from radionuclides incorporated by the mother was considered The external gamma dose rate at Munich-Neuherberg had been monitored by the Institute for Radiation Hygiene and the National Research Centre for Environment and Health GSF using a scintillation dosemeter and a proportional counter with a filter for energy compensation, respectively To estimate external shielding, the assumptions of the German Commission on Radiological Protection were adopted Shielding factors for buildings range from 0 03 to 0 3 Our calculations are based on a value of 0 15 The mother is supposed to stay indoor 80% of time The internal shielding factor was calculated taking the ground deposition of radionuclides at Munich-Neuherberg [6] and the resulting gamma spectrum into account It was derived from Ref [7] which refers to a female adult according to ICRP Publication 23

To estimate foetal doses for areas with different ground depositions, available data on mean soil contamination of the 328 administrative districts with ^{137}Cs in May 1986 were used to subdivide West Germany into regions of low (less than 6 kBq m^{-2}), intermediate and high contamination (more than 10 kBq m^{-2}) For 28 of the 328 districts no measurements were available and the contamination was estimated by using the measurements from the neighbourhood areas

Internal radiation predominantly arose from ^{134}Cs, ^{137}Cs, and to a lesser extent from ^{131}I In view of large-distance distribution of foodstuff, data for the whole of Germany were used for the monthly intake of ^{137}Cs [8] The intake rate of ^{134}Cs was estimated from ingestion data of Chernobyl ^{137}Cs and the isotopic ratio $^{137}Cs/^{134}Cs$ = 1 75 of the Chernobyl fallout at Munich-Neuherberg [6]

Ingestion of ^{131}I is only significant for May and June 1986 It was derived from the specific activity of ^{131}I in raw milk in southern Bavaria assuming a consumption rate for dairy produce of 120 kg/a Foetal doses due to ingested radionuclides were derived from an elaborate model which takes into account morphology and growth during pregnancy and appropriate biokinetic models for different gestational stages [9]

Estimates of inhalation doses were based on measurements of activity concentrations of radionuclides in air at Munich-Neuherberg using a filter unit which consisted of aerosol filter, molecular sieve and charcoal

Results

In utero exposure of children was estimated for a hypothetical high-exposure period of pregnancy It starts at 1 May 1986 and lasts until 31 January 1986 The embryonic/foetal doses originating from external gamma radiation and from radionuclides incorporated by the mother were evaluated

The measured external gamma dose rate at Munich-Neuherberg, corrected for the contribution of natural radionuclides, reached values of about 0 9 mSv/h beginning of May 1986 For the gestation period mentioned above a total dose due to external gamma radiation of 447 mSv is calculated Taking a shielding factor of 0 15 for buildings and assuming that the mother stays indoor 80% of time, an external shielding factor of 0 32 is derived For the internal shielding by mother's body, a shielding factor of 0 66 is deduced from Ref [7] The internal shielding factor is based on a reference female adult according to ICRP Publication 23 To give a rough idea about the possible variation of this value, it should be mentioned that an additional layer of 1 cm adipose tissue would reduce the intensity of incident 600 keV photons to about 92% and hence the internal shielding factor would be lowered from 0 66 to 0 61 Variations in mother's dimensions may appreciably change the internal shielding factor In summary, the foetal dose due to external sources is calculated to be about 95 mSv for the hypothetical gestation period

Concerning ingestion, only ^{134}Cs, ^{137}Cs, and ^{131}I (during May and June 1986) significantly contribute to the embryonic/foetal dose The embryonic/foetal doses due to ingestion of ^{134}Cs, ^{137}Cs, and ^{131}I were calculated from the intake rates using the gestation-stage-dependent dose conversion factors listed in Ref [9] For the period May 1986 to January 1987, the foetal dose due to ingestion is about 23 mSv, approximately a fourth of the shielded external gamma dose

To estimate foetal doses in parts of Germany with considerably different ground depositions, an approximate relation between ground deposition in Germany and foetal doses can be derived. Deposition of Chernobyl ^{137}Cs at Munich-Neuherberg amounts to 20 kBq/m^2. The contribution of external gamma radiation to the foetal dose roughly scales linearly with ground deposition within Germany. Hence, for the hypothetical period of pregnancy the total foetal dose is given by

$$H_{foetal} \approx 4.8 \cdot D_{137Cs} + 23 \qquad \text{(for period May 1986 to January 1987)} \qquad (1)$$

where D_{137Cs} denotes the ground deposition of Chernobyl ^{137}Cs in kBq m^{-2} and the foetal dose H_{foetal} is calculated in mSv. The constant term refers to the ingestion pathway. Contributions arising from inhaled activity are not significant.

Table 1 shows the incidence rates and rate ratios for children with acute leukaemia in the first year of life. The incidence of infant leukaemia in cohort B compared to the combined cohorts A and C is significantly increased. The rate ratio is 1.48 with a 95%-confidence interval from 1.02 to 2.15. Calculation of incidence rates for regions with different exposure levels revealed that the greatest difference between the exposed and unexposed birth cohorts is observed for children living in areas with lowest exposure (rate ratio 1.84, 95%-confidence interval 1.21-2.78).

Table 1: Numbers, incidence rates and rate ratios of children with acute leukaemia in the first year of life for the exposed and unexposed birth cohorts in West Germany and regions according to three levels of contamination. In the last column the 95%-confidence intervals are given.

Areas with mean ground deposition of ^{137}Cs	Exposed birth cohort		Unexposed birth cohorts		Rate ratio	95% CI
	Number	Incidence rate*	Number	Incidence rate*		
< 6 kBq m^{-2}	29	41.6	96	22.7	1.84	1.21-2.78
6 - 10 kBq m^{-2}	1	8.9	24	35.1	0.26	0.03-1.89
>10 kBq m^{-2}	5	41.5	23	32.1	1.29	0.49-3.40
total West Germany	35	37.7	143	25.4	1.48	1.02-2.15

* per 10^6 new-born

Radiation exposure after the Chernobyl accident showed quite steep dose rate gradients with time in West Germany. Therefore, a potential excess of infant leukaemia due to intrauterine radiation exposure should be more clearly marked in times of higher exposure. In order to study a potential time trend, the birth cohort B is divided into two parts. The subcohorts comprise children born in the 9 months from 01.07.1986 to 31.03.1987 and from 01.04.1987 to 31.12.1987, respectively. The results of the corresponding calculations showed a trend which was opposite to the hypothesis: The rate ratio for the first subcohort of B in comparison to cohorts A and C is smaller (1.29, 95%-CI 0.76-2.20, based on 15 cases in the exposed time interval) than the corresponding value for the second subcohort (1.67, based on 20 cases in the exposed subcohort).

Discussion

Based on data of the German Childhood Cancer Registry it was analysed whether similar to the observation of Petridou et al. an increase of infant leukaemia for children born after the Chernobyl accident could be shown. Comparable effective dose equivalents resulting from the contamination due to the accident were calculated for children in Greek and parts of West Germany, so that many children in both countries had comparable risks.

The analyses of the German incidence rates are based on a population at risk in the exposed time period which is about six times as large as that in the study of Pertridou et al.. Therefore estimates of a potential risk may be more precise.

Similar to the results of Petridou et al. the analyses of the West German data showed an increase in the incidence of infant leukaemia for children of a birth cohort born after the Chernobyl accident in comparison to two unexposed cohorts. However, the highest rate ratios were observed in regions of lowest contamination and a partition of the „exposed" birth cohort in an early and a late subset showed

higher rate ratios in the less exposed late subset These findings do not support a causal relationship between intrauterine exposure and the occurrence of infant leukaemia

Although the observed increase of the incidence of infant leukaemia cannot be attributed to an *in utero* exposure to ionising radiation originating from the Chernobyl accident, it may still be explained as an effect of the accident Possibly, the accident has caused an increased diagnostic awareness of physicians who may have diagnosed the disease somewhat earlier A similar mechanism was also discussed in relation to an incidence peak of neuroblastoma following the Chernobyl accident [10]

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RADIO-EPIDEMIOLOGICAL SURVEY IN CLEANUP WORKERS WHO TOOK PART IN THE LIQUIDATION OF THE ACCIDENT AT THE CHERNOBYL NPP

I.V. ROLEVICH, I.A. SIVOLOBOVA, A.E. OKEANOV, Ja.E. KENIGSBERG
Ministry of Emergencies of the Republic of Belarus,
Ministry of Health of the Republic of Belarus,
Belarus

Abstract

Diseases of digestive organs, nervous system and sense organs, bone-muscle system, cardio-vascular system prevail in group of liquidators. For the last 6 years two peaks of primary morbidity (1992-1993 and 1995-1996) were observed. Growth of psycho-somatic and somatic pathology was marked in 1996. The given tendency foretells noticeable increase in primary physical inability rate and requires urgent development of measures on its correction.

Analysis of medical consequences of the Chernobyl accident is closely connected to determination of biological effects, caused by ionising radiation. It is especially important to evaluate specific effects within those workers who participated in liquidation of the Chernobyl (liquidators), particularly in the group of liquidators of 1986-1987, who received the most significant radiation dozes.

Analysis of morbidity within the liquidators is based on the data received after examination of 79,700 people, including 49,600 liquidators of 1986-1987. Dozes were analysed within the group exceeding 7,700 people.

Evaluating the health status of the given cohort of Belarus population one should note its unsatisfactory status. Thus, according to the data received by the end of 1996, only 13,5 % of all liquidators and 10,7 % of the liquidators of 1986-1987 are considered as "healthy", accordingly 25,4 and 24,3 % of the liquidators (health groups D1 and D2) are considered to be "practically healthy" and 61,2 and 65 % (health group D3) have chronic diseases of a different level of compensation. Growth of chronic morbidity at liquidators is a natural consequence of their getting old for the 11 years after the moment of the Chernobyl accident. It is also the main reason of the increase of their physical inability. During the last year a primary physical inability was registered as 76,4 per 10 thousand of liquidators. Within the liquidators of 1986-1987 the number reached 87,8. Almost every second liquidator's physical inability is connected to the consequences of the Chernobyl accident (45% and 54,2% of cases accordingly).

Morbidity of the liquidators, as a whole, is much higher, than of the adult population of the republic. Comparing dynamics of the general morbidity, starting from 1993 it is possible to conclude, that it was exceptionally high in 1993. During the subsequent years its gradual decrease was marked, and in 1996 the primary morbidity exceeded overall indices in the republic in 1,7 times. This characteristic relates mainly to nozological forms of illnesses. Nevertheless there is a number of exceptions: continuing increase of frequency in such classes of illnesses as endocrine system illnesses, digestion disorders, disorders in metabolism and immune system

Analysing the data on general morbidity of the liquidators one needs to take into account distinctions in demographic parameters of the liquidators and population of the republic. Thus, if the overwhelming majority of the liquidators (88%) is aged 25-59 years old and are basically men, then among the population of the republic this age group makes up 68%, with women prevalence.

Examination of certain nozological forms of illnesses shows high frequency of morbidity of the liquidators by neoplasms On the average it is 1,6-1,7 time higher in the liquidators, than in the population of the republic, though disclosure of neoplasms in the first group is slightly lower For the period from 1993 to 1996 the increase in occurrence is noticed among the following malignant neoplasms thyroid cancer (growth in 1,7-2,8 times), lymphatic and blood tissue neoplasm (growth in 2,3-2,6 times), as well as severe leukosys (growth in 2,4-3,9 times)

Among the diseases of endocrine system in liquidators the leading place is occupied by illnesses of thyroid gland Growth in quantity of this illness reaches 11,8 times and was especially noticeable in 1993 (12,7 times)

In the structure of illnesses of the endocrine system this pathology is observed in liquidators in 74-83% of all cases (in the population of the republic - 49-60%)

The most widespread illness of thyroid gland is goiter, especially its nodular forms and thyroiditis, and thyrotoxicosis, chiefly auto-immune and acquired thyroprivia In the structure of thyroid illnesses in 1996 in the liquidators 78% was occupied by goiter, thyrotoxicosis - 6,5%, thyreonditis - 5,9%, acquired thyroprivia 1,4% (last 3 nozological forms make for the population of the republic accordingly 2,7%, 10,2% and 2,6% of cases). Increase of diabetes mellitus cases in liquidators in 2,4-3,6 times is accompanied by similar decrease of specific weight of diabetes mellitus in the structure of illnesses of endocrine system

Cataracts are also rather frequently observed in liquidators These cases are detected around 3,9 times oftener than in the republic as a whole, though during the last years their slight reduction was noticed

In general morbidity of the liquidators the first place is occupied by illnesses of digestion, nervous system and organs of sense Boundary nervous-psychological disorders can be also attribute to this group of illnesses since they are extremely frequently meet in the liquidators The second place of illnesses is composed of illnesses of bone-muscle system, cardio-vascular system and breath organs They have practically similar values of frequency of occurrence with chronic diseases Illnesses of endocrine, urine system and oncological pathology are on the third place

According on the degree of distribution of illnesses the primary morbidity is arranged in the following way pathology of digestion organs, nervous system, bone-muscle, cardio-vascular system, breath organs, endocrine system, psychological disorders, urine system illnesses, neoplasms, illness of skin and under skin cellular system, blood system However, according to the rates of growth for the investigated period the first place is occupied by illnesses of endocrine system, the second - bone-muscle system illnesses, the third - nervous, the fourth - blood circulating organs, the fifth - urine system and the sixth - breath organs

Attention must be paid to a significant increase in morbidity on the majority of classes and headings in 1995 In 1992-1993less expressed peak of morbidity was observed on such headings as viral illnesses, thyroiditis, essential hypertension, ulcer, gastro-duodenitis, urolithiasis, obesity, trauma and poisoning

One can notice high frequency of neoplasms in the liquidators - 1,7-1,6 times oftener, than in republic as a whole

Mortality of the liquidators for the last four year has increased - average rate for each year reaches 16,6 times, however it is lower, than mortality of the general population of the republic The main reasons of death of the liquidators, as well as of the population of the republic, are illnesses of cardio-vascular system, neoplasms, trauma and poisoning There is also a high frequency of self-murders in the liquidators observed

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RADIATION RISK IN SPACE EXPLORATION

W. Schimmerling, J. W. Wilson, F. Cucinotta, and M-H Y. Kim
National Aeronautics and Space Administration
Washington, DC 20546-0001
United States of America.

Abstract

Humans living and working in space are exposed to energetic charged particle radiation due to galactic cosmic rays and solar particle emissions. In order to keep the risk due to radiation exposure of astronauts below acceptable levels, the physical interaction of these particles with space structures and the biological consequences for crew members need to be understood. Such knowledge is, to a large extent, very sparse when it is available at all. Radiation limits established for space radiation protection purposes are based on extrapolation of risk from Japanese survivor data, and have been found to have large uncertainties. In space, attempting to account for large uncertainties by worst-case design results in excessive costs and accurate risk prediction is essential. It is best developed at ground-based laboratories, using particle accelerator beams to simulate individual components of space radiation. Development of mechanistic models of the action of space radiation is expected to lead to the required improvements in the accuracy of predictions, to optimization of space structures for radiation protection and, eventually, to the development of biological methods of prevention and intervention against radiation injury.

1. SPACE ENVIRONMENT

Human crews engaged in exploration of space will be exposed to weightlessness and to space radiation. The effects of radiation exposure thus need to be considered in the context of weightlessness. Removal of the force of gravity results in structural and functional changes, especially in weight-bearing muscle, bone, and connective tissue. Changes also occur during space flight in endocrine, hematological, immunological, metabolic, nutritional and gastrointestinal, renal, sleep, biological rhythms, and temperature regulation; changes in pharmacokinetics and pharmacodynamics may further confound crew health care. Changes in immune function may be related to living in a "closed environment" -- the space habitat, the effect of stress during launch or landing, inhibition of white cell maturation due to microgravity or other factors.

Outside the protection afforded by the Earth magnetic field and atmosphere, the main penetrating components of ionizing space radiation are protons (and some heavier particles) emitted in the course of solar energetic particle (SEP) events, and protons and the energetic nuclei of other elements (HZE – high atomic number Z and energy E – particles) that constitute galactic cosmic rays (GCR). The SEP protons have energies up to several hundred MeV and intensities that can increase by four or five orders of magnitude within a few hours during a solar disturbance. In an unshielded environment, SEP particle fluxes have the potential to cause acute radiation effects, but several techniques, such as seeking refuge in a

well shielded "storm shelter", can be used to keep the dose from SEP particles within acceptable limits. The important open questions related to SEP events deal with the solar physics of their origin. While some biological questions remain about the radiation risk induced by protons, the physical aspects of their interaction with matter are relatively well-known. Thus, from the point of view of radiation protection, given adequate monitoring and warning, the risk can be predicted fairly accurately and managed using operational procedures.

This is not the case for HZE particles, which present new and significant problems for radiation protection, that have not yet been resolved. The relative abundances of GCR particles between protons and iron, and typical energy spectra, are shown in Fig. 1. Such heavy particles, with energies of several hundred MeV per nucleon, will suffer nuclear interactions in spacecraft materials that result in fragmentation of the projectile into lighter nuclei proceeding roughly in the direction of the incident nucleus.

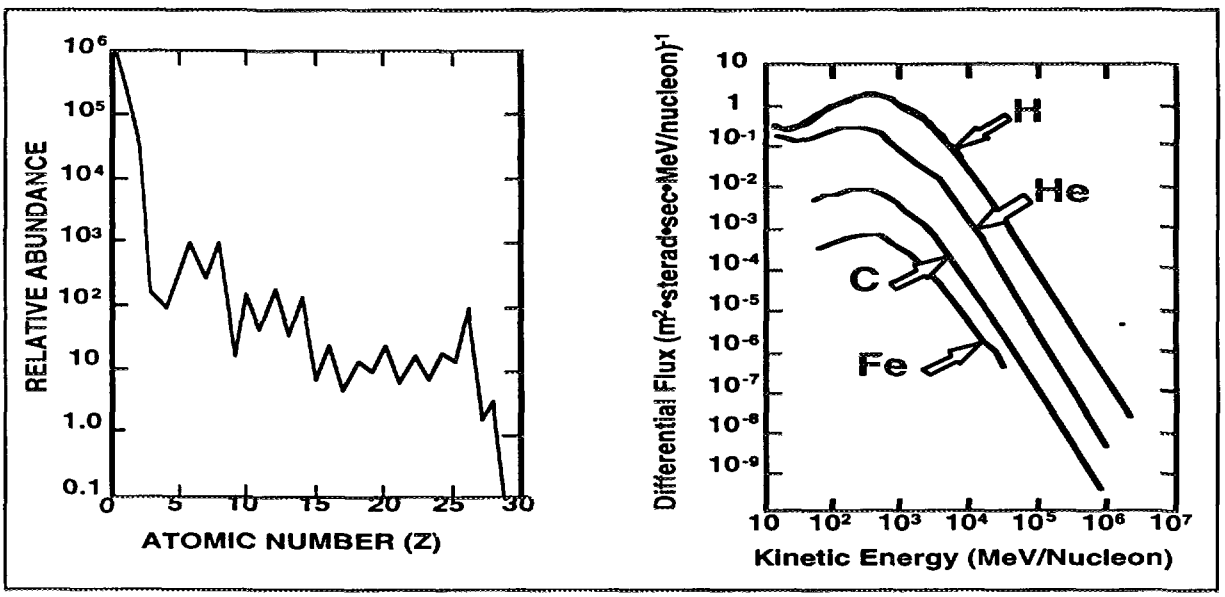

Figure 1. Relative abundances, redrawn after Mewaldt [1] and selected energy spectra, redrawn after Simpson [2], for galactic cosmic ray nuclei.

2. RADIATION RISK

The HZE particles are highly penetrating, with ranges comparable to body dimensions. The linear energy transfers (LET) are in the range of 10 to several thousand keV/μm. The relative biological effectiveness (RBE) of high-energy heavy ions has been measured for various end-points. It increases non-linearly from ~ 30 to ~ 200 keV/μm, with a peak around 100 keV/μm. A plot of LET vs. range is shown in Figure 2(a), and the maximum RBE region has been shaded, showing that HZE particles fall in the region of maximally effective radiation. The quality factor, Q, used in radiation protection, is correlated conceptually with RBE. Average quality factors, Q, for the GCR component, evaluated using measured distributions of LET and internationally recognized assumptions regarding the dependence of Q on LET [3,4] are between 2.3 and 3.4 [5].

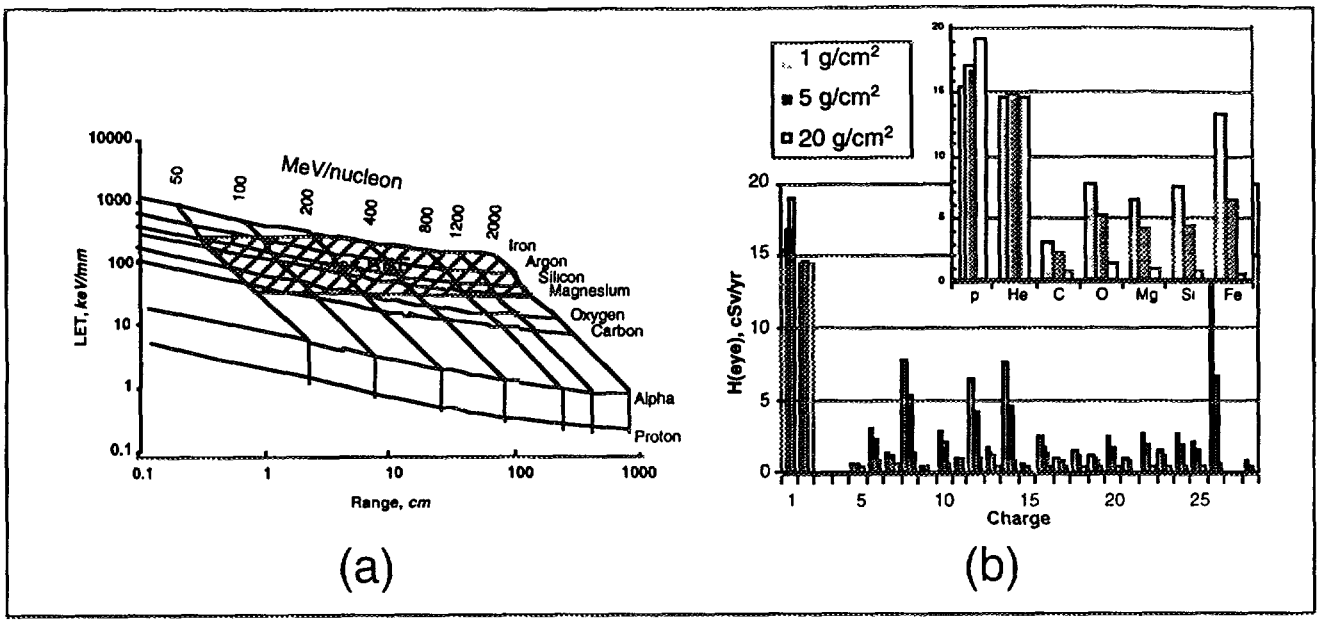

Figure 2. (a) Linear energy transfer (LET) as a function of range in water for selected HZE particles. Lines of constant velocity (expressed as energy per nucleon) have been indicated for each particle. The region corresponding to particles of maximum relative biological effectiveness (RBE) has been shaded. (b) The most significant components of space radiation, according to the dose equivalent to the eye behind 1, 5, and 20 g/cm^2 of polyethylene (approximately tissue-equivalent).

Current radiation limits (Table I) apply only to low Earth orbit activities, such as the International Space Station. Short-term radiation limits for astronauts are intended to ensure

TABLE I. Low Earth orbit radiation limits [3]

	Blood-forming organs (5 cm depth) Sv	Eye (0.3 cm depth) Sv	Skin (0.01 cm depth) Sv
30-day	0.25	1.0	1.5
Annual	0.5	2.0	3.0
Career	2.0 + 0.075 x (age - 30) for males 2.0 + 0.075 x (age - 38) for females		

that exposure to space radiation does not result in acute effects. Annual and career limits are intended to limit the risk to be less than an "acceptable risk" [6]. The acceptable risk is currently defined as a 3 per cent excess probability of fatal cancer above the background rate for the working US population.

The uncertainties associated with estimation of the risk from long-term exposure to HZE [7] are sufficiently large to prevent a meaningful definition of this risk at the present time. The conventional prediction of risk due to HZE particles for a given mission proceeds by evaluating the interplanetary space radiation environment during the mission. For a given spacecraft mass distribution and assumptions about the geometry of crew member bodies,

radiation transport calculations [7] are used to calculate the radiation field inside the spacecraft and at crew organs. The cancer risk associated with the physical dose is estimated based on extrapolation of the risk obtained from atomic bomb survivor studies, corrected for dose rate effects and for the different biological effectiveness of HZE particles. A Task Group of the US National Academy of Sciences recently estimated [8] the resulting uncertainties to be within a factor of 4-15.

A substantive research program is currently sponsored by NASA, with collaboration of other national and international agencies, using ground-based simulation of space radiation to develop the radiobiological knowledge required to predict risk from HZE particles accurately enough to define radiation limits for the human exploration of space.

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CYTOGENETIC INVESTIGATION OF THE INHABITANTS OF THE RADIATION POLLUTED DISTRICTS OF KAZAKHSTAN

Nazira B. Achmatullina

Institute of General Genetics and Cytology of Ministry of Science - Academy of Science of the Republic of Kazakhstan

Abstract

Since 1993, genetic consequences are investigated of nuclear testing at Semipalatinsk, including chromosome aberration studies of 200 inhabitants from six regions near the test ground. Preliminary data on percentage of cells with aberrations versus ranges of age are given.

During half century on a territory of Kazakhstan placed some test nuclear grounds of armed forces of the former Soviet Union. One of them - Semipalatinsk's Test Ground (STG) came into the number of the largest in the world. There were made 473 nuclear bursts (among them 87 air bursts and 26 ground bursts). The numerous direct and analytical measurements of our and foreign researchers have revealed the significant pollutions of the territory, bordering to this test ground by radionuclids Cs 137, Sr 30, H3, C14, U235, U239, Pu239, Pu241 etc. The regions of these testgrounds were studied weakly or not studied absolutely.

Long existence of the testgrounds, variety of tested kinds of a weapon and size of a left radiating trace turned the territory of Kazakhstan to unique laboratory.

The hard regime of secrecy, created around the activity of state ground didn't permit to realise any estimation of its action at the health of millions people, living in this region. Only since 1993 we have received the opportunity to study genetic consequences of actions of radiating conditions.

For the present we were successful in investigation of about 200 inhabitants from 6 regions close fitting to the territory of STG. At cytogenetic analysis we took into account the aberrations of the chromatidic and chromosomal types of about 20000 methaphases. As markers of radiating effect are considered free pair fragments, dicentrics, translocations, ring chromosomes (Tabl. I).

In all inspected groups the statistically authentic increasing of frequency of chromosomal aberrations are discovered in comparison with the spontaneous level (1,0-1,2% in the middle band of Russia). The constancy of detection of increased number of chromosomal aberrations at the young people (till 40 years) and at the children of 15-17 years i.e. in the second and third generations of the people, living not far from the test ground. These data are confirmed by independent researches of the foreign scientists.

Table I

The frequency of chromosomal and chromatidic aberrations of inhabitants of the region of STG

Inspected inhabitants of settlements, age	Total, persons	% cells with aberrations		
		total	chromosomal	chromatidic
Sarjal	35	3,77±0,23	1,29±0,13	2,48±0,22
> 40 years	22	3,80±0,25	1,23±0,18	2,57±0,10
< 40 years	7	4,36±0,61	1,43±0,25	2,93±0,66
under 17 years	6	3,60±0,76	1,60±0,16	2,00±0,45
Buras	23	3,21±0,17	1,75±0.14	1,46±0,18
> 40 years	10	3,35±0,7	1,8±0,45	1,55±0,20
< 40 years	13	3,12±0,46	1,7±0,35	1,42±0,27
Dolon	29	4,0±0,23	2,3±0,19	1.7±0.17
> 40 years	10	3,10±0,6	1,85±0,36	1,25±0,30
< 40 years	8	4,56±0,74	2,56±0,44	2,0±0,32
under 15 years	11	4,6±0,35	2,6±0,30	2,0±0,22
Mostic	12	4,0±0,27	2,3±0,24	1,7±0,32
> 40 years	12	4,0±0,27	2,3±0,24	1,7±0,32
Karaul	28	4,1±0,37	2,3±0,33	1,8±0,22
> 40 years	28	4,1±0,37	2,3±0,33	1,8±0,22
Kurchatov	13	3,62±0,29	1,85±0,26	1,77±0,2
> 40 years	13	3,62±0,29	1,85±0,26	1,77±0,2

XA9745596

LEVELS OF ENDOGENOUS REGULATORY FACTORS IN LIQUIDATORS OF CONSEQUENCES OF THE CHERNOBYL ACCIDENT

Liasko L. I., Souchkevitch G.N.*, Tsyb A.F.

Medical Radiological Research Center of RAMS, Obninsk, Russia
Present address: World Health Organization, Office for Environmental Health, Geneva Switzerland

Abstract: Dynamics of endogenous regulatory factor levels was studied in liquidators of consequences of the Chernobyi accident (mean age - 42 years). Irradiation dose for 90 % of examined individuals was within 100 mSv range. We observed a decreased level of synthesis of intracellular processes regulators (cAMP, cGMP) and biased ratio of arachidonic acid metabolites (TxB2, 6-Keto-PGF1α) in persons worked in the zone of accident at different time during the period of 1986-1988. The parameters measured were preserved even 4 years later and the changes apparently did not depend on the individual's age and work conditions. However they were most pronounced in liquidators of 1986 and in those who stayed in the Chernobyl accident zone for a long time. There was no evident connection between the dose and extent of the parameter alterations.

Analysis of liquidators' morbidity reveals an increase in diseases of hematological organs and endocrine system as well as nerve system, sensation organs and mental disorders i.e. in such pathological manifestations which are not characteristic for radiation damages but rather reflect functional imbalance of polyethiological nature occurring in protective and regulatory systems of organism.

This observation comprised a basis for the detailed examination of intracellular regulators' status which was ascertained by levels and ratio of cyclic nucleotides (cAMP, cGMP) and of stable metabolites of arachidonic acid (TxB2, 6-Keto-PGF1α) in blood of 130 liquidators in dynamics. Levels of the above parameters in donors served as a control.

Table I. DYNAMICS OF ENDOGENOUS REGULATORY FACTORS INDICES IN LIQUIDATORS AND INDIVIDUALS OF CONTROL GROUP

Parameters	Controls	Liquidators (M±m)		Units
		After 2 Yr.	After 4 Yr.	
6-keto-PGF1α	160.5±23.50	71.5±5.30*	56.5±6.03*	pg/ml
TxB2	19.4±3.00	249.2±16.09*	90.8±18.29*	pg/ml
6-keto/TxB2	7.9±2.9	0.2±0.08*	1.0±0.33 *	index
cAMP	113.6±15.20	14.9±0.76*	14.1±1.00*	pmol/ml
cGMP	30.1±2.62	11.1±0.64*	1.3±0.24*	pmol/ml
cAMP/cGMP	3.6±0,49	1.4±0.25*	19.5±2.29*	index

* significant difference between liquidators and controls

Analysis of data obtained allowed us to demonstrate certain changes in endogenous regulator levels in approximately 80 % of examined individuals (Table I). Two years after the accident level of 6-Keto-PGF1α had decreased and along with this TxB2

concentration had gone up. As a result a marked (up to 30 times) decrease in ratio of these metabolite concentrations was observed, what reflects an unambiguous change of ratio of their active precursors content - prostacyclin (PGI2) - strong endogenous vasodilator, and thromboxane A2 - most powerful vasoconstrictor known. Concentrations and ratio of cyclic nucleotides content corresponded to the minimal levels in control samples too. The observed changes suggest that the impair of intracellular regulatory processes has taken place and since the phenomenon was observed in both 2- and 4-year time points one may assume that it was stably persisting for whole 4 year long period of observation.

Analysis of data regarding to the liquidators' age showed that the revealed imbalance of prostanoid and cyclic nucleotides content was characteristic for whole cohort of liquidators and it was most pronounced in persons aged 40 years and more (Table II).

Table II. LEVELS OF ENDOGENOUS REGULATORY FACTORS IN LIQUIDATORS OF DIFFERENT AGE GROUPS 4 YEARS AFTER THEY HAD LEFT THE ZONE.

Parameters	Liquidators (M±m)			Units
	30 - 40 years	41 - 50 years	> 50 years	
6-keto-PGF1α	46.2±6.13	58.9±10.92	58.4±11.54	pg/ml
TxB2	71.3±8.51	130.1±41.32	119.1±19.04	pg/ml
cAMP	10.0±0.51	14.2±1.21	13.8±1.27	pmol/ml
cGMP	1.4±0.16	1.6±0.48	1.1±0.48	pmol/ml
Mean dose	55	27	107	mSv

Study of endogenous regulatory factor levels in liquidators in regard to the character of jobs performed demonstrated that the revealed bias occurred in any generalized group of specialists: drivers, builders, service engineers and design engineers (Table III).

Table III. LEVELS OF ENDOGENOUS REGULATORY FACTORS IN LIQUIDATORS OF DIFFERENT PROFESSIONAL GROUPS 4 YEARS AFTER THEY HAD LEFT THE ZONE.

Parameters	Liquidators (M±m)				Units
	drivers	builders	service engineers	design engineers	
6-keto-PGF1α	44.76±15.28	44.9±9.68	47.7±0.52	57.8±8.29	pg/ml
TxB2	121.3±22.46	104.9±14.09	67.5±3.71	101.6±22.93	pg/ml
cAMP	10.5±0.94	12.6±0.84	16.3±0.75	14.3±0.89	pmol/ml
cGMP	1.2±0.70	1.1±0.17	1.6±0.32	1.0±0.49	pmol/ml
Mean dose	22	93	15	79	mSv

Comparative analysis of prostanoid levels as a function of duration of liquidators' stay in the accident zone suggests there is a positive correlation between these two parameters (Table IV). Minimal level of prostanoids in 4 year time point was registered in those individuals who have spent long time (more than 3 months) in the zone of accident and maximal one in those with short time of stay. There was no apparent correlation between the changes observed and irradiation dose. Parameters other than the discussed ones showed no conformity regarding the duration of stay in the zone.

Table IV. ENDOGENOUS REGULATORY FACTOR PARAMETERS AS A FUNCTION OF DURATION OF STAY IN THE ACCIDENT ZONE

Parameters		Units	Liquidators (M±m)			
			0 - 1 month	1.1 - 2 months	2.1 - 3 months	> 3 months
6-keto-PGF1α	1	pg/ml	60.9±12.24	38.9±14.37	47.1±9.16	70.4±33.52
	2			61.7±11.48		4.4±11.36*
TxB2	1	pg/ml		297.7±52.87		283.0±46.24
	2		134.0±26,70	101.1±16.08	76.2±13.64*	38.1±12.10*
cAMP	1	pmol/ml		18.8±7.98		8.9±1.84
	2		16,2±1.36	12.4±0.73	13.5±0.84	16.7±0.72
cGMP	1	pmol/ml		10.0±1.73		12.9±3.49
	2		2.1±0.60	1.2±0.28	1.2±0.34	1.7±0,28
Mean dose	1	mSv		33±1.01		255±2.10
	2		89±2.71	30±1.56	86±5.59	98±2.23

* significant difference from the group of individuals stayed for 0-1 month in the accident zone
1- after 2 years; 2- after 4 years

Analysis of endogenous regulatory factor levels in liquidators of 1986, 1987 and 1988 years certifies that the observed alterations occurred in all these groups and they were most pronounced in liquidators of 1986 (Table V). Maximal level of TxB2 was found to be in liquidators of 1986 and 1987 years and minimal one in those of 1988. Level of final prostacyclin metabolite was found to be diminished in all the groups and minimal values were observed in liquidators of 1988. Prostanoid levels ratio was biased from normal in all the groups either, being most demonstrative in liquidators of 1986. Cyclic nucleotides ratio changed in the same manner. In the group of liquidators of 1986 this value exceeds the control index 5-fold and in the groups of 1987 and 1988 cAMP/cGMP ratio is twice as normal.

Table V. LEVELS OF ENDOGENOUS REGULATORY FACTORS IN LIQUIDATORS OF 1986,1987 AND 1988 AS MEASURED 4 YEARS AFTER THEY HAD LEFT THE ZONE

Parameters	Liquidators (M±m)			UNITS
	1986	1987	1988	
6-keto-PGF1α	56.5±6.03	49.7±0.20	19.8±0.69	pg/ml
TxB2	90.8±18.31	96.0±21.09	39.1±7.17	pg/ml
6-keto/TxB2	1.2±0.33*	0.7±0.20	0.6±0.13	index
cAMP	14.1±1.00	18.8±0.79	14.3±1.07	pmol/ml
cGMP	1.4±0.24	1.5±0.37	1.4±0.37	pmol/ml
cAMP/cGMP	19.5±2.30*	9.2±2.70	10.2±2.28	index
Mean dose	61	62	28	mSv

* significant difference from data for liquidators of 1987 and 1988.

Thus individuals participated at different time in works in the Chernobyl accident zone 2 years later exhibit the alteration of intracellular regulator levels. These changes persist for 4 years and don't depend on individual's age and character of work performed in the zone of accident. However the alteration is most pronounced in liquidators of 1986 and in those who stayed in the zone for a long period of time. We did not find connection between the changes revealed and the dose. Broad spectrum of physiological effects of prostanoids allows one to suggest their possible involvement into primary biochemical processes arising as a response to chemical, physical, toxic, stress and other types of extremal factors.

HEALTH EFFECTS OF LOW-DOSE RADIATION: MOLECULAR, CELLULAR, AND BIOSYSTEM RESPONSE

Myron Pollycove* and Carl J. Paperiello**
U.S. Nuclear Regulatory Commission, Washington, DC

XA9745597

Abstract **- Since the fifties, the prime concern of radiation protection has been protecting DNA from damage. UNSCEAR initiated a focus on *biosystem response* to damage with its 1994 report, "Adaptive Responses to Radiation of Cells and Organisms." The DNA damage-control biosystem is physiologically operative on both metabolic and radiation induced damage, both effected predominantly by free radicals. These adaptive responses are suppressed by high-dose and stimulated by low dose radiation. Increased biosystem efficiency reduces the number of mutations that accumulate during a lifetime and decrease DNA damage-control with resultant aging and malignancy. Several statistically significant epidemiologic studies have shown risk decrements of cancer mortality and mortality from all causes in populations exposed to low-dose radiation. Further biologic and epidemiologic research is needed to establish a valid threshold below which risk decrements occur.**

For more than 40 years radiation protection has been primarily concerned with protecting DNA against radiation damage. This predominant concern was the logical consequence of new data in the fifties on the molecular structure of DNA and its damage in linear proportion to radiation dose, and the newly observed roughly linear increase of leukemia and cancer in atomic bomb survivors in proportion to high-doses of radiation. In 1994, after two decades of epidemiologic and biologic research at molecular, microdosimetric, cellular, organ, and intact organism levels, UNSCEAR focused upon *biosystem response* to damage and in 1994 published its watershed report, "Adaptive Responses to Radiation in Cells and Organisms." [1]

Over eons of time, as multicellular animals developed and metabolized oxygen, a complex DNA damage-control biosystem evolved (Fig. 1) [2]. In this attempt to place metabolic DNA damage into perspective, estimates are based on the literature. Human metabolism produces about 10^6 metabolic DNA alterations per cell per day from thermal instability, DNA replication, and, predominantly, from free radicals that are derived from 2-3 % of all metabolized oxygen. Corresponding cellular and DNA damage is largely prevented by antioxidants that scavenge approximately 99% of these free radicals. The resultant ~10^6 DNA alterations/cell/d are then efficiently repaired enzymatically so that only ~1 in ten thousand is mis-or unrepaired. These are defined as mutations. Most of these remaining ~10^2 mutations/cell/d are eventually removed by apoptosis, induced differentiation, immune response, and tissue necrosis. Relatively few persist, ~1/cell/d, accumulating during a lifetime to decrease DNA damage-control with resultant aging and malignant growth, still removable by the immune system [2]. This remarkably efficient biosystem prevents precocious aging and malignancy unless impaired by genetic defects, or damaged by high doses of radiation or other toxic agents.

How does background radiation add to this metabolic accumulation of mutations? A much larger fraction of double strand breaks within 5 base positions occurs in DNA alterations produced by radiation than in those produced by metabolism ($2x10^{-2}$ vs $2.5x10^{-5}$). The mis-unrepaired fraction of these double strand breaks is also much larger than that of other metabolic DNA alterations (~10^{-1} vs ~10^{-4}). Nevertheless, the number of metabolic DNA alterations (~10^6/cell/d) is so much greater than the number of alterations from low LET background of 100 mr/y ($5x10^{-4}$/cell/d), that just ~10^{-5} radiation mutations/cell/d are added to ~10^2 metabolic mutations/cell/d [2]. These relatively few radiation induced mutations also are almost all removed by the DNA damage-control biosystem (Fig.1).

*Visiting Medical Fellow **Director, Office of Nuclear Materials Safety and Safeguards

The efficiency of this biosystem is increased by the adaptive responses to low-dose ionizing radiation This is well documented in UNSCEAR 1994

"There is substantial evidence that the number of radiation-induced chromosomal aberrations and mutations can be reduced by a small prior conditioning dose in proliferating mammalian cells *in vitro* and *in vivo* "

"There is increasing evidence that cellular repair mechanisms are stimulated after radiation-induced damage Whatever the mechanisms, they seem able to act not only on the lesions induced by ionizing radiation but also on at least a portion of the lesions induced by some other toxic agents "

"As to the biological plausibility of a radiation-induced adaptive response, it is recognized that the effectiveness of DNA repair in mammalian cells is not absolute An important question, therefore, is to judge the balance between stimulated cellular repair and residual damage "

This statement applies not only to the mutations produced by radiation and other toxic agents, but also to the unmentioned *enormous number of daily metabolic mutations The operative effect of reducing metabolic mutations by the adaptive response of the DNA damage-control biosystem to low-dose radiation is the critical factor*, not the insignificant number of mutations produced by low-dose radiation This factor must be considered, "to judge the balance between stimulated cellular repair and residual damage "

Assuming a 10% increased efficiency of biosystem control in response to an increase of annual background radiation from 1mGy/y, to 1cG/y, radiation mutations would indeed increase from $1/10^5$cells/d to $9/10^5$cells/d but *metabolic* mutations would *decrease* from ~$10^7/10^5$cells/d to ~$9x10^6/10^5$cells/d "The balance between stimulated cellular repair and residual damage" is a *decrease* of total mutations from ~$10^7/10^5$cells/d to ~9 00009x$10^6/10^5$cells/d, a net reduction of ~10^6 mutations/10^5cells/d, every day

UNSCEAR did not consider that the non-linear increase of radiation mutations is negligible compared to the operative effect of the adaptive response to low-dose radiation upon the very high background of metabolic mutations *The biological effect of radiation is not determined by the number of DNA mutations it creates, but by its effect on the body's protective processes* At high levels, radiation suppresses them, at low levels, it stimulates the DNA damage-control biosystem

These biologic findings predict that exposure to low-dose radiation would decrease mortality from aging and malignancy, and these predictions are confirmed by many epidemiologic studies Decreased mortality and decreased cancer mortality have been observed in populations exposed to high natural background radiation in the U S , China, Japan India, Austria, and the U K , and with *high statistical significance* in the following studies

- U S Nuclear Shipyard Worker Study (1991) Mortality of exposed workers is decreased 24% below unexposed workers (Fig 2) [1]
- Atom Bomb Survivor Mortality (1993) Mortality is decreased in the exposed survivors [3]
- Irradiated Eastern Urals Population (1994) Cancer mortality of the groups exposed to 120mSv and 500mSv is decreased by 39% and 28%, respectively [4]

- University of Pittsburgh Radon Study (1995). Lung cancer mortality decreases progressively as residential radon increases from 1 to 7pCi/L (Fig. 3) [5]. Similar findings in Japan and China.

- Canadian Fluoroscopy Breast Cancer Study (1989). Breast cancer mortality of the groups exposed to 150mSv and 250mSv is decreased by 34% and 16%, respectively (Fig. 4) [6].

Similar carefully controlled epidemiologic studies are needed for other malignancies and for mortality from all causes. In this way, a valid threshold can be established for the general public.

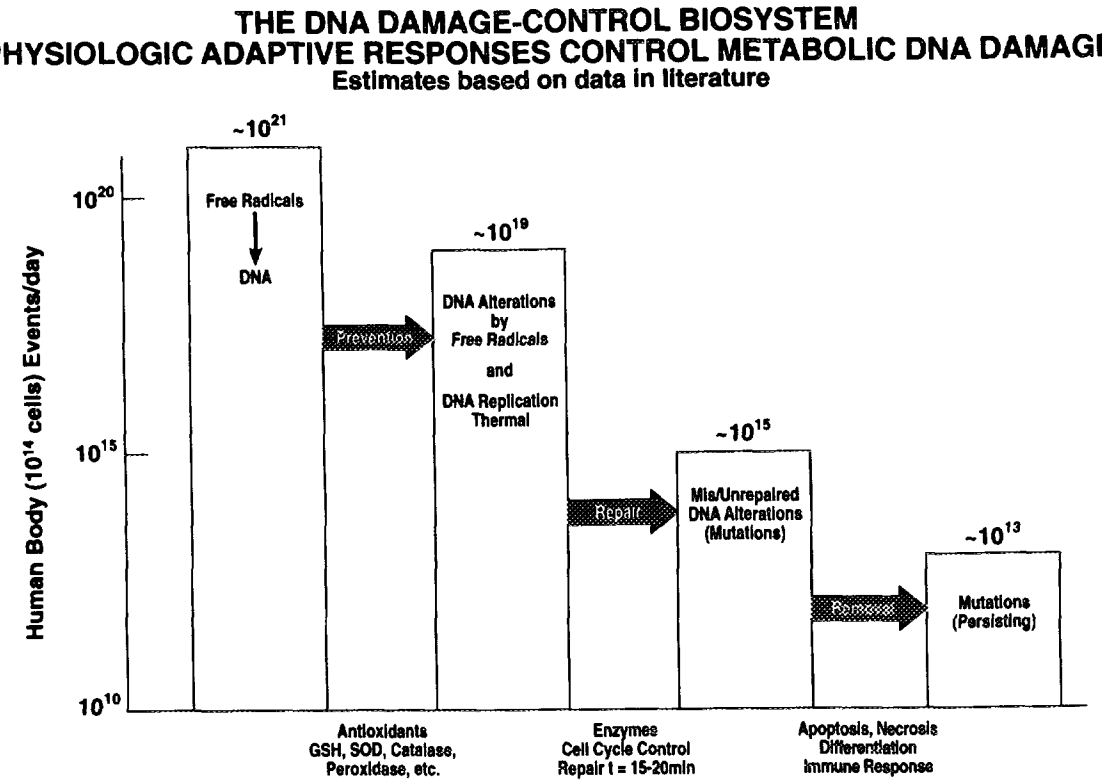
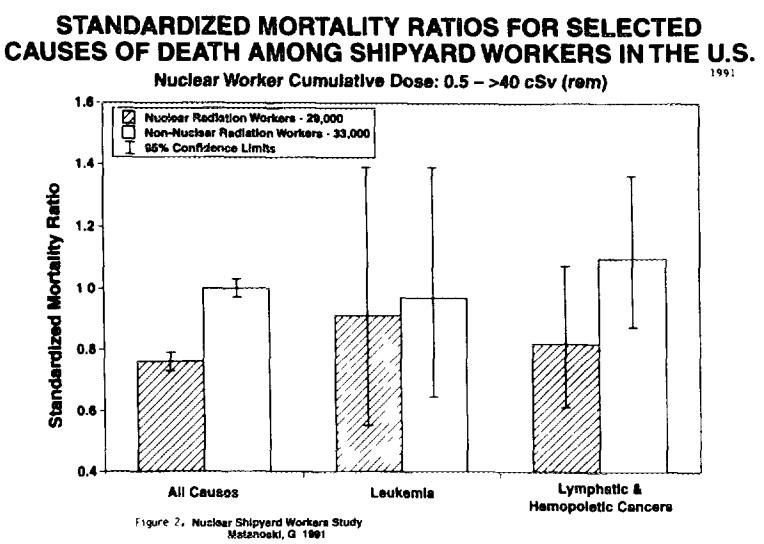


Figure 1. The DNA Damage-Control Biosystem. Pollycove, M and Feinendegen, LE [2].



U.S. Residential Radon Study, Cohen B. 1995

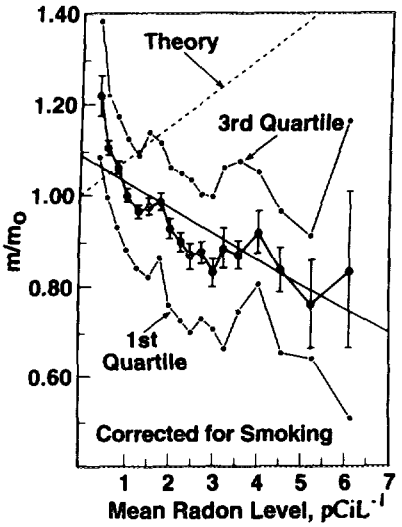


Figure 3. Plots of lung cancer rates corrected for smoking prevalence vs. average home radon levels are presented for U.S. counties with a wide variety of socioeconomic characteristics.

Canadian Breast Fluoroscopy Study

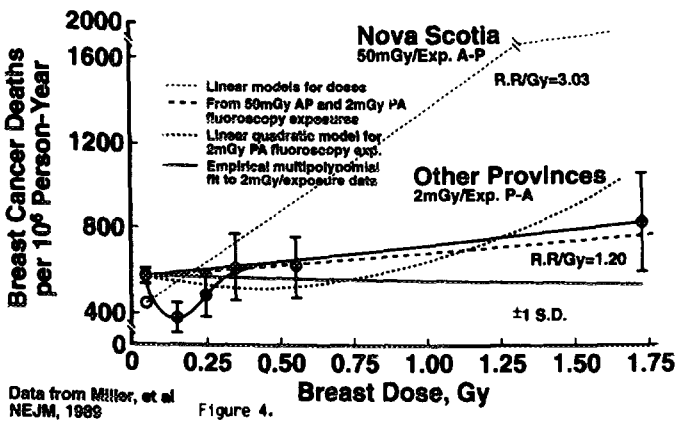


Figure 4.

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Additional references available upon request.

This presentation represents the views of the authors and not necessarily those of the U.S. Nuclear Regulatory Commission.

IONIZING RADIATION DECREASES HUMAN CANCER MORTALITY RATES

T. D. Luckey,
1009 Sitka Ct., Loveland, CO 80538, USA

XA9745598

ABSTRACT

Information from nine studies with exposed nuclear workers and military observers of atmospheric bomb explosions confirms the results from animal studies which showed that low doses of ionizing radiation are benefical. The usual "healthy worker effect" was eliminated by using carefully selected control populations. The results from 13 million person-years show the cancer mortality rate of exposed persons is only 65.6% that of carefully selected unexposed controls. This overwhelming evidence makes it politically untenable and morally wrong to withold public health benefits of low dose irradiation. Safe supplementation of ionizing radiation should become a public health service.

INTRODUCTION

Conservative radiation protection practice assumes a "linear no threshold" dose response to keep exposures to ionizing radiation "as low as reasonable achievable". Extensive compelling results from biology and epidemiology contradict the linear no threshold hypothesis [1-6].* High and low doses of ionizing radiation elicit opposite effects. Low doses stimulate physiologic functions in humans and experimental animals. The epidemiologic evidence reviewed here shows reduced total cancer mortality rates in exposed nuclear workers and other populations. The cumulative knowledge indicates exposures to the general population should be raised to a minimum yearly recommended allowance (MYRA) of about 1 cGy/y [2]. A public health evaluation should be undertaken to establish the bases and methods of providing radiation supplementaation as a public health service.

DATA REVIEW

Available data are summarized in Table 1. The first three studies show exposed workers in shipbuilding and energy producton have lower cancer death rates than controls in the same plants [7-9]. This result was confirmed in workers exposed in weapons plants [10-12]. Data from military observes of atmospheric atomic bomb blasts supports the same conclusion [13-15]. Seven of the studies were statistically significant.

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* More information is available from a non-profit group: Radiation, Science & Health, Inc., Box 834, Needham, MA 02194; Phone 617 449 2214, Email: jmuckerheide@delphi.com.

TABLE 1

CANCER MORTALITY RATES IN CONTROL AND EXPOSED PERSONNEL

REF[a]	YR[b]	mSv[c]	CONTROL/EXPOSED PERSONS[d]	DEAD[e]	%[f]	p<	PERSON YEARS
7	34	27	33.4/28.5	13.4/9.8	73.1	0.001	1,592,000
8	20	7	21/4	22.0/2.0	9.1	0.01	500,000
9	29	20	4.7/3.3	23.7/20.3	85.7	0.01	112,000
10	33	90	58.9/36.3	9.9/2.8	28.2	0.001	3,237,000
11	38	66	20.6/15.3	34.8/20.8	59.8	0.001	2,132,000
12	47	25	11.4/2.9	20.5/17.7	86.3	0.01	457,000
13	33	4	11.1/21.0	26.5/21.0	79.2	0.001	1,479,000
14	28	12	1.9/1.0	38.1/33.4	87.7	NS	74,000
15	46	6	35.0/38.7	68.6/67.8	98.8	NS	3,500,000
AVERAGE & TOTAL					65.6		13,085,000

a. Reference. b. Years of observation. c. Estimated lifetime dose per exposed person (1 mSv = 0.1 Rem). d. In thousands. e. Number dead per 1,000 workers. f. Exposed/control X 100.

The above results are supported by information from a variety of exposed populations. Although exposed to 2-6 Gy from a rain of fallout for four hours from a hydrogen bomb explosion in 1954 at Bikini Island, none of the 23 Japanese fishermen died from cancer within 25 years [16]. Of the 10,000 Ural Mountain villagers evacuated following the 1957 nuclear waste explosion, those exposed to about 12 cSv had only 61% the cancer death rate of controls in the nearby area [17]. None of the workers at the Chernobyl explosion who received less than 2 Gy died with cancer within 10 years [18]. Increased leukemia has not been found in the exposed population within these 10 years. Finally, eight "terminally ill" patients lived 5-44 years after injection of plutonium; none died from cancer [19].

DISCUSSION

Low dose irradiation is a negative risk! Overwhelming evidence shows that low doses of ionizing radiation reduce premature cancer mortality 34%. The principle mechanism appears to be increased immune competence [2-6]. Statistically significant data negate the linear no threshold hypothesis. No deaths are attributed to whole body exposure to low dose irradiaton. Exposure limits for both workers and the general population should be raised. Safe radiation supplementation should be a public health service.

Two examples demonstrate the urgent need for safe radiation supplementaton. The results from 13 million person-years (Table 1) indicate that safe supplementaton of the 61 million white male workers in the USA would prevent 75,000 premature cancer

deaths each year. When extrapolated to the 500,000 cancer deaths in the USA annually, low dose irradiation would prevent 150,000 premature cancer deaths each year. Obviously, present regulations and constraints on public health applications are politically irresponsible and morally abhorrent.

A minimum yearly recommended allowance (MYRA) of 1 cGy/y should be considered for the general population. This MYRA is about four times the average background in the United States. Much of the radiation received by workers (Table 1) would be dissipated within one year. Populations throughout the world live with $\geq$1 cGy/y: Kerala (India), Espirito, Guarapari, Meaip, Gerais, Araxi (Brazil) and Ramasar (Iran) [2]. The threshold for ionizing radiation was estimated to be about 1000 cGy/y [2]. This provides a substantial safety factor.

The evidence is strong enough to over-ride the moral indiscretions of governments which offer no opportunity to decrease cancer mortality rates with low dose irradiation.

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Risk of lung cancer in animals following low exposures to Radon-222 progeny

Philippe Duport*, Georges Monchaux**, and Jean-Paul Morlier**
*Institute for Research on Environment and Economy, University of Ottawa, 5 Calixa-Lavallée St, Ottawa, ON, Canada, K1N 6N5
**CEA, DSV, DRR, LCE, CEN-FAR, B.P. 6, 92265 Fontenay-aux-Roses Cedex, France

Abstract

Owing to the facts that a) large uncertainties affect the epidemiology of radon progeny-induced lung cancer in humans (especially at low exposures), and b) the rat is a good model for studying the carcinogenicity of radon progeny in humans, the risk of lung cancer following low exposures to low concentrations of radon progeny can be estimated from data obtained in the laboratory on rats exposed under controlled conditions. From the limited set of laboratory data on the induction of lung cancer in laboratory rats it appears that, at low exposures, the risk of lung cancer decreases with decreasing concentration, and that exposures of the order of 25 WLM, at an exposure rate of 2 WL do not produce any excess lung cancers. Since 20 WLM is a lifetime exposure comparable to those expected in occupational or indoors conditions and 2 WL is an exposure rate about 20 times higher than current occupational exposures rates and 100 times higher than ondoor ones, these observations may be indicative of threshold exposure conditions for the induction of lung cancer by radon progeny.

Introduction

There is ample evidence that prolonged exposure to large concentrations of airborne of Rn-222 progeny is the cause of an increased risk of lung cancer in man [1] and in animals [2]. At sufficiently high exposures, there is a clear relationship between the cumulative exposure received by individual persons or animals in a given cohort and the overall incidence of pulmonary cancers in that cohort. It is also clear that, at high exposures, the risk of pulmonary cancer increases with increasing cumulative exposure. This leaves no doubts of a causal relationship between exposure to Rn progeny and the risk of pulmonary cancer. However, a causal relationship between exposure to Rn-22 progeny and pulmonary cancer is more difficult to establish at lower exposures. From the examination of epidemiological data in underground miners, it appears that the confidence intervals in the risk per unit exposure are so large that it is not possible to exclude harmful effects, the absence of an effect, or even the existence of beneficial health effects at exposures lower than about 200 WLM. For this reason, and for the purpose of this paper, exposures below 200 WLM are considered to be low, although 200 WLM is a very high exposure indeed in current occupational conditions, and even more so for indoor situations. In animal experiments, uncertainties on the existence or magnitude of risk of lung cancer at low exposures still exist but to a lesser extent, and they are not confounded by exposures to several potentially carcinogenic substances.

Radon-induced cancer risk in man

The risk of lung cancer at low exposures to Rn-222 progeny is extrapolated from the risk observed in underground miners at high exposures. However, depending on the specific mines in which they worked, the miners have also inhaled several other potentially carcinogenic substances, such as diesel exhaust products containing carcinogenic hydrocarbons, arsenic, mineral fibres, or haematite. In addition to Rn-222 decay products, uranium miners have inhaled mixtures of radioactive ore dust particles and/or Rn-220 decay products, and they were exposed to the field of gamma radiation emitted from the ore body. These factors may have acted synergistically with, or in complement to, the inhalation of Rn-222 progeny in the induction of lung cancer. Furthermore, in most of the miner cohorts large, or even huge uncertainties exist concerning

the exposure of Rn-222 progeny attributed to each worker Uncertainties in Rn-222 progeny exposures are due to any combination of the following factors: absence of measurements when the workers were being exposed, low sampling frequency, variability in time and space of the concentration of Rn-222 progeny, and unrecorded employment in mines other than that for which exposure records exist. These factors, compounded by the fact that, with few exceptions, all excess lung cancers are attributed to the exposure to Rn-222 decay products alone (neglecting the possible role of other cocarcinogens) make it difficult to draw firm conclusions concerning the influence of low exposures to Rn-222 progeny alone in the induction of lung cancer in underground miners. Therefore, in order to have a better insight in the effects of low exposures to Rn-222 progeny, it is necessary to rely on the data provided by well controlled animal experiments.

The rat model for the induction of lung cancer following low exposures to Rn-222 progeny.

The information on the carcinogenicity of Rn-222 progeny in the lung observed, in the laboratory, in Sprague-Dawley or Wistar rats is more reliable than that obtained form human epidemiology, for four reasons

- (1) at high exposures, the risk of lung cancer per unit exposure is comparable in man and rat, which makes the rat a good model for Rn-induced lung cancer in man [3];
- (2) with the exception of oat-cell carcinomas which are common in man but not found in the rat, other histological types of lung cancer induced in the rat, especially squamous cell (epidermoid) carcinoma and adenocarcinoma, are very similar to those found in humans;
- (3) exposures received by laboratory animals are known with a much greater accuracy than those received by miners; and
- (4) animal data are not blurred by confounders. When selected specific potential confounding factors are used in animal experiments, the corresponding exposures are fully determined and quantified.

The body of information concerning the effects of low exposures to Rn-222 progeny is limited to the experiments conducted at the CEA-COGEMA laboratory of Razès (France) [4][5], and to those conducted at the Pacific Northwest National Laboratories (PNNL) [6]. These two laboratories investigated systematically the relationship between the exposure to Rn-222 progeny and the concomitant risk of lung cancer. At PNNL, low exposure experiments were conducted in atmospheres containing Rn-222 progeny and uranium ore dust (carnotite) at the concentration of 2.10^{-5} kg/m^3 (20 mg/m^3). At the CEA-COGEMA laboratory, low-exposure experiments were conducted with pure Rn-222 progeny. The range of exposure conditions examined here spans from 20 to 200 WLM, with concentrations from 2 to 1200 WL for the CEA-COGEMA experiments, and from 20 to 320 WLM, with concentrations from 10 to 100 WL for PNNL experiments. Exposure conditions and corresponding cancer incidence are given in Table 1. In this Table, it must noted that the lowest experimental exposures - 2 and 10 WLM - are comparable to those experienced indoors, and that the whole exposure range is commensurable with the maximum occupational exposure limits for today's uranium miners - 4 WLM per year over 30 years. On the other hand, experimental exposure rates (concentrations), are about 20 times larger than those found in mines, and not comparable at all - about 200 times larger - than indoor concentrations. These considerations must be kept in mind when interpreting the decreasing effectiveness of Rn-222 progeny as a cause of lung cancer with decreasing dose rate. As discussed in [5], Table 1 shows that dose rate alone (concentration) is a determining factor in the induction of lung cancer by Rn-222 progeny, and that the risk of lung cancer decreases with decreasing concentration of radon progeny, that is, decreasing dose rate. The decrease of risk with decreasing concentration is also noted by Gilbert et al [6] but, in PNNL experiments, the risk does not disappear totally as it does in the CEA-COGEMA experiments. This may be explained by the combined effects of relatively high grade uranium ore in the air(the uranium ore used at PNNL contained about 2 to 4% uranium, and also about 80% SiO_2) [7] and higher radon progeny concentration (the lowest concentration in PNNL experiments was 10 WL, which is about 100 times higher than today's mine concentration and 5 times higher than the low concentration in the CEA-COGEMA experiment.

Table 1. Cancer incidence and OR for lung cancer in Sprague-Dawley rats exposed to Rn-222 progeny only (Ref: Cogema, 1994), and to Rn-222 progeny and uranium ore dust at PNNL (Gilbert et al, 1996)
* Effect of Rn-222 (radon gas) alone. Equilibrium factor ≈ 0.01, Rn-222 concentration = 22 000 kBq/m^3

Exposure (WLM)	Concentration (Exposure rate) (WL)	No. of rats	Type of cancer: Squamous cell (Epidermoid	Mixt carcin.	Adenocarcin.	Bronchio-alveolar carcin.	Total	Odds ratio (C.I.)
(CEA-Cogema)								
Controls								
≈0.25	≈0.007	1290	2	4	0	6	12	
Exposed								
25	2	500	1	0	1	1	3	0.65 (0.18-2.3)
25	100	500	3	0	5	3	11	2.4 (1.05-5.5)
25	150	500	5	0	4	5	14	3.1 (1.4-6.7)
50	100	500	8	0	9	2	19	4.2 (2.0-8.7)
50	115	300	5	0	3	3	11	4.0 (1.8-9.3)
200	60*	21	1	0	0	1	2	11.2
200	1200	200	1	0	19	9	28	17.0 (8.7-35.0)
(PNNL)								
Controls	540						6	
Exposed								
20	100	541					9	1.5
40	100	479					9	1.7
80	10	383					8	1.9
80	100	382					15	3.6
160	100	191					6	2.9
320	10	128					19	15
320	100	127					8	6
320	100	82					2	2.2

Interpretations

The disappearance of lung cancer risk in animals, at the exposure of 25 WLM, when the exposure rate is decreased from 100 to 2 WL, illustrates the role played by dose rate in the induction of lung cancer by alpha emitters. This observation is in line with the fact that the inverse dose rate effect seen at exposures of several hundreds WLM disappears when the cumulated exposure decreases [6]. Furthermore, apparent thresholds in the induction of lung cancer have been observed following low doses of alpha radiation in animals [8][9], and in man, in radium dial painters [10]) and Thorotrast-exposed patients [11]. Taking these observations together with the fact that the risk of lung cancer due to radon progeny exposure in underground miners is overestimated by neglecting the effect of other potentially cocarcinogenic exposures, it is reasonable to suggest that the risk of lung cancer due to low exposures and very low concentrations of Rn-222 progeny may not have any detrimental health effect, and that regulatory requirements should reflect these converging factual observations.

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INCREASING THE TRANSPARENCY OF SITE DISCHARGE RISK TO THE PUBLIC

A.J. MORRIS
Maritime Faculty,
Southampton Institute,
Southampton, United Kingdom

Abstract

This paper will demonstrate how a relative radiotoxicity classification of discharge inventories will enable greater public understanding of the risks and hazard posed by a nuclear site. Its universal applicability allows inter-site comparison of discharges to take place within the risk, policy and regulatory fields. After briefly introducing the concept, its application is demonstrated by consideration of the airborne and liquid discharges from the "nuclear fuel cycle" sites in the UK. These encompass the activities associated with the manufacture, use and reprocessing of nuclear fuel used in the civil nuclear power stations owned by British Energy plc and Magnox Electric plc. These sites were selected because they are quantitatively responsible for the majority of discharges in the UK, with the reprocessing plants at Dounreay and Sellafield predominating.

1. INTRODUCTION

In the UK nuclear facilities have been developed in remote wilderness or rural areas either for site security or subsequently to remove nuclear power station discharges from nearby population centres.[1,2] Consequently, the nuclear industry in the UK is somewhat unique in terms of its environmental management when compared to other industrial sectors especially in terms of public risk perception.[2]

The Chernobyl accident brought the potential contamination and biological risks associated with the nuclear fuel cycle into sharp public focus within Western Europe. In the UK, public risk estimates have traditionally been based on the 'critical group' dose rate.[3] Though of obvious importance for radiation protection, such analysis of exposure pathways does not readily allow the public at large to assess the potential detriment posed either biologically or environmentally by a site. Also, the diverse and distinct nature of these discharges make direct inter-site comparisons difficult, e.g. is the liquid discharge inventory from an advanced gas-cooled reactor station (AGR) more or less dangerous than that from the fuel fabrication plant at Springfields? Relative radiotoxicity classification of discharge inventories allow such comparisons to be undertaken.

2. RELATIVE RADIOTOXICITY

The relative radiotoxicity classification of radioisotopes has long served as the basis for international industrial regulations concerned with the protection of workers using ionizing materials.[4,5] Using the known physical properties of radioisotopes it is possible to classify a range of them, both man-made and natural, into one of four categories based upon their relative radiotoxicity to humans. Classification is based upon a number of physical properties including the Relative Biological Effectiveness of the incident radiation, its energy (in eV), half-life, physical and chemical properties and its metabolism within the body, e.g. gut transfer factors and bioaccumulation.[4] The relative radiotoxicity classification is sub-divided into four categories in ascending order of hazard:

i) Group 1 - Nuclides of very high radiotoxicity.
ii) Group 2 - Nuclides of high radiotoxicity.
iii) Group 3 - Nuclides of moderate radiotoxicity.
iv) Group 4 - Nuclides of low radiotoxicity.

The majority of the group 1 radioisotopes comprise the heavy actinides. These are primarily alpha emitters and thus exhibit a high RBE. Group 2 contains a variety of actinides and fission products. The fission products included in this list either exhibit high energy decay or have a tendency to accumulate within the human body, e.g. Ca-45, Co-60, Sr-90 and I-131. Group 3 is the largest category and represents the 'average' radioisotope. Group 3 isotopes tend to have lower associated energy levels than either groups 1 or 2 and/or accumulate less in the human body. Some are only included in this category as opposed to group 4 because of relatively energetic gamma emissions, e.g. Ar-41. Group 4 radionuclides have very low associated energy emissions, thus not warranting inclusion in group 3.[4]

3. RELATIVE RADIOTOXICITY CLASSIFICATION OF SITE DISCHARGE INVENTORIES

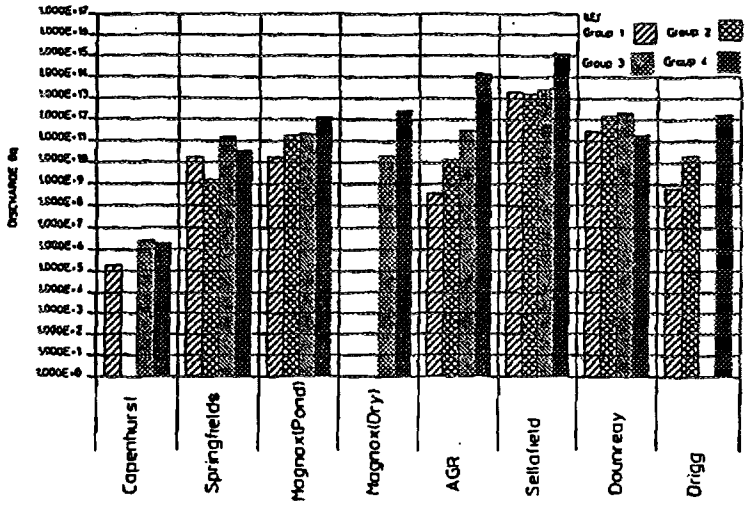
A relative radiotoxicity classification of a site's discharges allows not only the identification of the relative biological hazard but also, to some degree, the potential for environmental impact. Sites can have their liquid and airborne inventory sub-divided into groups 1, 2, 3 and 4 according to each radioisotope's specific relative radiotoxicity. The aggregated discharge values of each group can then be tabulated and/or graphically represented (Figure 1).[2]

The processes carried out at the fuel manufacturing sites of Capenhurst and Springfields result in the discharge of uranium, thorium and their decay daughters in both gaseous and liquid forms from the uranium ore concentrates utilized. However, the use of re-processed uranium has resulted in the discharge of limited quantities of both group 2 Np-237 and group 3 Tc-99 from both sites. These isotopes are regarded as 'impurities' from the re-cycled uranium's sojourn in the reactor environment.[6]

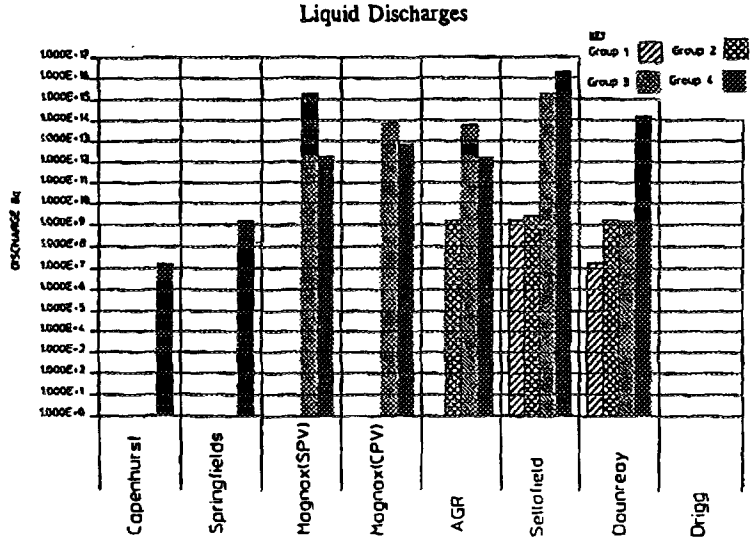
The reprocessing plants are the principle source of the highly radiotoxic group one actinides consisting of the alpha emitting plutonium isotopes Pu-238,-239 and -240, Am-241 and the beta emitter Pu-241.[6,7] Despite the liquid waste streams from both Dounreay and Sellafield containing a wide variety of other isotopes they are dominated by group 3 Cs-137 although Sn-125 (also group 3) quantities are almost equivalent at Sellafield. Group 4 Kr-85 and group 2 I-131 liberated from fuel rods during their dismantling for reprocessing dominate airborne emissions although secondary quantities of the group 2 isotopes Ru-106, Co-60 and Sr-90 are also released. At Dounreay the predominant radionuclides are Sr-90, Cs-134 and Ru-106 (all belonging to group 2) reflecting the differing processes involved.[7]

Trace quantities of Pu-241 are found in the liquid discharges from nuclear power stations and are due to leakage from perforated fuel elements stored in station cooling ponds. AGR discharges are typically two orders of magnitude less than for Magnox ponds reflecting the greater integrity of the AGR fuel.[8,9] The inventory of the radionuclides released in liquid effluent streams vary considerably between the AGR and Magnox stations using pond storage and Wylfa which uses refrigerated dry storage. Pond stored magnox fuel leaks fission products such as Cs-137, and has small quantities of surface activation products associated with them. The integrity of AGR fuel means that only the group 3 activation products Mn-54 and Fe-55 occur in any significance. The quantity of Cs-137 discharged depends upon the station's authorization and its interpretation of Best Practicable Means to keep dose rates As Low As Reasonably Achievable in relation to the cost of the non-renewable cleaning resin.[10] However, the dry refrigerated storage of magnox fuel at Wylfa results in the absence of measurable quantities of both fission and activation products in the liquid waste stream from fuel storage and represents a significant improvement. Airborne discharges from power stations are numerically dominated by Ar-41 (group three). The

use of shield cooling air results in Ar-41 discharges at SPV Magnox stations being about two orders of magnitude greater than CPV Magnox or AGR stations of like capacity. The group 2 airborne releases from AGR represent the maximum allowable I-131 leakage due to a fuel pin breach.[1]



Liquid Discharges



Airborne Discharges

Note:
- Activities represent the typical discharge levels between 1986 and 1991.
- For nuclear power stations activities are typical for one station.
- Within the liquid category stations are sub-divided into stations using pond storage or dry refrigerated storage.
- In the airborne category stations are divided into those using Steel Pressure Vessels (SPV) and Concrete Pressure Vessels (CPV).

Figure 1 Relative Radiotoxicity of Liquid and Airborne Discharges from UK nuclear sites. (Morris, 1997)

Finally, solid LLW disposals for the nuclear industry are centered on Drigg which receives wastes from most sites in the country. Past waste management techniques have given rise to significant quantities of contaminated liquid seepage which is collected by a drainage system and released via pipeline to the sea.[6]

4. CONCLUSION

Relative radiotoxicity is capable of making the biological and environmental risks from a site's discharges more readily apparent to the general public. The ease of interpretation combined with

its existing familiarity to the nuclear industry make it a useful addition to the various risk assessment methodologies currently available. Also, as it is universal in application, it can be used to assess any site discharging radioisotopes worldwide.

In addition to conveying risk, this classification technique may also be used for discharge policy assessment and regulatory control. Its application at the individual site level has already been discussed yet it may be utilized at a variety of scales. For example, an analysis of Figure 1 demonstrates how the activity from liquid discharges dominate airborne releases from the industry on a national scale. This is due to a land-based bias in controlling pollution which utilizes the ability of the marine environment to "dilute-and-disperse" pollutants to low levels before they can impinge upon the on-shore habitats populated by mankind.

Thus, relative radiotoxicity can contribute to risk assessment by making discharge inventories more transparent to the general public, especially when used to supplement current risk methodologies. Additionally, it may also aid discharge policy formulation and regulatory assessment techniques.

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A TWO PHASE DOSE-RESPONSE RELATIONSHIP AT LOW DOSE RATES

XA9745601

Carl M. Fleck*, Markus M. Kottbauer*, Helmut Schöllnberger#, Siegfried Pfandler*

*Atomic Institute of the Austrian Universities, Stadionalle 2, A-1020 Vienna

#University of North Carolina, Chapel Hill, NC 27599-1105

Abstract

With a new model concerning the dose-effect relation, the Random Coincidence Model (RCM), it is possible to explain the radiobiological effect of a two phase dose-response relationship. This model describes the formation of cancer caused by a multistep series of fixed lesions in the critical regions of tumor associated genes such as proto-oncogenes or tumor-suppressor genes. It is the central thesis of the model that in the case of spontaneously occurring mutations mainly the random coincidence of two base lesions or two single strand breaks of complementary DNA bases (strands) during the repair time of the first base lesion or single strand break leads to a fixation. In that case the stimulation of detoxification and repair systems by radiation reduces the mutation rate to a large extend. On the other hand the energy transfer of radiation generates a large number of radicals at each single point of interaction, so that the cloud of radicals can neither be reduced by detoxification to a large extend nor is there any possibility to repair in between the interaction with the DNA; a so called causal coincidence leads to a fixation.

1. INTRODUCTION

During the last few years new data in the low dose range as well as new results in radiobiological research have been starting again a discussion on this topic. Most importantly, the research of Bernhard L. Cohen [1] showed a decrease of the spontaneous rate of lung tumors at increasing levels of radon concentrations in homes. This research has been carried out over the whole U.S. in the energy dose rate range from 0.1 mGy/a to 1.8 mGy/a (which corresponds to effective organ dose rates of 2 mSv/a to 36 mSv/a) for many years, indicating a minimum of spontaneous tumors between 12 mSv/a and 20 mSv/a.

At the same time experiments on "radiation adaption" [2,3] showed very clearly, that cells irradiated at low doses (2.5 mGy to 20 mGy) developed an adaptive response that could be measured in subsequently irradiating them with a high "challenge" dose (in the range of 1 to 10 Gy during some minutes). Preirradiated cells showed genetic damages down to 30% compared to untreated cells.

At the meeting of the International Radiation Protection Agency (IRPA) in Vienna, April 1996, it was stated that modeling in this dose range in consideration of new results of molecular biology, cancer research and epidemiology could offer a new approach to this problem. One of these new models solves the problem of low doses in a very appealing way [4]. It consistently combines results of radiation adaption with the findings of Cohen: while radiation induced mutations increase nearly linear with dose, the spontaneous mutation rate and in consequence the tumor rate decreases (Fig.1). So at low dose rates the total dose-effect relationship will decrease with increasing radiation, an effect called "two phase relationship".

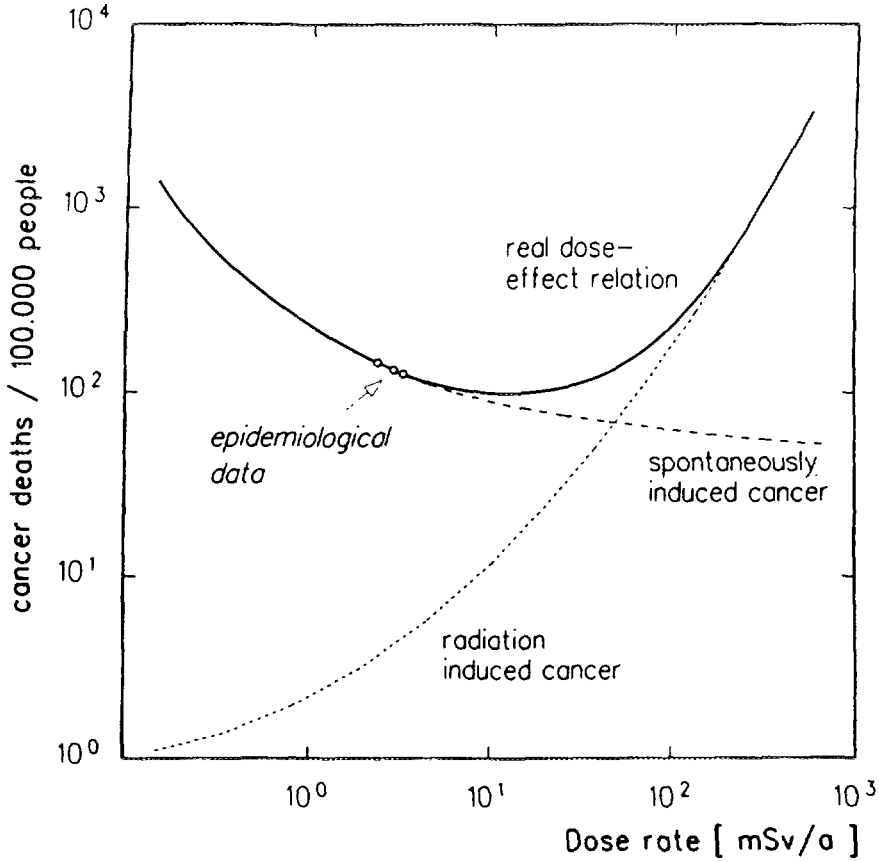

Fig. 1 At the low end of the dose-effect relation the increase of the radiation induced cancer is predominated by the decrease of the spontaneously induced cancer.

2.THE RANDOM COINCIDENCE MODEL

The mentioned model is called "Random Coincidence Model" (RCM) and gives a very simple explanation for the apparent thresholds in the dose-response relationship for radiation without contradiction to the classical assumption that radiation is predominantly bionegative at doses typically found in occupational exposures. The series of spontaneously occuring genetic damages in the critical regions of tumor associated genes such as proto-oncogenes or tumor suppressor genes, which are crucial for the developement of cancer, are caused mainly by single radicals or other impacts, which mostly damage only one of the two strands ore bases of the DNA. So the damages have to be fixed by a "random coincidence" before or

during the repair process This is the point where the findings of radiation adaption [5] appears to be very helpful in the explanation of the epidemiological data. The stimulation of detoxification and repair systems by radiation reduces the number of occuring radicals, shorten the time of repair respectively and reduces in consequence the random coincident fixation rate

On the other hand the energy transfer of radiation generates a large number of radicals at each single point of interaction, so that the cloud of radicals can neither be reduced by detoxification to a large extend nor is there any possibility to repair in between the interaction of this cloud with the DNA In this case the radiation induced damage of the DNA and its fixation happens instantaneously by a "causal coincidence" This is the phase one of the dose-respone relationship, a more or less linearly increasing curve

Phase two of the dose-response is a distinct reduction of the spontaneously occurring cancer rate by increasing radiation This effect can be observed only at organspecific tumors where the spontaneous cancer rate is high and the dose rate is low enough, so that mechanisms of adaptive response can respond to the radiologically induced oxidative stress The RCM allows the direct quantitative treating of this interaction between spontaneously occurring and radiation induced mutations in one formula and also contributes decisively to the discussion "linear or not linear". A further development of the RCM, altered for the case of a single hit radiation makes clear predictions on the dose-response relationship [6,7] For the case of short time irradiation, no radiation hormesis occurs

The process of carcinogenesis essentially needs a series of 5 to 8 genetic transformations on tumor associated genes [8]. In the low dose region a short irradiation may perform just one or two of these genetic transformations [6]. This mixture of one or two induced transformations for a given developing cancer can be explained with a "linear" or a "mixed linear-square" dose effect relationship and supports also the dose-response suggested by the ICRP for very small doses linear, turning to a linear-square mixing at increasing doses, where the probability for inducing two transformations by the applied radiation dose increases

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THRESHOLD DOSE-RATE OBSERVED BY ADMINISTRATION OF TRITIATED WATER IN MICE FOR RADIATION RISK

OSAMU YAMAMOTO: Faculty of Life Science, Yasuda Women College, Hiroshima 731-01, Japan; TOSHIO SEYAMA: Radiation Effect Research Fundation, Hiroshima 732, Japan

XA9745602

Abstract

This paper is the final report of the study series for the dose-rate effect of tritiated water on mice. In the present experiments, mice ([C57-BL/6N x C3H/He]F_1 female) was exposed to β-rays by daily adiministration of tritiated drinking water throughout of life at very low dose-rates, 3.6, 0.9and 0.2 mGy/day. When compared with the groups exposed at higher dose-rate previosly reported, it was found that frequency of tumors was 70~80% in therange from 240 mGy/day to 9.6 mGy/day and decreased to 50% as same as control with decrease in dose-rate. A linear relationship in semi-log scale was found between the life-shortening and the dose-rate, showing a threshold dose-rate. The threshold dose-rate of ^{3}H β-rays, 2 mGy/day (0.2 mGy/day as tailing threshold dose-rate) was much lower than that of γ-rays, 15 mGy/day(2 mGy/day as tailing threshold dose-rate). In addition, it was observed that the body weight increased by exposure at low dose-rates, most markedly at 0.9 mGy/day.

Introduction

As for the low dose-rate irradiation on animals, Lorenz and collaborators completed a study of γ-ray effects [1,2]. Other most thorough and systematic studies were reported by Sacher and collaborators [4,5] who used γ-irradiation and their data was discussed in NCRP Report 64 [6]. Upton et al. [7,8] also studied the tumour development using X- and γ-rays and fast neutrons. Ootsuyama and Tanooka [9] reported the tumour induction in mouse skin irradiated with ^{90}Sr-^{90}Y β-rays. Recently Morlier and collaborators presented the effect of ^{222}Rn gas from the viewpoint of

the frequency of lung carcinoma [10]. We have administered tritiated water (HTO) as drinking water in mice. This paper deals with the threshold dose-rate resulted from the ^{3}H β-irradiation [13-15] comparing with the above data from X- and γ-irradiation.

Material and Methods

Five-week-old (C57BL/6N and C3H/He)F_1 female mice were housed in a closed animal chamber consisting of four compartments in the tritium experiment facility of Hiroshima University. Mice were kept in each room maintained at a temperature of 24±2°C and humidity of 50±10% with a daily light cycle of 10 hr light and 14 hr darkness. Continuous oral administration of HTO was started on mice weight-selected (24±1 g) at 10 weeks. A complete autopsy wasimmediately performed on every dead mous and killed moribund mouse. To deter-mine organ doses, a direct measuring method and a linear extrapolation were used [13-15].

Results and Discussion

Cumulative mortality curves of mice administered various concentrations of HTO as compared with the controls. The mean survival time (MST) after starting HTO administration was more close to the life span of controls at the lower dose-rate. 0.9 and 0.2 mGy/day groups no longer showed significant life-shortening in comparison to the control group.

The total tumour frequency was decreased from 80% to 50% at about 3.6 mGy/day. At the higher dose-rate range, while thymic lymphoma decreased with decrease in dose-rate, other tumours increased linearly in semi-log scale, keeping the same frequency in total. In the decrease of thymic lymphoma, thelinear line crossed to the base lineat 12 mGy/day which is a threshold dose-rate (essential threshold dose-rate). However, this linear line has a tailing. Tailing part becomes linear in normal scale. This linear line crosses to the base line at 9 mGy/day which is another threshold dose-rate (tail threshold dose-rate).

The relationship between life-shortening and dose-rate also linear with a tail in semi-log scale. 2 mGy/day was found to be the essential threshold dose-rate and 0.2 mGy/day the practical tail threshold dose-rate. It is noticed that there exists two types of threshold dose-rates, essential

and practical, not only in the frequency of thymic lymphoma but also in the life-shortening.

In the case of γ-irradiation, a similar pattern resulted when the data presented by Lorenz et al. [1] and modified by Failla and McClement [13] and those presented by Grahn et al. [5] and averaged by NCRP [6] were plotted, the essential and the practical threshold dose-rates being 20 mGy/day and 2 mGy/day. It is clear that the effect of ^{3}H β-rays is greater than that of γ-rays. The two curves of ^{3}H β-irradiation and γ-irradiation are closer to each at higher dose-rates, which supports the proposal of Yamamoto et al. [10-12] that the effect depends on the produced active oxygen density. This implies that the life-shortening rate may be the higher the higher the LET.

The linear no-threshold theory had been adopted. Recently Abelson [14], Jovanovich [15], Becker [16], Goldman [17] and Patterson [18] have questioned the validity of this theory and emphasized the need for stuides of radiation risk at low exposures. If there is a threshold, it would allay the fear of the public and save billions of dollers spent in unnecessary remediation of low level waste sites. From this point of view, the existence of the threshold dose-rate resulted in the present study would be an important evidence.

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BREAST CANCER INDUCED BY PROTRACTED RADIATION EXPOSURES

Mortimer M. Elkind; Department of Radiological Health Sciences, Colorado State University, Fort Collins, Colorado 80523, U.S.A.

Abstract

The experience at Hiroshima/Nagasaki demonstrated that breast cancer can be induced by single doses of ionizing radiation following latencies of 10-40 years. Several epidemiological studies, usually involving ancillary low-LET radiation to the breast, have demonstrated that breast cancer can be induced by protracted exposures, with similar latencies, and with similar dependencies on dose. Radiobiologically these results suggest that the target cells involved were deficient in repair of low-LET damage even when the protraction was over months to years. Since three-quarters of breast tumors originate in the ducts where their proliferation is controlled by menstrual-cycle timed estrogen/progesterone secretions, these cells periodically were in cycle. Thus, the two main elements of a conceptual model for radon-induced lung cancer -- **kinetics** and **deficient repair** -- are satisfied. The model indicates that breast cancer could be the cumulative effect of protracted small exposures, the risk from any one of which ordinarily would be quite small.

1. EPIDEMIOLOGICAL STUDIES

Several different uses of radiation in the past have involved direct or ancillary radiation of the breast and a number of these [1] have been shown to have dose dependencies and latencies similar to what has been observed among the A-bomb survivors [2]. The following are examples:

(a) Women treated over many months for *postpartum mastitis* [3].
(b) Women receiving weekly fluoroscopies for collapsed-lung therapy of *tuberculosis*, 88 average number of exposures [4].
(c) Women receiving diagnostic X-rays over years for *scoliosis* [5].
(d) Infants treated for *skin hemangiomas* [6].
(e) Infants treated for enlarged *thymuses* [7].

In mammalian cells, protracting a dose of radiation generally leads to a reduced effect as was first shown by the repair of sublethal damage [8]. In cells, protraction also reduces neoplastic transformation [9], similarly for tumor induction in mice [eg, 10], and lung cancer in women fluoroscoped during tuberculosis treatment where, in contrast to breast cancer, no increase was observed over controls [11]. The difference between the breast cancer studies and the more general result of protracted exposures suggests that in a large fraction of breast cancer cases damage in the target cells persisted because of deficient repair.

The cycling of ductal cells is hormonally controlled during the menstrual cycle. Hence, the growth and division of target cells is assured by the normal physiology of the breast. This fact plus the epidemiological data suggest that the target cell can be described as periodically **cycling** and **repair deficient**.

2. CELL DATA AND RADON

In the course of studies of the survival and neoplastic transformation of cells in culture, an anomalous observation was made. With low-LET radiation, as expected cell killing and transformation were reduced if the dose was protracted [eg, 9]. With fission-spectrum neutrons, also as expected killing was not modified by protraction but, anomalously, transformation was. At low dose rates or with multifractionation, transformation was **increased**. Figure 1 summarizes the anomalous neutron data [1; see refs. 12 & 13 for survival data]. The closed circles show that for low doses transformation was enhanced by five daily doses by as much as it was at low dose rate [14].

Based upon the low-dose-rate data, Rossi and Kellerer proposed that enhanced transformation could be explained if it was assumed that

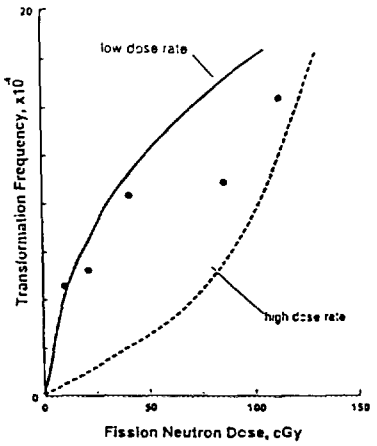

Fig.1 Sketch of the anomalous enhanced transformation frequency observed when protracted doses of fission-neutrons were used. (From refs. 12 & 14.) The points refer to five fractions each separated by one day.

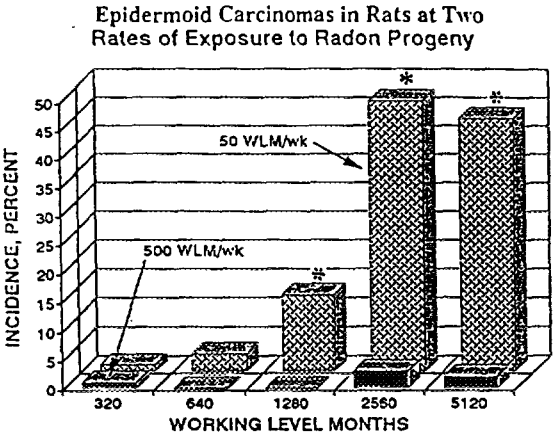

Fig.2 The incidence of epidermoid carcinomas in rats breathing air containing radon at two different concentrations. WLM (WLM = *working level month*) is a unit of dose resulting from the alpha-particle emission during radon decay. (From ref. 22.)

a narrow sensitive window existed in the growth cycle [15]. The location of the window was not specified and their model did not account for the results with multifractionation [16]. Some years later, it was proposed that the window was around mitosis [17]. Subsequently, **late G_2/mitosis** was shown to be the window [18].

In the context of risks due to indoor radon [19], it follows from Fig. 1 that *risk* should vary inversely with ambient *concentration* when the kinetics of the target cells assure that the window is occupied during the exposure. For the α-particles associated with radon, their killing efficiency would facilitate compensatory repopulation but non-radiation factors like smoking also could stimulate division. Two examples of inverse relationships between *risk* and *radon concentration* are the study by Lubin *et al.* [20; see Table C2(a), page C-4] and that of Darby and Samet [21]. In the former [20], the combined data for 11 hard-rock mines are analyzed, and in the latter [21], relative risks for five uranium mines are compared.

A more direct example of enhancement varying inversely with dose rate comes from Cross, Fig. 2 (dose=WLM; dose rate=WLM/wk) [22]. The lack of clear differences for the first two doses in Fig. 2 probably reflects the reduced signal for compensatory repopulation plus the shortened time for cell division during these smaller exposures.

3. APPLICABILITY OF THE MODEL TO BREAST CANCER

In the case of radon, deficient repair is attributed to the high-LET of the α-particles. Radiobiologically, they would be expected to be similar to the secondaries due to reactor neutrons. Even in repair-competent cells high-LET damage is largely unrepairable. Even though the target cells in breast cancer are usually exposed to low-LET radiation, the epidemiological data indicate little if any sparing of tumorigenesis from even extensive dose protraction. The weeks-to-months between exposures suggests that a condition of genomic instability may have been induced. Indeed, in the instance of the thymus treatments of infants, a prolonged instability is suggested by an average latency of 39 years [7]. If instability was induced, it was not reversed between fractions indicative of deficient repair. Hence, the two requirements of the model -- **cell kinetics** coupled with **deficient repair** -- appear to be fulfilled.

4. PERSPECTIVE

Radiation to the breast may come from different sources, the most direct ordinarily being from mammography. Modern technology has considerably reduced the average dose per examination but the dose was larger when the procedure was introduced. Currently, women are examined more regularly than heretofore. Although average doses have been reduced, doses to target cells near the radiation entrance

surface still can be appreciably larger because of the soft quality of the radiation that is used. In any case, recent results still indicate a significant risk of breast cancer in postmenopausal women who received estrogen-replacement therapy and regular mammographic examinations [23].

Roentgenographic relative density has been studied for prospective indications of incidence. Indeed, the density of parenchymal tissue has been correlated with risk, up to 4-5 times for high densities [24]. A correlation is logical if dose to the target cells increased with roentgenographic density. Such a relation strengthens the implication that the diagnostic potential of mammography at the same time includes a risk of inducing cancer some years later. For mammography, a preferred period during the menstrual cycle could be when fewer target cells are in cycle [25].

In addition to the epidemiologic data, a number of cell studies support the inference that repair deficiency underlies the incidence [eg, 1]. These studies have been small in size and should be enlarged first, to uncover the molecular basis for the deficiency, and second, to develop a screening approach to breast cancer susceptibility.

Lastly, the model does not rest on the oncogenic properties of breast cancer. At this stage, it is cell-based and radiobiological. This limited scope follows from the fact that radiation has been shown to cause breast cancer presumably by inducing the somatic mutation(s) to initiate the process.

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LUNG CANCER RISK FROM RADON AT LOW EXPOSURES AMONG CZECH MINERS

Ladislav Tomášek [1], Václav Plaček [2], and Alena Heribanová[3]

XA9745604

[1]National Radiation Protection Institute, Prague

[2] Institute for Emergency Expertises and Control, Příbram-Kamenná

[3] State Office for Nuclear Safety, Prague

ABSTRACT

Results of three studies of carcinogenic effect from occupational exposure to radon are presented in order to compare risks from low and high exposures. By 1995, a total of 888 cases of lung cancer were observed, 771 of them in the cohort followed since 1952. Exposures in this cohort are relatively high (40-800WLM). The other two cohorts are characteristic by exposures of about an order of magnitude lower. In the previous analyses, numbers of cases in the latter two cohorts were not sufficient to demonstrate any significant findings. In the present follow-up, 170 cases have been observed in exposure categories below 50 WLM, with a significant excess already in the category 10-20 WLM (about 0.1-0.2 Sv in terms of effective dose). The present analyses suggest that the assumption of linear non-threshold relationship is justifiable.

INTRODUCTION

Epidemiological studies of workers have provided a great part of knowledge on carcinogenic effects of ionizing radiation. Historical studies of uranium miners, who experienced in the past relatively high exposures, have clearly demonstrated the linear effect of cumulative exposure. One of such studies is the cohort of uranium miners in West Bohemia (Jáchymov) established by the late Josef Ševc in 1970. As occupational and environmental exposures today are generally much lower, it is more difficult to demonstrate any effect. For instance, in the lowest exposure category, no significant increase of lung cancer mortality had been observed by 1980 [1]. Nevertheless, the risk from lower exposures is assumed to follow the same linear (non-threshold) relationship. The verification of this assumption was possible by virtue of further cohort studies delineated also by Ševc.

METHODS

The study population involve three cohorts of miners exposed to radon and its progeny. The oldest cohort (S) comprises 4320 uranium miners at Jáchymov and Horní Slavkov firstly exposed in the period 1948-59, 5624 miners of the second cohort (N) entered the Příbram uranium mines in 1968-74, and the third cohort (L) includes 914 burnt-clay miners in the Rakovník district employed underground in the period 1960-80. The follow-up of the studies relied on the population registry, the pensions office, local enquiries, and direct

correspondence, the details are given elsewhere [2]. As the employment of miners cover distinct calendar periods, the exposures experienced by the members of the three cohorts substantially differed (Tab.I). In the S study, exposure estimates were derived from large numbers of measurements of radon concentrations made in each mine-shaft since 1949. Mean number per year and shaft was 223 in the period 1949-60. Each man's annual exposures to radon progeny were estimated combining measurement data with the men's registered employment details (time spent underground in particular mine-shafts and job category). In the whole N study and in the L study since 1978, the exposure estimates were based on personal dosimetric records. Before 1978, the radon concentrations in the L study were extrapolated using ventilation data. For historical reasons, the exposures are given in terms of Working Level Months (WLM) [1].

The statistical analyses were based on relative risk models in the general form $O = c\,E\,(1 + ERR(W,Z))$, where O denotes the observed number of cases, E is the number expected from national mortality data (age- and calendar year- specific), ERR is the excess relative risk function depending on exposure W and modifying variables Z, and c is an intercept term that allows the mortality rate for the 'unexposed' cohort to differ from that in the general population, in other words, the value cE stands for an estimated number of cases in the cohort at hypothetical zero exposure. The most simple model of relative risk (used here) assumes a linear dependence on total cumulative exposure W lagged by 5 years. The coefficient of proportionality b (=ERR/WLM - Excess Relative Risk per WLM) is constant in time and does not depend on any other factors: $ERR(W,Z) = b\,W$.

RESULTS AND DISCUSSION

By the end of 1995, a total of 888 cases were observed in the three cohorts (Tab.I), most of them in the S cohort which reflects the high exposures and age.

Tab.I: Cohorts status by 1995

Cohort	Since	Size	Cases	O/E	Died	WLM	Duration
S	1952	4320	771	4.67	66 %	155	9
L	1960	914	67	2.23	45 %	18	14
N	1969	5624	50	1.38	11 %	6	5

The simple model of relative risk gives the ERR/WLM estimate of 0.014 for the whole range of cumulative exposures 1-860 WLM (Fig.1). It is also obvious that the slope of the estimated line is driven by high exposure categories (over 300 WLM). The intercept estimate in this model is 1.58 (95%CI[2]: 1.32-1.89). The data relevant to very low exposure categories suggest somewhat steeper slope.

[1] One Working Level equals any combination of radon progeny in one liter of air which results in the ultimate emission of 1.3×10^5 megaelectronvolts (MeV) of energy from alpha particles. WLM is time-integrated exposure measure, i.e. the product of time in working months (170 hours) and working levels ($1\,WLM = 3.54\ mJh\ m^{-3}$).

[2] CI = confidence interval

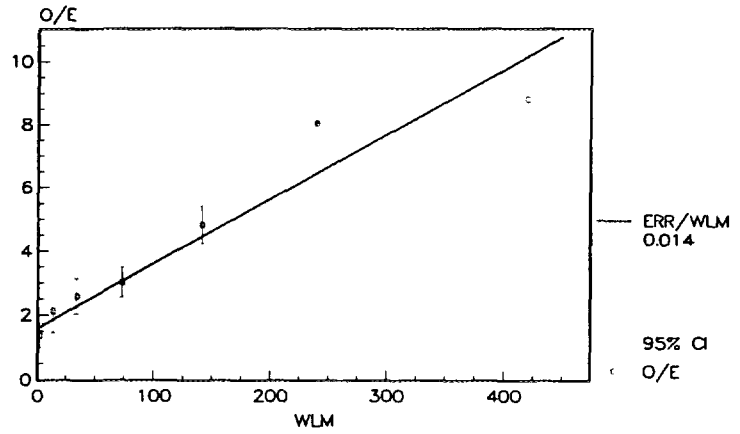

Fig.1: Relative risk by cumulative exposure in the S+N+L cohort

When exposures are restricted to <100 WLM (Fig.2), the ERR/WLM estimate is 0.023 (95%CI: 0.004-0.043). The intercept estimate of 1.25 (95%CI: 1.14-1.37) corresponds better to relative mortality (O/E) in the cohorts for very low exposure categories.

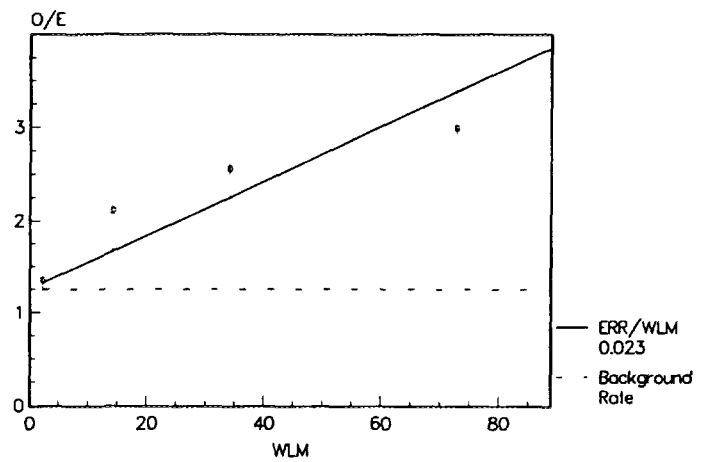

Fig.2: Relative risk by cumulative exposure below 100 WLM

It is worth noticing that the relative risk in the exposure category 10-20 WLM already shows a significant difference from the baseline rate. The conversion from exposure to effective dose based on lifetime risk coefficients (1 WLM = 0.005 Sv; [4]) transforms the exposure of 15 WLM into a value of 0.075 Sv. On the other hand, the comparison of time-since-exposure (TSE) relative risk models in BEIR IV and V [5] [6] (Tab.II) gives a conversion factor of 0.017 Sv/WLM. A compromise between these two approaches suggests a conversion factor of 0.01 Sv/WLM. By this calculation, the exposure of 15 WLM would correspond to the effective dose of 0.15 Sv.

Tab.II: BEIR IV and BEIR V models of relative risk for lung cancer

TSE	BEIR IV ERR/WLM	BEIR V ERR/Sv	Conversion factor Sv/WLM
10y	0.025	1.72	0.015
20y	0.0125	0.64	0.020

The difference between the above two estimates of ERR/WLM in the cohorts (Fig.1 and 2) is partly due to the so-called exposure rate effect, which was observed in most miners studies [3], and partly due to better exposure estimates in low exposure categories corresponding to the N and L cohorts. The importance of quality of exposure estimates can be illustrated by ERR/WLM estimates before and after exposure revision in the S study (Tab.III). Most of the revised exposures (10% of miners) consisted in completing subsequent exposures (in the 1970s) that had not been available for earlier analyses. This improvement in exposure estimates resulted not only in the increase of the coefficient, but also in its precision (Z-score).

Tab.III : Summary of relative risk coefficients

Exposure	ERR/WLM	95% CI	Z-score
S cohort - original estimates	.0028	.0015 - .0042	4.13
S cohort - revised estimates	.0136	.0098 - .0175	6.96
S+N+L cohort <100 WLM	.023	.004 - .043	2.37
S+N+L cohort <50 WLM	.032	.007 - .056	2.51

The risk model derived from recent data observed at low exposures 10 - 100 WLM (0.1 - 1 Sv) suggests no serious departure from models derived at higher exposures. The estimate of relative risk coefficients (ERR/WLM) for low exposures in the range 0.02 - 0.03 are not definitely lower than those for higher exposures as it might be expected if the threshold theory were true.

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ESTIMATION OF THE RISKS OF STOCHASTIC EFFECTS ATTRIBUTABLE TO THE RADIOLOGICAL CONDITIONS IN TBILISI

VEPKHVADZE N.R., GELASHVILI K.D., KILADZE N.A.
TBILISI STATE MEDICAL UNIVERSITY

XA9745605

Abstract

Radiation background in Tbilisi City has been studied; collective and annual average statistic dozes have been ascertained, parameters of stochastic effects' (cancerogenic, genetic) risks caused by low dozes of ionizing radiation have been calculated. From 21 cases of total risk 7 are stipulated by genetic defects, 14 - by lethal malignant tumor.

The conclusion is that we shouldn't expect important changes in health condition of population caused by existing in Tbilisi City radiation background.

Introduction

Biological aspects of chronic action of low doses of ionizing radiation are in the center of scientists' attention. The prognosis of harmful biological effects of dozes of radiation existing in environment is of special importance.

As the stochastic effects of ionizing radiation activity (cancerogenic, genetic) and "doze-effect" unlimited linear dependence hypothesis are already known, any lowest doze, even radiation background aren't harmless for the organism. That's why it's necessary to estimate quantitatively the risk factors that accompany people in their lives and industry. For this reason the collective doze of outside radiation received by Tbilisi population, has been defined. The prognosis of possible stochastic effects and their contrasting against real situation were held.

Material and methods

For measuring the radiation background device "CP -68 -01" was used. Measuring was held in open air places (260 points) on the height of 1 m from the earth, in buildings (1052 points) -1 m from ceiling and walls. In each point the measuring was held several times and average value was calculated.

Average of doze power of annual radiation <D> and collective doze $\int$ of population radiation was calculated by formula: $< D> = \int_0^\infty Dw(D)\, d\, D$, $S= N<D>$, where W(D) - is distribution density of doze power probability N - total number of population, that comes to 1 200 000 person in Tbilisi.

The risk parameters, i.e. average individual probability of mortality on doze unit [1], recommended by ICRP, were used for prognosing stochastic effects formed in the result of population radiation.

Risk parameters are: extra parameter of mortality by malignant tumor - Pc, parameter of genetic risk development - Pg, total risk - P.

If average doze of radiation is known <D> , then these parameters give opportunity to calculate the probabilities of mortality, caused by malignant tumor and genetic defects by formulae:

$Rc= Pc < D>$; $Rg= Pg < D>$; $R = Rc+Rg$, where

$Pc=1{,}25 \cdot 10^{-2}\ Sv^{-1}$ $Pg= 0{,}4 \cdot 10^{-2}\ Sv^{-1}$.

If collective dozes of radiation are known it's possible to calculate the supposed number of extra mortality by formula: $K = P \cdot S$, where

$P = 1{,}65 \cdot 10^{-2}\ Sv^{-1}$.

Results

Power of radiation background in Tbilisi open places (8,4 ±0,9 -12,0 ± 2,3 mcr/ h in comparison with the world countries (3,6 - 9,1 mcr/h) [2] data as in minimum, so in maximum value is rather high.

The power of average statistic annual doze received by Tbilisi population, taking into consideration [2,3,4] the time spent out of buildings, comes to 0,01424 ± 0,00179 Sv/y. Power of radiation background in Tbilisi buildings averagely 13,3± 1,75 mcr/h fluctuates with the interval of 3,0÷23,0 mcr/h, that corresponds with the world data [5,6]. The doze of average statistic annual radiation received by the population in buildings, taking into consideration the time spent in buildings [2,3,4] comes to 0,0936 ±0,00104 cSv/y. Total doze of radiation received from open air places and buildings comes to 0,10784 cSv/y; Hence these data, the risk parameters and total risk have the following meaning: $Rc = 13{,}4 \cdot 10^{-6}$; $Rg = 4{,}3 \cdot 10^{-6}$; $R = 17{,}7 \cdot 10^{-6}$; $K = 21$.

From 21 cases of total risk 7 are stipulated by genetic defects; 14 - lethal malignant tumor. In Tbilisi City 1406 person annually die of oncologic diseases, and almost 1076 babies are born with genetic defects. In this number only 14 lethal oncologic cases and 7 genetic defects can be stipulated by radiation background. As we see, figures are rather unimportant, but by rectilinear-square conception this risk will be even less.

FCRP systematically consider that as the biological effects of activity of low dozes aren't discovered yet, we should consider quantitative estimation of risk as the highest level of estimation. They can be used for estimation and planning of defensive measures and not as prognosis of future losses. Researches that we've conducted in fact prove all this.

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HEALTH INDICES OF THE RURAL POPULATION LIVING IN THE AREA AFFECTED BY THE KRASNOYARSK MINING AND CHEMICAL COMBINE

V.F.Mazharov*, I.V.Tikhonova*, S.V.Babyonyshev*, V.I.Konenkov**, B.V.Protopopov**, G.I.Miretsky***, V.N.Kashin***, O.A.Theodorovich***

*Institute of Complex Problems of Hygiene and Occupational Diseases (Krasnoyarsk - Novokuznetsk)
**Institute of Clinical Immunology (Novosibirsk)
***Institute of Radiation Hygiene (St.Petersburg)

XA9745606

Abstract

Radioactive contamination of the floodplain of the Yenisei River with the wastes dumped by the Krasnoyarsk Mining and Chemical Combine (MCC) might cause external and internal irradiation of a large part of rural population inhabiting the banks of the Yenisei. Contrary to official data, a few independent studies of the doses received by the exposed population showed that they were quite significant though within the range of low doses. Due to the lack of comprehensive data on the dose status and doses received by the population, the health parameters of the population were studied by comparing the recorded incidences of diseases and mortality in the areas located at different distances from the MCC, in the periods before and after the MCC was put into operation, and in different age groups (younger and older than 30, children, working-age persons, and retirement-age persons). Also studied were territorial differences in the immunologic and immunogenetic statuses of some groups of population. It has been found out that in the district subjected to radioactive contamination (RAC-districts) there are characteristic shifts in the pathologies that are the main markers of the radiation factor. With possible accumulation of radiation doses the shifts become more distinct, and with the distance from the MCC less distinct. Time and space gradients of the cancer morbidity and mortality rate in the RAC-area have been found. In the riverside settlements of the RAC-area the mortality from malignant neoplasms (MN) of blood, blood-forming organs, and lymphatic system is higher than in the settlements located farther from the Yenisei. As the distance from the MCC down the Yenisei gets longer, the mortality of children due to congenital developmental defects and leukaemia decreases. The space gradient has been also found for most somatic disorders originating from stressogenic (psycho-emotional strain) and immunodeficient states. Besides increased incidence of cancer, in the RAC-area there is a higher incidence of pathological states determined to a large extent genetically - complicated pregnancies and their outcome, mortinatality, and congenital developmental defects. Investigations of immunologic and immunogenetic statuses of the RAC-district population have shown negative deviations from the Middle Siberian norm.

Spot investigations made by independent regional radioecological centres (Krasnoyarsk, St.Petersburg) revealed local, extremely high levels of contamination of the Yenisei floodplain - gamma-radiation of 60 mcr./h. and over - downstream of the place where the Mining and Chemical Combine (MCC) dumps its radioactive water, and trace levels of environmental contamination with nuclides, products of fission and neutron activation, as far as 300 km downstream of the nuclear facility. These facts prove that the radiation situation in the Yenisei floodplain is unfavourable.

Hygienists, however, find no violations of the principal hygienic regulations (exceeding of the dose limits) affecting the rural population, as a result of the operation of the MCC. They overlook the fact that inhabitants of the riverside settlements traditionally use the Yenisei floodplain for recreation, fishing, dairy cattle production, vegetable growing, collection of berries and mushrooms; the Yenisei has long been used

as a communication line. Over the period of the MCC operation a large part of rural population inhabiting the banks of the Yenisei might be exposed to external and internal radiation.

Contrary to official data, a few independent studies of the doses received by the exposed population showed that they were quite significant though within the range of low doses (N.N.Ilyinskikh, 1997). For this reason, we performed integrated socio-hygienic investigations in the rural districts located in the vicinity of the Krasnoyarsk MCC (RAC-districts). The aim was to find out possible health divergences among the population. The choice of the control rural district was rigidly limited by its geographical position (common border, the side windward of the RAC-district, non-Yenisei catchment basin, the absence of a large city near by).

Due to the lack of comprehensive data of the dose status and doses received by the population, the health parameters of the population were studied by comparing the recorded incidences of diseases and standardised mortality in the areas located at different distances from the MCC, in the periods before and after the MCC was put into operation, and in different age groups (younger and older than 30, children, working-age persons, and retirement-age persons). Also studied were the immunologic and immunogenetic statuses of some groups of population.

We have found that the incidences of infectious diseases as well as diseases of the endocrine and urogenital systems, and congenital defects are higher in the group of the RAC-districts than in the "uncontaminated" ones. Both children and adults in the RAC-districts significantly more often visit doctors, complaining of mental disorders. There are also differences in the number of visits to medical institutions due to respiratory and cardiovascular diseases. The integrated health index is significantly lower in the RAC-districts than in the control ones.

An analysis was made to study the dynamics of the parameters of the reproductive state of women living in the RAC-districts over the period between 1966 and 1993. It did not show any regularities which could suggest that pathological divergences were due to the effect of radiation. The exceptions are a much higher incidence of the revealed disfunctions of the thyroid in the pregnant women (over 4 times higher than in the control area), recorded in some years, higher incidences of congenital developmental defects (6.66 as compared with 4.22 per 1,000 new-born babies), bleeding in childbirth (36.0 as compared with 25.4 per 1,000 births), and multiple pregnancies. These data are all for the years of intensive operation of the MCC (1980 -1992).

The population of the RAC-districts has been found to have lower immunologic health indices than it is considered normal for Middle Siberia. There is a deviation in every link of the immune system, i.e. in the cell, humoral, and phagocytic links. Among other things it has been found that the incidences of the major viral infections of herpetic, cytomegaloviral, and chlamydic aetiologies are 1.5 to 2 times higher. The rate of occurrence of laboratory evidence of autoimmune processes is 5 to 7 times higher and that of immunodeficient states twice higher.

Sharp distinctions are recorded in the immunogenetic structure of the inhabitants of the RAC-districts: the incidence of the B51-antigen is 41 times as high as in the control group, that of the C5-antigen is 13 times higher, while the C6-antigen occurs 10 times less frequently.

With the distance from the Krasnoyarsk MCC some parameters of somatic health tend to improve, this tendency being more conspicuous in children. The same tendency is noted in the cancer mortality rate, including leukaemia, as well as infant mortality due to congenital defects of development incompatible with life.

The results of the analysis of the total incidences of malignant neoplasms (MN) show that in the RAC-districts they were significantly higher than the control rates for practically all localisations and during most years of survey. The total MN mortality during the period after the MCC was put into operation (1960-1993) increased in the RAC-districts both in men and in women. The differences from the rates of the control area and those of the period before the beginning of operation (1950-1959) are statistically significant.

Clearly related to the operation of the MCC are the indices of mortality from the so-called radiosensitive MNs (ICRP 45) -breast cancers, leukaemia, bronchopulmonary cancers, thyroid cancers, bone cancers, and skin cancers. The overall mortality from the cancers of respiratory organs has increased in every age and sex group in the RAC-districts, the recorded rates being above the control ones. During the period of MCC operation mortality from breast neoplasms in the women of the RAC-districts increased from 1.9 to 10.9 per 100,000 adult women (t=4.1). In the control district the mortality from this cause remained at practically the same level (5.3-4.7 0/oooo).

In a similar manner, the overall mortality caused by cancers of blood and blood-forming organs is different for the periods before and after the MCC was put into operation, increasing in the RAC-districts and remaining the same in the control ones. The integrated mortality from the neoplasms of lymphoid tissue over the period of MCC operation is 3 times higher in the RAC-districts than in the control area. With leukaemia mortality the difference is less pronounced but the mortality peak in the RAC-district was during the years of the MCC construction and the first 10 years of operation (1960-1969), while in the control area more than a quarter of all cases (3 of 11, or 27.3%) were recorded before the beginning of MCC operation.

On the whole, the trend of increase in radiogenic cancer mortality in the RAC-districts between 1950 and 1992, has a steep increment, with a rise of the level by several times, sometimes by an order of magnitude. In the control district these indices were at the same level over the period surveyed. We have studied the time (1951-1958, 1971-1978, and 1988-1995), space (settlements at the banks of the Yenisei and away from it), and age (persons younger than 30 and older population) gradients of the indices of cancer mortality in the RAC-area and the control one.

In the cohort of the population cumulated over the period between 1988 and 1995 there is a statistically significant difference in the indices of total and cancer mortality between the RAC-districts and the control area. This is true of all the groups under comparison except women. However, the relationship between the MN mortality rate and the location of the district has not been confirmed by the Pearson criterion of correspondence (X2) for the cohorts cumulated over the period between 1988 and 1995, i.e. the null hypothesis that there is no relationship between the MN mortality rate and the location of the district is NOT REJECTED.

In this period, in the RAC-area the total mortality rate in the men was higher than in the control one in all integrated age groups: infants of the first year of life, children aged 1-14, pensioners. Between 1988 and 1995 the infant mortality in the RAC-district was steadily higher than in the control one. Ambiguous results have been obtained in studying losses of active life in different districts. In the integrated cohorts of 1988-1995 the number of lost person-years of active life due to cancer mortality in women turned out to be less in the RAC-area than in the control one, while the losses due to other "leading" causes of mortality and the total mortality were much more significant in the RAC-area.

The analysis of the dynamics of the standardised by age population indices of cancer mortality (i.e. for all ages) in certain periods between 1951 and 1995 shows that in the control area the population mortality caused by MN tends to decrease. In the

RAC-area there is a tendency for increase. The revealed differences are statistically significant, with a reliable level of probability ($p>0.01$).

On the other hand, the cancer mortality rate in the age group under 30, the most sensitive to radiation injury and its neoplastic consequences, does not seem to be higher in the RAC-area than in the control one. The only thing that has engaged our attention is a steady increase in mortality in the men of the RAC- district during the periods under survey, as distinct from all the other groups of population (divided by age and territory). Comparison of age distribution of mortality due to MN in the RAC-area in 3 periods - 1951-1958, 1971-1978, and 1988-1995 - shows a steady increase of mortality in older (> 34) age groups after the Krasnoyarsk MCC was put into operation.

In the groups compared there are no statistically significant differences in the mortality caused by congenital developmental defects, but the incidence of congenital defects of development incompatible with life is twice lower in the control area than in the RAC-area (0.662 as compared with 1.12 per 1,000 new-born babies, but with $t<2.0$). In the RAC-districts the integrated average indices of mortality due to congenital developmental defects are always higher than those in the combined control group, but also with $t<2.0$.

Of all the northern-central districts of the Krasnoyarsk Territory, the RAC-area is characterised by the highest index (integrated for 8 years) of still-births, but because of the considerable confidence interval the mean values of the index of difference are again statistically insignificant. In 2 districts located downstream of the site where the MCC dumps its radioactive water the incidence of still-births decreases steadily as the distance from the MCC gets longer.

In the cohort of the population cumulated over the period of 1988-1995 the data on still-births in the RAC-area and the control one are significantly different from the data we obtained for 1960-1992, when the analysis was made in the blocks aggregated by five-year periods. According to the data for 1960-1992, in some five-year periods the incidence of still-births in the control area was several times higher than in the RAC-area. Nevertheless, it had a steady tendency for decrease, from 4.4% in 1965-1969 to 1.1+-0.28% in 1988-1995, while in the RAC-area it steadily increased from 0.2-0.3% in 1965-1969 to 1.14+-0.21% in 1988-1995.

In conclusion, we can estimate as clearly unfavourable the dynamics of the health indices of rural population of the RAC-area over the period of MCC operation, while there have been no other evident sources affecting the health of the population. The differences from control populations are not always statistically significant but, basing on the totality of the main and additional criteria, we can still attribute them to the consequences of radiation exposure.

NEUROPHYSIOLOGICAL APPROPRIATENESS OF IONIZING RADIATION EFFECTS

Angelina I. NYAGU & Konstantin N. LOGANOVSKY
Department of Neurology, Institute of Clinical Radiology,
Scientific Centre for Radiation Medicine of Academy of Medical Sciences of Ukraine,
53 Melnikov Str., 254050, Kiev-50, Ukraine

Abstract

The goal of this study was to compare bioelectrical activity of the brain in remote period of acute radiation sickness (ARS), chronic and prenatal irradiation as a result of the Chernobyl disaster. Registration of computerized 19-channel EEG, visual and somato-sensory evoked potentials have been carried out for 70 patients who had a verified ARS, 100 Chernobyl disaster survivors, who have been working in the Chernobyl exclusion zone since 1986-87 during 5 and more years, 50 prenatally irradiated children, and relevant controls. The relative risks of neurophysiological abnormalities are 4.5 for the ARS-patients, 3.6 for the chronically irradiated persons and 3.7 for the prenatally irradiated children. The data obtained testify to possibility of radiation-induced neurophysiological abnormalities in examined Chernobyl accident survivors which seems to be non-stochastic effects of ionizing radiation. For all examined irradiated patients it was typically an increasing of δ- and β-powers of EEG, particularly, in the frontal lobe shifted to the left fronto-temporal region, but spectral power of both θ- and α-range was significantly depressed. Aforesaid signs together with data of evoked potentials reflect the structural and functional abnormalities of limbic system and the left hemisphere as the first revealed neurophysiological appropriateness of ionizing radiation effects.

1. INTRODUCTION

H.Davis & P.Davis (1939) for the first time used EEG for ionizing radiation influence on the brain and revealed the brain bioelectrical activity changes in irradiation monkeys [1]. In 30 A-bomb survivors with ARS symptoms the EEG study was performed where an epileptic activity like bilateral spikes and spike-and-slow wave complexes observed in 3 patients. According to the spectral EEG analysis data in the ARS-patients in comparison with the non-exposed control there were a depression of α-power, especially in the left posterior region together with an increase of δ (2.5-3 Hz)- and β (14-28 Hz)-power, predominantly in the left hemisphere [2,3]. Seizures are typical aftermath of brain damage in utero, especially among those patients exposed to ionizing radiation with doses more than 0.1 Gy on 8-15th weeks after fertilization [4]. In the 60-s it was established an extreme radiosensitivity of EEG-patterns [5-9]. Some later it was shown the direct radiation effect of 6-8 mGy on the endogenous (pacemaker) mechanism of nervous impulse generation in hippocampus neurons [10]. Chronic irradiation caused the clear changes of EEG-pattern: an increase of β-activity together with abnormal slow activity in proportion to dose of irradiation [11]. Twenty years after radiotherapy of tinea capitis (averaged dose on the brain -1.3 Gy) the delayed radiation brain damage was revealed, where a significant increase of β-range power of EEG was estimated as the "trace" of radiation exposure [12].

It has been also observed the EEG-abnormalities caused with general total irradiation as follows: a slowing in the trace with occurrence of slow polymorphous patterns and/or sometimes deformed spikes and spike-and-wave complexes; an increase in percentage energy of electrical cerebral activity between 0 and 4 Hz, with maximum peak position of less than 2 Hz. The changes in electrical activity of the brain are related to the degree of irradiation although the relationship is not a straightforward linear one. they occur at thresholds of 0.3 to 1 Gy and increase with the dose absorbed. Abnormalities in electrical activity of the brain can persist for 3-4 years after recovery of ARS, subsequent to a dose of 4 Gy [13,14].

There are many publications with results of EEG-studies in different categories of the Chernobyl accident survivors [15-25], describing structural and functional changes in the brain. However, there is no one available work concerning a simultaneous neurophysiological investigation of acute, chronic, and prenatal effects of ionizing radiation in human. That is why the goal of our

study was to compare bioelectrical activity of the brain in remote period of ARS as well as after chronic and prenatal irradiation as a result of the Chernobyl disaster.

2. OBJECTS AND METHODS

I group - 70 patients who had a verified ARS (absorbed doses - 0.7-6.6 Gy) as a result of the Chernobyl disaster; all of them were right-handed men, age at the time of examination - 35-59 years.

II group - 100 Chernobyl disaster survivors, who have been working in the Chernobyl exclusion zone since 1986-87 during 5 and more years. The patients (males) were 25-48 years old. Fifty four from them (*IIA group*) were chronically irradiated in doses below 0.30 Sv (averaged dose - 0.16±0.05 Sv), and 46 (*IIB group*) - above 0.30 Sv (averaged dose - 0.69±0.15 Sv). The controls for these two group were: 15 practically healthy men, 30 veterans of the Afghanistan war with PTSD, 50 veterans of the Afghanistan war with both PTSD and mild closed head injury consequences.

III group - 50 children born from April, 26th, 1986 to February, 26th, 1987 by pregnant women evacuated from the 30-km exclusion zone of the Chernobyl NPP. These children have been prenatally exposed to ionizing radiation. Their age at the time of examination was 8-9 years. External γ-radiation doses of whole fetus were until 13 mSv and thyroid gland doses - 100-1200 mSv. The control were 20 practically healthy non-exposed children of the same age.

Registration of computerized 19-channel EEG, visual (on chess-board) evoked potentials (VEP), and somato-sensory evoked potentials (SSEP) have been carried out according to traditional system. Statistical processing included summarizing data, Student's *t* test, the Chi-square test, correlation and multifactorial analyses.

3. RESULTS

3.1. ARS remote consequences

The typical routine EEG-patterns in the remote period of ARS was a polymorphous "flat" (low-voltage) EEG together with paroxysmal activity (spikes, polyspikes, acute and δ-waves, sometimes - spike-wave) shifted to the left fronto-temporal region. According to spectral EEG-analysis, among all patients of the I group it has been established in comparison with the control a significant predominance of δ- and β (dominant frequency - 20 Hz)-powers of EEG, particularly, in the frontal lobe also shifted to the left fronto-temporal or parieto-temporal regions, that correlated with severity degree of ARS and, consequently, with absorbed doses of ionizing radiation. At the same time, spectral power of both θ- and α-range (especially, in the left occipito-parietal region) was significantly depressed in the ARS patients in comparison with the control. The visual evoked potentials in the I group patients had a decreased latency and an increased amplitude for P_{100} ($p<0.01$) or a total deformation of main components (P_{100}, N_{145}, and P_{200}). The somato-sensory evoked potentials in the ARS patients had an increased latencies and a decreased amplitude of late (P_{300} and N_{400}) components together with an increased contralateral latency of N_{20} for right medianus nerve stimulation. Clinically and pathopsychologically in the ARS patients the schizoid-like brain organic syndrome with apathy, abulia, autism, paranoia, and hypochondria symptoms prevalence has been revealed. The organic nature of this syndrome was also verified by the MRI-findings, testify to brain atrophy with enlargement of sylvii fissure (S>D), IV ventricle, basal and brainstem cisterns. Mental disorders in the remote period of ARS have been diagnosed as postradiation encephalopathy. The pathophysiological basis of postradiation encephalopathy is the abnormalities of diencephalo-limbic-reticular complex and associative cortex of frontal and parietal regions, predominantly of left - dominating - hemisphere, together with central disorders of afferentation.

3.2. Chronic irradiation

It has been established that 39 (72.2 %) patients of the IIA group had a right hemisphere diencephalic-limbic-reticular pattern of dysfunction: the disorganized α-activity was shifted to the frontal regions together with bilateral paroxysmal activity and δ- and θ-activity lateralized to the right hemisphere. A decrease in the amplitude of SSEP component with latency P_{300} was found when compared with the normative groups ($p>0.05$). It was characteristically associated with affective (dysthymia) and somatoform disorders in individuals irradiated less than 0.30 Sv.

However, in 29 (63.0 %) patients of the IIB group the left hemisphere limbic-reticular pattern was observed. The EEG was disorganized and flat with paroxysmal activity, slow activity, bilateral bursts of polyspikes with no clear localization. Spectral δ- and β_1-powers dominated the EEG with left frontal-temporal lateralization. Alpha and θ-power was reduced. SSEP were characterized by a decrease in amplitude ($p<0.05$) and an increase ($p<0.05$) in latency both for the early (N_{20} and P_{25}) and later (P_{300} and N_{400}) components. The middle latency components were of higher amplitude than the later components when compared with the controls. On right median nerve stimulation, unlike the controls, the contralateral latency (N_{20}) at (C_3) was significantly increased (instead of being reduced). On the otherhand the situation was reversed on when considering the amplitude which instead of being increased contralaterally was decreased. It was characteristically associated with both schizoid-like organic and schizotypical disorders in individuals irradiated by doses above 0.30 Sv with a non-linear relationship "dose-effect".

The basis of psychophysiological changes in the chronically irradiated persons as a result of the Chernobyl disaster is microcirculatoric-dysmetabolic disorders of cortex neurons functioning and dysfunction of diencephalic-limbic-reticular complex together with the brainstem reticular formation inhibition and the thalamic structures hyperactivation. It is significant to note that the left fronto-temporal dysfunction and the left hemisphere hyperactivation are the most characteristic psychophysiological consequences of chronic irradiation. According to multifactorial analysis the influence η^2 of the chronic irradiation doses in the psychophysiological changes reaches 0.84 and the duration of working in the Chernobyl exclusion zone - 0.60 that, possible, reflects the cumulative effect of chronic irradiation. The psychophysiological effects seem to be possible after 0.15 Sv of general chronic irradiation but their specific peculiarities can be revealed after 0.30 Sv only. It is possible to suppose the threshold of psychophysiological disorders in consequence of general chronic irradiation is 0.30 Sv.

3.3. Prenatal irradiation

The typical routine EEG-patterns among the in utero irradiated children was a disorganized EEG with a lot of slow and paroxysmal activity (acute and high voltage δ-waves, sometimes - spike-wave) shifted to the left fronto-temporal region. According to spectral EEG-analysis and Berg-Fourier EEG-analysis, among all children of the III group it has been established in comparison with the control children a significant predominance of δ- and β (dominant frequency - 20 Hz)-powers of EEG, particularly, in the frontal lobe also shifted to the left fronto-temporal region. At the same time, spectral power of both θ- and α-range (especially, in the left occipito-parietal region) was significantly depressed in the children irradiated in utero in comparison with the control children. The more disorganized EEG-patterns have been observed in the children exposed at 8-15th weeks of prenatal development, but the left-hemisphere abnormalities were more typical for those, exposed at 16-25th weeks after fertilization. No one case of mental retardation among examined children has been revealed. At the same time, the children irradiated in utero in comparison with the control had significantly more emotional and behavioral disorders like social estrangement, exhaustion, emotional lability, tearfulness, apathy. We suggested that data obtained testify to the structural and functional abnormalities of the developing brain, particularly limbic system and left hemisphere, in prenatally irradiated children as a result of the Chernobyl disaster.

4. CONCLUSION

The relative risks of neurophysiological abnormalities are 4.5 for the ARS-patients, 3.6 for the chronically irradiated persons and 3.7 for the prenatally irradiated children indicate that all these Chernobyl accident survivors are associated with more than triple increase in the risk of brain pathology. At the same time this relative risks are 1.3 only for PTSD and 2.0 for both PTSD and mild closed head injury consequences. Thus, it is clear, that all examined irradiated patients have significantly higher risk of brain damage than those, suffering from stress and both stress and mild closed head injury consequences. The data obtained testify to possibility of radiation-induced neurophysiological abnormalities in examined Chernobyl accident survivors which seems to be non-stochastic effects of ionizing radiation, that is closely corresponding to literature data.

For all three groups of examined irradiated patients it was as a rule typically an increasing of δ- and β (dominant frequency - 20 Hz)-powers of EEG, particularly, in the frontal lobe shifted to the left fronto-temporal region. At the same time, spectral power of both θ- and α-range (especially, in the left occipito-parietal region) was significantly depressed. Aforesaid signs together with data of evoked potentials reflect the structural and functional abnormalities of limbic system and the left hemisphere as the first revealed neurophysiological appropriateness of ionizing radiation effects.

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EPIDEMIOLOGICAL STUDY OF SCHIZOPHRENIA IN THE CHERNOBYL EXCLUSION ZONE PERSONNEL

Konstantin N. LOGANOVSKY & Angelina I. NYAGU
Department of Neurology, Institute of Clinical Radiology,
Scientific Centre for Radiation Medicine of Academy of Medical Sciences of Ukraine,
53 Melnikov Str., 254050, Kiev-50, Ukraine

XA9745608

Abstract

Nakane & Ohta (1986) revealed very high (6 %) prevalence rate of schizophrenia in A-bomb survivors. The goal of this study was the epidemiological investigation of schizophrenia in the Chernobyl exclusion zone personnel on the base of 10-years follow up study and analysis of the psychiatric archives (1986-1996). As a result the register of schizophrenia spectrum disorders has been created, including 65 staff members. According to both ICD-9 and ICD-10 criteria there were 48 patients with schizophrenia. It has been revealed a statistically significant increase of the schizophrenia percentage amongst all psychoses in the Chernobyl exclusion zone personnel in comparison with the general Ukrainian population. It has been established that among 48 cases of schizophrenia there were 39 (81.2 %) of schizophrenia onset occurred in the zone. Since 1990 a significant increase (more than 4 times: 5.4 per 10,000 in the zone and 1.1 per 10,000 in Ukraine) in schizophrenia incidence has been taking place among the irradiated population of the exclusion zone in comparison with the general population. Our data testify to possibility of radiation-induced schizophrenia onset, which seem to be like stochastic effects of ionizing radiation. The mechanisms of these effects realization are the subject of further investigations.

1. INTRODUCTION

At the present time an influence of environment in genesis or redoubling of mental disorders remain unclear. It has been also revealed no one external environmental cause which could evoke invariably or probably schizophrenia in persons without genetic predisposition of schizophrenia [1]. The combination of genetic effect and environmental influence in the etiology of schizophrenia is undoubted [2-4].

There is only one available correctly performed epidemiological study of schizophrenia related to exposure of ionizing radiation [5]. The Life Span Study (LSS) started by Radiation Effect Research Foundation (RERF) did not include data on patients with severe mental disorders. Nakane & Ohta (1986) have therefore collated the schizophrenia register kept in their Department of Neuropsychiatry, University School of Medicine, Nagasaki with that of the LSS. Of the 26,678 original subjects, 1,589 were included in the schizophrenia register in 1978. The register has been in operation since 1960 and it was not possible to calculate annual inception rates since 1945. Moreover, migration out of Nagasaki cannot be estimated. Inspite of aforesaid methodological limitations the prevalence rate of schizophrenia in A-bomb survivors is very high - 6 % [5], while the schizophrenia prevalence is no more 1 % in general population [3-4].

Schizophrenia takes the second place (after oligophrenia) in the structure of mental disorders prevalence among the people living in the region of the Semypalatinsk nuclear weapon experimental site [6]. Twenty-nine percent of all psychiatric patients living near the nuclear weapon site are schizophrenics [6], whereas in former Soviet Union in 1965-1990 there were 17.3-23 % schizophrenics only amongst all mentally ill patients [7].

Nine years after the Chernobyl accident it was found no increase of schizophrenia prevalence in Byelarus among the people living in radioactively contaminated areas [8]. At the same time some authors noted that the clinical manifestations of schizophrenia were atypical among the inhabitants of Byelarus and Kiev after the Chernobyl accident [8,9]. In 1962 yet Golodetz [10] described the atypical clinical picture of schizophrenia secondary to the chronic influence of ionizing radiation as follows: predominance of asthenic symptoms together with autonomic instability associated with hypochondrial and psychosensory (senestopathias) disorders, as well as mild organic symptoms. The

point of view concerning recognition of ionizing radiation effects on schizophrenia clinical pattern did not supported by another authors [11].

Thus the influence of ionizing radiation in the etiology of schizophrenia remains uncertain. The most important methodology for study any radiation effect on the onset of schizophrenia is an epidemiological one. Unfortunately, until now the epidemiological data concerning severe mental disorders like schizophrenia among the Chernobyl accident survivors are practically absent. It could be explained as follows: 1) lack of radioepidemiologists' interest to this problem in comparison with traditional topics like radiation induced malignancies, hereditary disorders etc.; 2) deficiency of psychiatric maintenance of radiological registers, and vice versa - radiological maintenance of psychiatric ones; 3) high level of the survivors' migration. That is why 10-years follow up study in the Chernobyl exclusion zone (EZ) personnel is a good opportunity for the first attempt of epidemiological investigation of low doses of ionizing radiation effects on schizophrenia.

2. MATERIALS AND METHODS

The material of this study was the psychiatric archives (1986-1996) of the Medical and Sanitary Department (MSD) in Chernobyl. This MSD has undertaken since 1986 the somatic and mental health monitoring of the EZ personnel. In 1986-1988 the MSD of Chernobyl surveyed ≈25,000 men every year; in 1989 - ≈12,500; in 1990 - ≈11,000; in 1991 - ≈11,250; in 1992 - ≈12,500; in 1993 - 12,963; and in 1994-1996 - ≈11,000 ones. There are 78.9 % of men and 21.1 % of women among workers of the EZ; from them - 32.9 % of 40-49-years old workers, 30.2 % - 30-39-years old, 24.7 % - 50-59-years old ones. The majority of them are engineers and technicians. The percentage of people working in the EZ 5 and more years is the most significant - 60.6 %. The distribution of the EZ personnel according to effective doses of irradiation is as following: ≤ 0.05 Sv - 81.8 % workers; 0.05-0.24 Sv - 13.6 %; 0.25-0.99 Sv - 3.7 %; ≥ 1 Sv - 0.82 % ones [12]. We have studied all records in the psychiatric archives of the MSD of Chernobyl. As a result the register of schizophrenia spectrum disorders in the EZ personnel has been created, including 65 patients. The data obtained have been analyzed with the Chi-square test and vital statistics methods (measures of morbidity) [13].

3. RESULTS

3.1. General mental health assessment in the Chernobyl exclusion zone personnel

In the psychiatric archives there were revealed cases of mental disorders according to the International Classification of Diseases of 9-th Revision (ICD - 9) criteria during 1986-1996 in the EZ personnel. Excluded the problems related to psychoactive substances abuse, the mental disorders cases presented on figure 1.

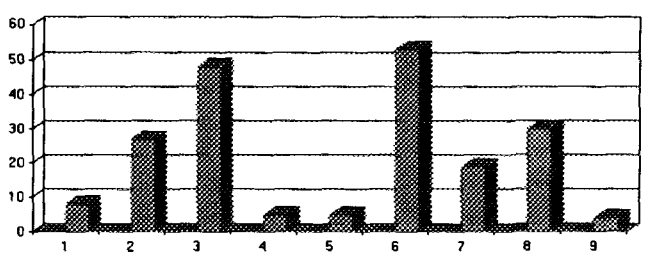

Fig.1. Mental disorders (without narcological) in the Chernobyl exclusion zone personnel
1 - organic non-alcoholic psychoses (8 cases); 2- epileptiform syndrome (27 cases); 3- schizophrenia (48 cases); 4 - affective psychoses (5 cases); 5 - reactive psychoses (5 cases); 6 - neurotic disorders (53 cases); 7 - disorders of personality (19 cases); 8 - organic brain damage (30 cases); 9 - oligophrenia (4 cases).

We must stressed that aforesaid data can be recognized as exhaustive ones for severe mental disorders only. The majority of borderline mental disorders in the EZ personnel has been classified as accompanying ones of somato-neurologic pathology and, consequently, excluded from the psychiatric archives. Thus, Vokhmekov et al. (1994) informed about the increasing prevalence of all mental

disorders (ICD-9: 290-310) from 156.6 per 1.000 zone workers in 1986 to 225.2 per 1.000 ones in 1992. Moreover, in 1992 those workers exposed to ionizing radiation in doses more than 0.25 Sv had the borderline mental disorders prevalence in 3.5 times higher than all EZ personnel: 805.1 and 214 per 1.000 workers correspondingly [12]. This is closely correlating with some literature data. It is knowing that the prevalence of autonomous nervous system dysfunction (vegetative dystonia) in harmful (chemical) factory personnel is 86 % and is increasing in proportion to length of work [14]. At the same time, in 89 % patients suffering with vegetative dystonia revealed psychiatric symptoms [1]. By another words, it is scientifically grounded to suppose that at least 76 % of the EZ personnel can suffering with mental disorders predominantly borderline ones. This calculation has been completely confirmed by our data obtained on the base of psychiatric examination of 400 randomly selected EZ workers: 316 (79 %) of them had a borderline mental disorders as follows: 104 (26 %) patients have been diagnosed with neurotic symptoms; 136 (34 %) ones - neurosis-like, and 76 (19 %) ones - organic mental disorders [15].

3.2. Schizophrenia study in the Chernobyl exclusion zone personnel

The schizophrenia spectrum disorders register includes 65 workers of the EZ. According to the ICD-9 criteria of schizophrenia (code 295, excluding "slow progredient schizophrenia") there were 48 schizophrenics met also the criteria of ICD-10 F20 - schizophrenia [16]. On figure 2 presented the proportion of schizophrenia to another psychoses both in the personnel and Ukrainian population.

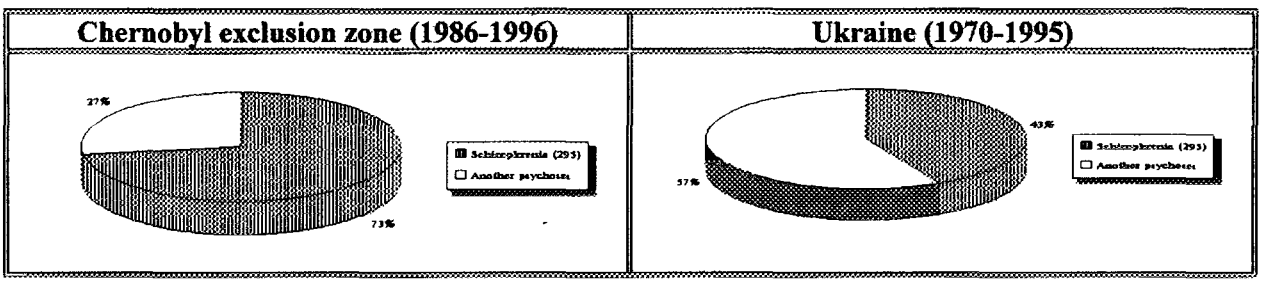

Fig.2. Proportion of schizophrenia to another psychoses

It has been revealed a statistically significant increase of the schizophrenia percentage amongst all psychoses in the EZ personnel in comparison with the general Ukrainian population (χ^2=18.5; $p<0.01$). The relative risk is 1.7 and indicate that working and living in the EZ is associated with practically a twofold (85 %) increase in the risk of schizophrenia in the structure of psychoses. There is no sense to calculate the prevalence rate of schizophrenia in the EZ personnel because of: 1) the personnel had been medically examined before job placement in the EZ and all mental patients (at least, revealed schizophrenics) were rejected and, as a result, among the personnel a natural "accumulation" of schizophrenia is absent; 2) every diagnosed schizophrenic must be rejected from the personnel. Both of these reasons are leading to an artificial reducing of schizophrenia prevalence. That is why we focused our study precisely on the schizophrenia incidence rate in the EZ personnel.

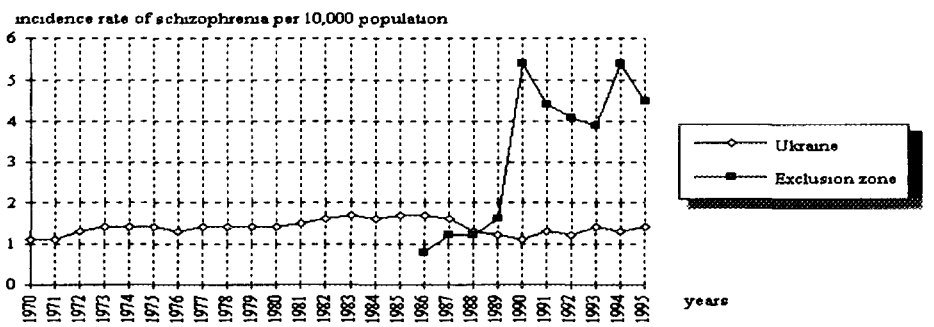

Fig.3. The incidence rate of schizophrenia in the Chernobyl exclusion zone personnel in comparison with Ukrainian population

It has been established that among 48 cases of schizophrenia there were 39 (81.2 %) of schizophrenia onset occurred in the Chernobyl exclusion zone The incidence rate of schizophrenia in the EZ personnel in comparison with Ukrainian population is presented on figure 3. Among those 39 patients there were diagnosed 31 (79 %) paranoid and 8 (21 %) simple forms of schizophrenia. Of the 39 cases there were: 32 (82 %) males, 37 (95 %) in the 15-54 years age group, 16 (41 %) of these patients in 1986 were evacuated from the exclusion zone, and 29 (74 %) of them had been taking part in the Chernobyl accident clean up since 1986-1987 before they became ill with schizophrenia.

It is clear, that since 1990 a significant increase (more than 4 times) in schizophrenia incidence has been taking place among the irradiated population of the EZ in comparison with the general population data The relative risks are 2 4 for 1986-1996 and 3.4 for 1990-1996 indicate that working and living in the EZ is associated with more than a twofold and even triple increase in the risk of schizophrenia onset.

The data obtained are completely confirming the results of Nakane & Ohta (1986) about an increase of schizophrenia in the A-bomb survivors. No one of postchernobyl non-radiation unfavorable factors can explain satisfactorily the significant increase of schizophrenia incidence rate in the most irradiated zone. Our data testify to possibility of radiation-induced schizophrenia onset, which seem to be like stochastic effects of ionizing radiation. The mechanisms of these effects realization are the subject of further investigations.

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LEUKAEMIA AND THYROID CANCER IN EMERGENCY WORKERS OF THE CHERNOBYL ACCIDENT: RADIATION RISKS ESTIMATION

V.K.Ivanov, A.F.Tsyb, A.I.Gorsky

Medical Radiological Research Center, Obninsk, Russia

Abstract. This work focuses on the direct epidemiological assessment of the risks of radiation-induced leukaemia and thyroid cancer in emergency workers (EW) after the Chernobyl accident The Russian National Medical Dosimetric Registry (RNMDR) contains data for 162942 EW as of January 1, 1997 The analysis relates to 48 leukaemias and 47 thyroid cancers, diagnosed and verified Radiation risks are estimated by comparing the EW data with national data for a male population of the same age distribution For leukaemia, an excess relative risk per Gy (ERR/Gy) of 4 30 (95% CI 0 83, 7 75) is obtained, while the excess absolute risk per 10^4 person-years (PY) Gy (EAR/10^4 PY Gy) is found to be 1 31 (95% CI 0 23, 2 39), for thyroid cancer an ERR/Gy of 5 31 (95% CI 0 04, 10 58) is obtained, and an EAR/10^4 PY Gy of 1 15 (95% CI 0 08, 2 22)

1 INTRODUCTION

Few, if any, estimates of radiation risk for low doses of ionizing radiation (0 2-0 3 Sv) exist that are based on direct epidemiological studies The prediction of the radiation induction of malignant tumours in this range of low doses is normally based on the extrapolation of observed risk coefficients from relatively high doses (>1 Sv) to low doses It is, therefore, of particular interest to determine risk coefficients directly at low doses and to provide, thus, for this range of doses an additional test of the presently recommended risk coefficients and prediction models

In this sense, the data accumulated since the Chernobyl accident are of singular value Indeed, during the first 10 years of follow-up, large volumes of epidemiological data have been collected, characterizing the health status of hundreds of thousands of persons who received low doses At the same time, there are few studies concerned with the estimation of the radiation risks due to Chernobyl, and, in fact, the question arises as to whether it is feasible to assess radiation risks in direct epidemiological studies of the effects of the Chernobyl accident

The increase of leukaemia and thyroid cancer incidence rates is one of the first manifestations of late radiation effects Among radiation-induced malignant tumours, leukaemia and thyroid cancer have the shortest latency periods (about 2-3 years for leukaemia, and 4-5 years for thyroid cancer) The time since the accident exceeds these latency periods

This study deals with the epidemiological analysis of thyroid cancer and leukaemia incidence among emergency workers Estimates of radiation risks based on observations up to the end of 1993 are presented, and they are then compared with current prediction models The cohort of emergency workers has been described in several of our earlier studies [1-3]

2 LEUKAEMIA INCIDENCE

The present analysis refers to 48 cases of leukaemia in emergency workers verified by the Medical Radiological Research Center of the Russian Academy of Medical Sciences (RAMS) and local health care establishments, as of January 1, 1994 The verification of leukaemia is a complicated and lengthy procedure, and therefore, this study contains the analysis of incidence beginning in 1986, but extending only to the end of 1993 By January 1, 1994, the RNMDR database contained medical and dosimetric information for 142 000 emergency workers, among which the 48 leukaemias were reported in the period specified

Table I summarizes the standardized incidence ratio (SIR) values for leukaemia in emergency workers for two time intervals 1986-1989 and 1990-1993 In both cases the SIR is more than 100%.

which means that the incidence among emergency workers is higher than the mentioned average. However, at the 95% confidence level, the difference is statistically significant only for the cases diagnosed in the period 1990-1993. The absence of a significant increase of leukaemia cases in the years 1986-1989 is in line with the latency period of 2-3 years for the induction of radiogenic leukaemia assumed in the risk models.

Table I

Standardized incidence ratio (SIR) of leukaemia among emergency workers (EW)

Observation period (years)	Observed number of cases	Expected number of cases	SIR	95% confidence interval
1986-1989	14	12.3	113	62, 190
1990-1993	34	19.2	177	122, 247

In the calculations of the number of anticipated cancer incidences, we used the time and dose dependence from the model derived for leukaemia (all types) in the Japanese cohort of atomic bomb survivors [4], taking into account the age and dose distribution of the cohort of emergency workers and the age-specific spontaneous leukaemia incidence rates for the Russian Federation.

Figure 1 shows data of the Chernobyl Registry on leukaemia incidence in emergency workers and the corresponding anticipated rates. There are several major conclusions. First, within the limits of the statistical errors, the prediction and the observed data are in good agreement. Secondly, in line with the prediction, it appears from the registry data that the peak of radiogenic leukaemia occurred 4-5 years after the accident, the attributable risk (AR) being 45%-60% (AR = 1-1/SIR).

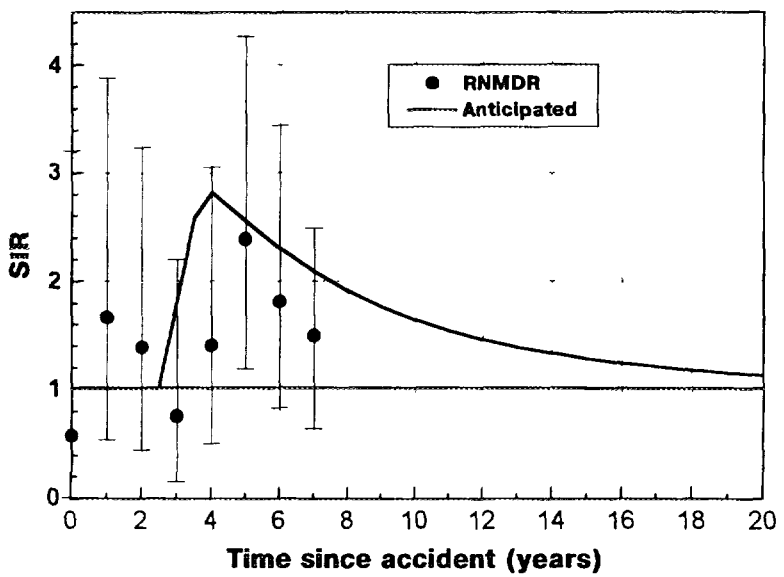

Fig. 1. Anticipated (solid line) and observed (dots) SIR of leukaemia in emergency workers cohort. Bars give the 95% confidence intervals.

3. THYROID CANCER INCIDENCE

By January 1, 1995, the RNMDR included 47 thyroid cancers in emergency workers. These were diagnosed at different times since exposure, ranging from 1 to 8 years.

Figure 2 presents the change of the SIR values in the 8 calendar years of the follow-up period for emergency workers of 1986 and 1987. The SIR values remain practically constant at 2.2-2.6 for the time period that corresponds to the latency period of 4 years. If during this period no induction of radiogenic cancers is assumed to occur, then the excess of the observed SIR over 1 (100%) accounts for the screening effect (improved medical examination).

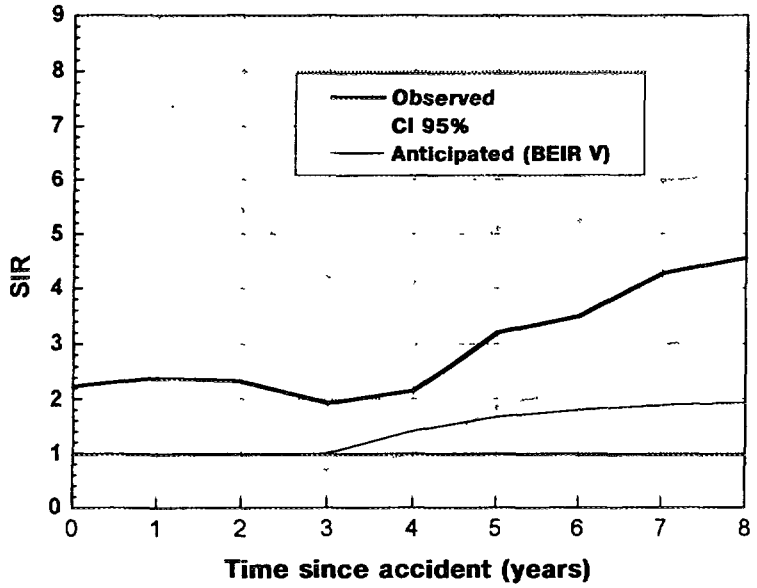

Fig. 2. Observed and anticipated SIR values for thyroid cancer among emergency workers of the period 1986-1987.

4. ESTIMATION OF RADIATION RISKS

As was stated above, the main aim of this study is not only epidemiological analysis in terms of SIR, but also the derivation of risk coefficients for leukaemia and thyroid incidence in emergency workers. Several risk coefficients are considered: excess relative risk per Gy (ERR/Gy), excess absolute risk per 10^4 person-years Gy (EAR/10^4 PY Gy) and attributable fraction of risk (AR%) at 1 Gy.

In the estimation of coefficients of radiation risk, it is assumed that the observed increases in leukaemia and thyroid cancer incidence are, indeed, due to radiation exposure. To ascertain this relation in an epidemiological investigation, an internal, dose-related analysis would be necessary. Our calculations suggest that such an analysis will require continued follow-up for the next 10-15 years; this would then provide about $2 \cdot 10^6$ person-years (PY) of observation of the cohort instead of the $1 \cdot 10^6$ PY achieved up to now.

The current follow-up of the emergency workers' cohort is too short to provide a sufficient number of cases of such rare diseases as leukaemia and thyroid cancer An external analysis using national rates instead of an internal control group has, therefore, been employed for the risk estimation

The EAR per Sv was estimated from the expression

$$EAR = (O - E \cdot c)/(N_{PY} \cdot D), \quad (1)$$

where

O is observed number of cases;

E is expected number of cases according to national rates;

c is coefficient allowing for the screening effect;

N_{PY} is number of person-years under observation;

D is dose due to external irradiation in Sv

The ERR per Sv was calculated in terms of the equation.

$$ERR = EAR \cdot N_{PY}/(E \cdot c) \quad (2)$$

The attributable risk at 1 Sv was obtained from the ratio

$$AR = ERR/(1 + ERR) \cdot 100\% \quad (3)$$

The confidence intervals were calculated using the method of linearization of the function of random variables

Risk coefficients are estimated merely for the cohort of the 1986-1987 emergency workers, as only for this cohort has the follow-up exceeded the latency periods for leukaemia and thyroid cancer

It is essential to introduce the parameter c here to account for the effect of in-depth screening in the emergency workers. In line with the regulations of the Russian Ministry of Health, the emergency workers undergo an extensive annual medical examination. As pointed out, this can lead - in comparison with the entire male Russian population (the control group) - to an increased number of diagnosed cancers, which needs to be taken into account.

For leukaemia incidence the coefficient c is set equal to unity, because, as seen from Table I (1986-1989), the SIR=113% during the latency period, which indicates no significant deviation from the national rates.

For thyroid cancer incidence c = 2.6. This corresponds to an increased value SIR=260% during the latency period (1986-1990), which is statistically significant and reflects the effects of in-depth screening (Figure 2).

Tables II and III present radiation risk estimates for the cohort of emergency workers and their comparison with literature data from other studies. As can be seen, there is good agreement between the risk values obtained by us and published coefficients. Further epidemiological follow-up will be required to derive basic dependencies of the risk on dose, age at exposure and time since exposure.

Table II

Radiation risk of leukaemia incidence among EW (1986-1993 observation period)

Data source	EAR/10^4 PY Gy (95% CI)	ERR/Gy	AR (at 1 Gy) %
This study	1.31 (0.23, 2.39)	4.30 (0.83, 7.75)	81
LSS cohort	2.38	7.8	88

Table III

Radiation risk of thyroid cancer incidence among EW (1986-1994 observation period)

Data source	EAR/10^4 PY Gy (95% CI)	ERR/Gy	AR (at 1 Gy) %
EWs	1.15 (0.08, 2.22)	5.31 (0.04, 10.58)	84
BEIR V	1.25	5.8	85

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REGULATORY ASPECTS OF LOW DOSES CONTROL IN ALBANIA

K. Dollani, R. Kushe
Institute of Nuclear Physics, Tirana, Albania

XA9745610

Abstract

In the present paper are described the status of regulatory aspects of low doses control as well as the existing procedures for their implementation in Albania. According to new Radiological Protection Act, approved by Parliament in 1995, the establishment of the infrastructures in radiation protection area is in course, accompanied by the installation and functioning of new equipment for low dose control. Based in many years experience it is concluded that personal doses of the workers added by practices in Albania are 1/10 of dose limits. Some particular cases of overexposured workers were investigated. Last times the elements of the optimisation procedures (QA and QC) are outlined in the frame of improving regulatory aspects of low doses control.

1. Introduction

The importance of the measuring and recording of low doses added by practices has been underlined from the first regulatory document on Safe Handling of Ionizing Radiation Sources, issued by Albanian Government at 1971 [1]. Only a year after, Institute of Nuclear Physics (INP) began the research work concentrated in measuring of low gamma doses by photographic film method. For this purpose has been used the ORWO RD 3+4 film (produced by former East Germany) in connection to FD-III-B filtered plastic badge. This work aimed to measure and to asses gamma and X-ray doses of the workers in diagnostic and therapy radiology as well in other nuclear techniques applications [2]. Later the measuring of beta and slow neutron doses were included in INP research works. Soon after receiving of the first results, photographic film method served as a solid base for measurements of low doses for the majority of radiation workers in Albania, especially in the field of diagnostic radiology, with wide spread in the country. By this method the radiation protection status of the workers was under regular control till 1986 when as result of difficulties in providing ORWO RD 3+4 film, IAEA had proposed the substitution of the film method by thermoluminescent dosimeters. For this purpose INP was furnished at that time with a Harshaw TLD Reader Model 2000 and a limited number of TL cards and chips. Since this period in Albania is in course the control of low dose added by practices through TLD method. Some important improvements in this area are performed last year in the frame of the participation of Albania in the IAEA Model Project on Radiation Protection and Waste Management.

2. Radiation Protection Infrastructures in Albania

The International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources [3] identifies the essential parts of a national radiation protection infrastructure as being: legislation and regulations; Regulatory Authority empowered to authorise and inspect regular activities and to enforce the legislation and regulations; sufficient resources and an adequate number of well-trained personnel. The mentioned Radiation Protection Decree [1] had tried to give due importance to these elements

through the establishment of Radiation Protection Commission as the National Regulatory Authority. This Commission had issued many important documents like Permissible Maximal Levels of Radiation, Medical Examination of Radiation Workers, Safe Transport of Radioactive Materials etc. Nearly in all nuclear facilities of the country were appointed Radiation Protection Officers. Two years ago Albanian Parliament had approved the new Radiological Protection Act [4]. According to this Act, last year has been done the reorganisation of Radiation Protection Commission within the Ministry of Health. From the other side was established the new executive organ of the Commission, Radiation Protection Office. The scheme of the actual Radiation Protection Infrastructure of the country is presented in Fig. 1.

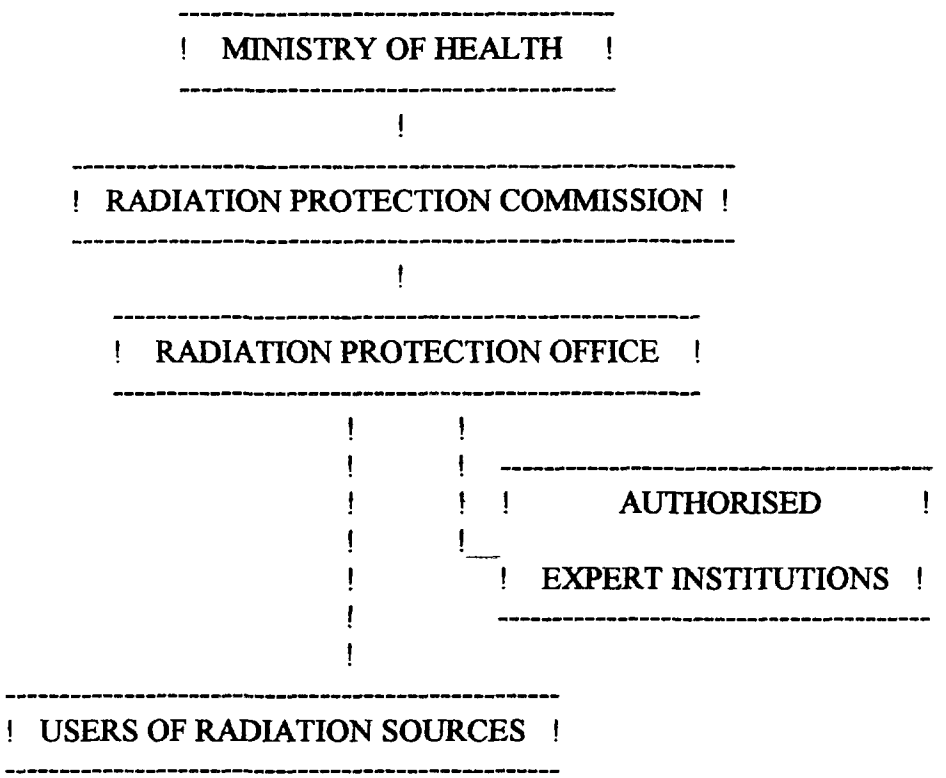

Fig. 1 Radiation Protection Infrastructure in Albania

Soon after its establishment, Radiation Protection Office began the preparation of two regulations:

1. Regulations on Licensing and Inspection of Ionizing Radiation Activities.
2. Regulations on Safe Handling of Radioactive Materials and other Radiation Sources.

The first document contains the principal rules for the processes of Notification, Registration or Licensing by any legal person intended to carry out any of the action specifies by Radiological Protection Act. The second one prescribes the basic rules which provide the safety of ionizing radiation sources activities. These two documents are intended to come under review by Radiation Protection Commission and later to be issued as governmental decrees. At the same time by the mentioned Office are outlined the preparation of the Codes of Practices, especially for Radiology and Nuclear Medicine with special emphasising to ALARA principle. Particular attention is given by the Commission to the problems of the education and training of the workers in the field of radiation protection. Some National Training Courses and Workshops are planned to be conducted for education, upgrading and updating of radiation protection knowledge and skills of workers and Radiation Protection Officers of the country. The participation of Albania in

the IAEA Model Project on Radiation Protection has provide a solid base for the strengthening of all radiation protection activities which are conducting in the country and their development in accordance to international well-known norms and equipment.

3. Control of Low Doses

In accordance to Radiological Protection Act, all legal persons are obliged to perform external dose monitoring of the workers based in appropriate personal dosimeters as well as to provide all the necessary measures for a safe activity toward the environment and public. At present time this monitoring is based on TLD cards and INP is appointed as accredited laboratory for this goal. INP provides TLD cards for all users on monthly base and after collecting and reading of all dosimeters prepares special lists for every user, which contain the averaged whole body doses of the workers. Copies of those lists are presented yearly to Radiation Protection Commission too. The calibration of dosimeters is carried out in INP through three standards gamma sources. The lower detectable dose is nearly 0,1 mSv [5]. INP posses a new Harshaw TLD Reader Model 4500, which was installed last year. With 1200 TLD cards of Bicron (type LBG 0110) INP actually has technically the possibilities for extension of dose monitoring to radiation workers all over the country. As result of dose monitoring activity, which was exerted during past 20 years it is concluded that in average the personal dose of the workers is nearly 5 mSv per year or 1/10 of dose limit. A special attention was paid to every exceeding of dose limit through the careful investigations. This was carried out not only to clarify the reasons of the event but to take necessary measures for prevention of such irradiation in the future. It is worth to mention two cases of overexposures, which were occurred during performing industrial field radiography and instrument calibration process in army. By the careful investigation in situ, it was concluded that in the first case the irradiation of the workers had been the result of a bad planification of irradiation process. In the second case there was a false irradiation, because the dosimeter was kept near the calibration source. In accordance to existing legislation, radiation workers are classified in two categories:
a) The workers of controlled areas and b) the workers of supervised areas.
Both workers categories need for dose control. Since in the past the number of TLD cards was not sufficient, in the dose monitoring system was included only the first category of workers; for the second category were performed periodical measurements. With new equipment INP now is in process of extending step by step the personal dose monitoring for all radiation workers. Nevertheless from the practical point of view some administrative issues create the barriers for a good practice in this field. Sometimes the responsible persons give not enough care to control of workers. It is often that TLD cards were not returned in defined delays or worse, a number of TLD cards were lost during keeping or transportation. Some workers put the cards near the radiation sources creating false exposures. A great deal of work was done during the Chernobyl accident for the environment dose control. This control was carried out based in regular measurements of principal radioisotopes concentration in air and foods. By this control were created the possibilities of public dose reducing through non consumption of contaminated fresh milk in north-east region of Albania or through continuous water washing of fruits and vegetables during the accident's days. The average dose for members of public by this accident in Albania was less than 1 mSv [6]. Last times in the country had been undertaken some effort toward the implementation of elements of Quality Control (QC) and Quality Assurance (QA) especially in the field of radiological medical examinations. The main source of exposures for both workers and public in the country is the diagnostic radiology. For this purpose it would be of great importance the development and implementation of Guidance Levels for

radiological procedures according to Basic Safety Standards, considering the actual status of the local equipment. Last years INP has carried out many measurements for patient entrance doses for different procedures using TL chips. Those measurements have shown that the ratio of measured dose to guidance dose has varied between 1 to 3, therefore one can deduce that Guidance Levels are restrictive for Albania. The main reasons for higher exposures are related to the obsolete X-ray machines, the lack of filtration or diaphragms etc. At the near future it is intended to begin the control of fluoroscopic X-ray machines, based in new X-ray Beam Quality Analyser. Just now in the country exist a great number of fluoroscopic X-ray machines and their contribution in medical exposures is very high. It is understood that the performing of QC and QA procedures is not an easy task for Albania. The issues of defining and implementing of Guidance Levels and other related procedures require common efforts by Regulatory Authority of the country and well-trained specialists like physicists, radiologists etc.

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MOLECULAR NATURE OF SPONTANEOUS AND RADIATION-INDUCED MUTATIONS WITH ALLELIC LOSS IN HUMAN CELLS

K. Tatsumi[1], A. Fujimori[1], A. Tachibana[2], Y. Houki-Fujimori[1]
I. Furuno-Fukushi[1], M. Takahagi[1] and M. S. Sasaki[2]
[1] Division of Biology and Oncology, National Institute of Radiological Sciences, Chiba 263, Japan; [2] Radiation Biology Center, Kyoto University, Kyoto 606-01, Japan

XA9745611

Abstract

An assay system was developed for dissecting the second step in loss of function mutations and for determining the potency of physical and chemical agents to produce such mutations. Results obtained suggest that somatic recombination and/or deletion occurs close to the border between the heterochromatic and euchromatic regions of chromosome 16q.

Constitutional loss or inactivation of one copy of a tumor suppressor gene, as exemplified by hereditary retinoblastoma, increases the propensity for malignancy by reducing the number of events required for the complete loss of the negative regulatory function. An immortalized B-lymphoblastoid cell line (LCL), WR10, derived from an obligate heterozygote of hereditary 2,8-dihydroxyadenine urolithiasis, adenine phosphoribosyltransferase (APRT) deficiency, has enabled us to develop an assay system for dissecting the second step in loss-of-function mutations, i.e. the forward mutation from *APRT* $^{+/-}$ to *APRT* $^{-/-}$ or *APRT* $^{o/-}$, and for determining the potency of physical and chemical agents to produce such mutations [1]. The non-functional *APRT* allele on the chromosome 16 (16q24.3) in WR10 cells bears a nonsense mutation in the exon 3. WR10 was found to be heterozygous also for a SphI RFLP associated with the gene, which allowed the functional and the constitutionally non-functional allele to be distinguished by Southern blot analysis using an *APRT* probe.

The base-line frequency of cells resistant to 100 μM of 2,6-diaminopurine (DAP) was found to be 1.1×10^{-5} with a mutation rate of 1.65×10^{-6} / cell / generation, which was 5-10 fold higher than the rates for 6-thioguanine resistant (TG^r) mutation measured with other LCLs from normal individuals. Recloned DAP^r mutants in general grew as rapidly as wild-type WR10 cells (the population doubling time of approximately 36 h). Exposure of WR10 cells to γ-rays resulted in a dose-dependent increase of DAP^r mutant fraction up to 2.5×10^{-4} at 2 Gy, whereas induced mutant fraction was 4.7×10^{-5} for TG^r with the base-line frequency of 1×10^{-6}. Irradiation of WR10 cells with far-UV light from a 15-W germicidal lamp resulted in

dose-dependent increases both for DAP^r and TG^r mutations. However, the increase in the fraction of DAP^r mutant was only 2.2 fold at most and statistically significant ($p< 0.05$) above 17.6 J/m^2 which allowed merely 15 % survival (Figure 1), whereas the doubling dose for TG^r mutations was approximately 2.2 J/m^2. Thus, in contrast with ionizing radiations, UV-light is not more effective in inducing mutations at the *APRT* locus than at the *HPRT* locus [2].

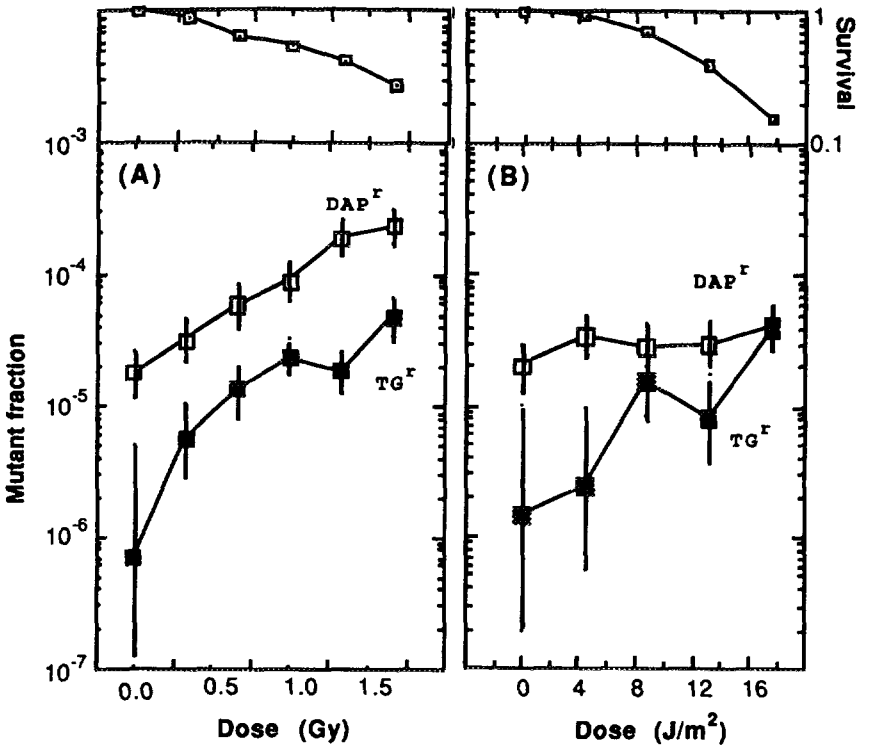

Figure 1. Cell survival and mutant fractions as a function of dose after irradiation with (A) γ-rays and (B) UV-light in WR10 cells. Open square, DAP^r; closed square, TG^r. Each point represents a single determination and bars represent 95 % confidence intervals.

Table 1 The structural change of *APRT* gene in DAP-resistant mutants

Treatment	number of mutant clones analyzed	number of clones with allelic loss
None (spontaneous)	26	22 (85%)
γ-rays (2 Gy)	69	64 (93%)
UV-light (17.6 J/m^2)	31	17 (55%)

The *APRT* gene, consisting of 5 exons, spans 2.5 kb. A substantial proportion of the spontaneously-arising mutants (22/26, 85 %) and virtually all of γ-ray-induced mutants (64/69, 93 %) lost the functional allele, judged from loss of heterozygosity (LOH). On the contrary, only 25 % of UV-induced mutants were considered to bear LOH (Table 1), when the contribution of spontaneous mutants with allelic loss was taken into account. Major DNA alterations are, therefore, unlikely to be involved in UV-induced mutations at the *APRT* locus, as previously demonstrated for the *HPRT* locus [3]. Dosage blotting revealed that about half of the spontaneously-arising and γ-ray-induced mutants with LOH showed a reduction to homozygosity of the mutant allele, implying that the mutated allele was duplicated due to mitotic recombination or gene conversion. Non-disjunction with reduplication of the mutant chromosome 16 was ruled out based on the retention of heterozygosity at 16p microsatellite loci (the D16S298 and the D16S292) in all of the mutants tested with LOH at the *APRT* locus. Approximately 70 % of mutants both arising spontaneously and induced by ionizing radiation showed LOH at three proximal loci on the long arm, the D16S266 (16q23.3), the D16S265 (16q21) and the D16S308 (16q12.2). The distribution of the sites for somatic recombination or for deletion breakpoints in radiation-induced mutants seemed to be non-random and indistinguishable from that in spontaneously-arising mutants. These results suggest that somatic recombination and/or deletion occur preferentially close to the border between the heterochromatic and the euchromatic regions of the chromosome 16q, implicating an untargeted nature of these events incurred by ionizing radiation.

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Thyroid cancer in Belarus after the Chernobyl accident: incidence, prognosis of progress, risk assessment.

E.Buglova, E.Demidchik*, J.Kenigsberg, A.Golovneva

Research Clinical Institute of Radiation Medicine and Endocrinology,
* Republican Scientific and Practical Center of Thyroid Tumours,
Minsk, Belarus

Abstract. Starting from 1990, an increasing number of persons, suffering from thyroid cancer was diagnosed in Belarus. These persons were exposed to radiation in 1986 due to the Chernobyl accident and were children and adolescents at the time of the accident. This paper gives an overview of the total number of thyroid cancer cases observed in Belarus after the Chernobyl accident among the persons exposed to radiation under 18 years of age. Duration of the latent period and background incidence rate are under discussion. Based on the most reliable data about thyroid doses and incidence rate among the persons exposed to radiation under 6 years of age, the estimation of risk coefficient for radiation induced thyroid cancer was carried out. For childhood exposure from I-131, the excess absolute risk per 10000 PYGy was 4.5.

It is well known that exposure of the thyroid gland to low doses of radiation may induce thyroid cancer in humans. The experience on external radiation and thyroid cancer comes mainly from studies of children irradiated for a variety of medical conditions and the Japanese atomic bomb cohort. The data about thyroid cancer following radioactive iodine exposure, in particular exposure from I-131, are limited. In this connection, investigation of the thyroid cancer incidence after the Chernobyl accident will provide the unique possibility to analyze new information on this issue.

The accident at the Chernobyl NPP released about 1.8×10^{18} Bq of I-131 [1]. As the result of the accident, the overwhelming part of the territory of the Republic of Belarus was contaminated with I-131. In five out of 6 regions of the Republic, density of contamination of I-131 ranged from 0.4 to 37 MBq/sq.m. [2].

Exposure from I-131, mainly formed by ingestion of radionuclides with contaminated milk, developed conditions for thyroid stochastic consequences among the exposed population.

The aim of this paper is to present the main aspects within risk analysis study that was carried out during the post-accidental period in Belarus. These aspects are:

- cohort under investigation,
- background level of thyroid cancer incidence rate,
- duration of the latent period,
- prognosis of the thyroid cancer cases based on known risk coefficients,
- preliminary estimation of the risk coefficient for specific conditions.

Correct determination of the cohort under investigation is an important aspect for making correct decision about the level of the incidence. For epidemiological purposes, it is no sufficiently informative to analyse incidence rates by the age at diagnosis, but is very important to analyse it by the age at the time of the accident. Such cohort should be followed up during a long period of time for clear estimation of risk coefficient. During the first stage of our study, a cohort of persons who were exposed to radiation at the age under 14 years was

selected [3,4]. In the course of time, reliable data about persons who were children and adolescents in 1986 became available. As a result, cohort of Belarusian people, exposed at the age under 18 is under investigation now. Within this cohort, there are 790 thyroid cancer cases diagnosed in 1986 - 1996. 755 cases were registered in 1990-1996 and 35 cases in 1986-1989 (Table 1).

Table 1. The incidence of the thyroid cancer after the Chernobyl accident among persons exposed to radiation under 18 years of age.

Years	Thyroid cancer cases			Thyroid cancer incidence rate per 100,000		
	Girls	Boys	Total	Girls	Boys	Total
1986	2	1	3	0.14	0.07	0.1
1987	10	3	13	0.71	0.21	0.45
1988	4	4	8	0.28	0.27	0.28
1989	6	5	11	0.43	0.34	0.38
1990	16	17	33	1.13	1.17	1.15
1991	55	23	78	3.90	1.58	2.7
1992	50	41	91	3.54	2.82	3.17
1993	94	33	127	6.66	2.27	4.42
1994	103	46	149	7.30	3.16	5.2
1995	95	49	144	6.73	3.37	5.0
1996	90	43	133	6.38	2.95	4.63
1986-1996	525	265	790	3.38	1.65	2.5
1990-1996	503	252	755	5.1	2.5	3.9

The level of the thyroid cancer incidence in Belarus before the Chernobyl accident (1971-1985) was low for children (0.04 per 100,000 children population annually) and relatively higher for adults (0.3-2.5 per 100,000 population for men and 1.2-3.9 per 100,000 population for women) [5].

For persons aged 0-18 in 1986, the thyroid cancer incidence rate during 1986-1989 did not differ significantly from the background level. To confirm this fact and to determine the duration of the latent period, three different levels of incidence rate were compared:

a).incidence rate for persons aged 0-18 before the accident;

b).incidence rate for persons aged 0-18 after the accident;

c).incidence rate among persons who were born since 1987.

It is obvious, that it is possible to compare the level of incidence rate among persons who were born since 1987 with other levels only with some assumptions, because the age of this cohort in 1996 was only 0-9. However, incidence rate among this group reflects the "pure" background level (Fig.1).

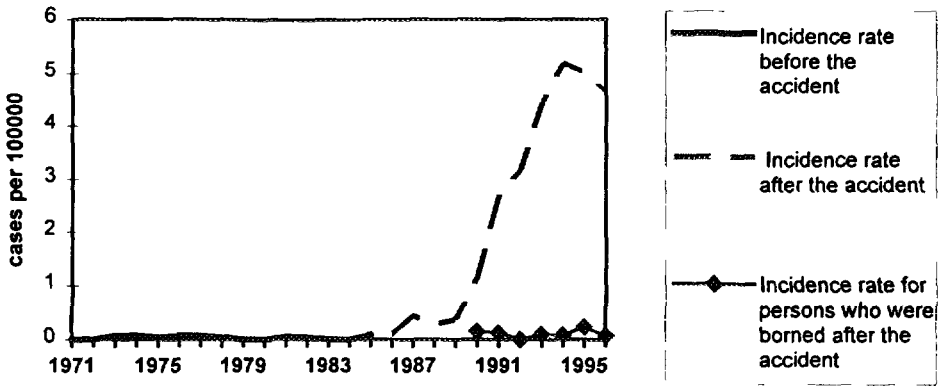

Fig.1. Thyroid cancer incidence rate during different periods.

Based on this comparison we confirmed the significant increase of thyroid cancer incidence rate since 1990 and came to the conclusion about the background level of incidence among persons under investigation during 1986-1989. So, the duration of the latent period in our study is 4 years, as described for Ukrainian cohort [6] and in our previous reports [3,7].

For cohort aged 0-14 in 1986, prognosis for thyroid cancer cases during the life period was carried out in our previous studies. For this purpose we used NCRP model of specific risk estimates for thyroid carcinogenesis and different values of absolute risk coefficient [8,9]. The comparison of numbers for predicted and observed thyroid cancer cases showed that the uncertainties of using this model were very high. There were different sources of uncertainties: the value of risk coefficient, demography and dosimetry, duration of latent period, value of dose effectiveness reduction factor. Some of this questions were defined more precisely and based on this, preliminary estimation of the specific value of risk coefficient was carried out. For this estimation, a cohort of persons aged 0-6 years in 1986 with the data about thyroid doses based on direct measurements [10] was selected. This selection was also based on the necessity of selecting of persons who were exposed to radiation in the young childhood due to the highest risk of radiation-induced thyroid cancer for them.

Risk coefficient was calculated based on the additive model using linear dose-response relationship. The calculated value of absolute risk coefficient for I-131 exposure of children is 4.5 per 10000 PYGy (Table 2).

Table 2. Preliminary estimation of absolute risk coefficient for children exposed to radiation under 6 years of age.

Dose interval, Gy	Number of settlements	Population	Average dose, Gy	Person-Year-Gy	Number of cases
<0.1	14	294664	0,061	125933	84
0.1 - 0.49	21	169602	0,349	414879	214
0.5 - 0.99	9	19722	0,715	98715	29
≥ 1	6	16359	1,58	181213	52
Total	50	500347	0,23	820740	379
Background					9
Excess cases					370
Absolute risk coefficient					4,508

The use of this value and a 4-year duration of the latent period for prognosis of thyroid cancer cases for all the cohort of persons aged 0 - 6 years in 1986 (with the data for direct measurements and without them) shows a good agreement between the prognosed and registered cases (Fig.2).

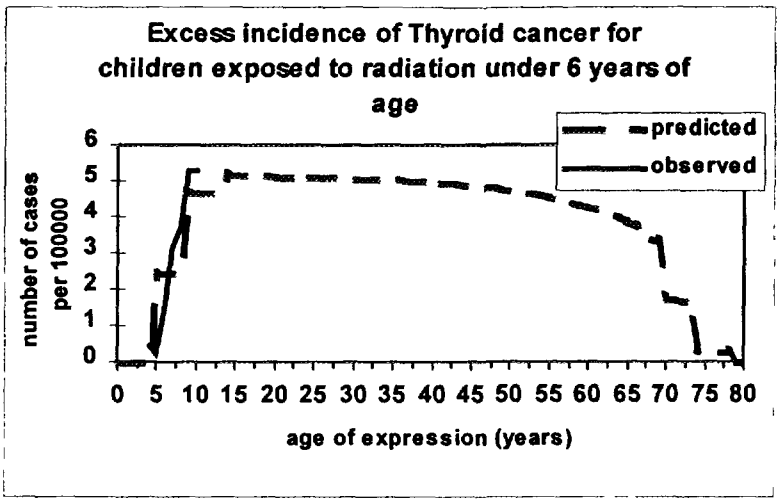

Fig.2. Comparison of the predicted and observed thyroid cancer incidence rate during life for exposed till 6 years children of Belarus based on specific risk coefficient.

Based on this prognosis we discovered that among the exposed persons of this age group, about 3,400 thyroid cancer cases may develop during the life period. About 2,200 may develop among the exposed inhabitants of the most contaminated Gomel Region.

Future activity. Investigation in the field of risk analysis will be continued in the future based on the obtained data. The main aspects under consideration will be:

- continuous collection of data about thyroid cancer cases for cohort under investigation;
- analysis of the role of short-lived isotopes in the thyroid exposure;
- estimation of risk coefficient for people of different age at the time of exposure taking into account their sex, years at risk, age-dependent background incidence rate.

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Intervention during late phase of the Chernobyl accident in Belarus: gained experience and future strategy.

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J. Kenigsberg, E.Buglova

Research Clinical Institute of Radiation Medicine and Endocrinology
Minsk, Belarus

Abstract

Various measures, introduced to reduce external and internal radiation doses of inhabitants of territories contaminated by the Chernobyl accident, are described. Average annual doses are given. It is concluded that while factors such as reduction of psychoemotional tension need to be explored, risk coefficients for chronic exposure at low doses should be specified.

In the result of the Chernobyl accident large territories of Belarus were contaminated by the long-lived radionuclides with different levels of density contamination. After 11 years of the post accident period doses for population who are lived on the contaminated territories are formed mainly from the alimentary intake of Cs-137 with the foodstuffs and external exposure. Ratio between the internal and external component of the total dose varies over a wide range, being depending on density of radioactive contamination of the territory, transfer coefficients on food chain and peculiarities of food consumption.

The average annual doses of the majority of the inhabitants of settlements located on contaminated territories do not exceed 5 mSv. From 2.2 million of Belarusian inhabitants, who were exposed in 1986, less than 300 thousand people receives the annual doses in a range 1-5 mSv at the present time. The maintenance of doses at such low level has become possible due to conduction and maintenance of a number of protective measures. To their number long-term protective measures on restriction internal exposure concern. For decrease of the cesium radionuclides in foodstuffs and milk agricultural protective measures were carried out. To them concern decrease of soil contamination through mechanical methods, change in land use, application of ameliorants and fertilizers to reduce soil to plant transfer of radionuclides. The

efficiency of the specified measures is various, their application allows to reduce soil to plant transfer of radionuclides from 1.5 up to several tens of time. Besides this, establishment of permissible levels for radioactive contamination of foodstuffs and conduction of regular control of foodstuff contamination are related to the protective measures for restriction internal exposure. During late phase of the accident different permissible levels for radiocaesium contamination of milk were carried out. Since 1986 till 1990 limit for radiocaesium content in milk was 370 Bq/l, since 1991 till 1992 -185 Bq/l and since 1993 - 111 Bq/l. Due to establishment of strict limits in 1990 and 1992 near 2.2 thousand person-Sv and 1.8 thousand person-Sv were averted for the urban population of most contaminated Gomel and Mogilev regions of Belarus correspondingly.

For restriction of external doses for population during post accident period a complex of decontamination measures has carried out, which have allowed in a number of cases to decrease external doses on the average on 10 %. The degree of decrease of a dose depends on parameters, describing professional and behavior peculiarities of the population. As decontamination requires high economical expenses, and its realization during late phase is characterized by low efficiency, this type of protective actions should have limited character.

With annual dose of, approximately, 1 mSv, a question arises about the expediency of further decrease of exposure doses of the population during the late phase of the large-scaled radiation accident. Specific experience of Belarus testifies to the fact that while choosing the lasting strategy of intervention, at least, two factors should be taken into account: radiation damage to the health of people and psychoemotional factor. The factor of possible radiation damage to the health of population, except purely the radiation component, has also the psychoemotional component. Radiation risk for the health is directly proportional to the collective exposure dose. Therefore, while choosing the strategy of intervention, annual exposure doses of less than 5 mSv should also be taken into account, though individual effects

from such doses can be only hypothetical. Nevertheless, continuing exposure of hundred thousands of people with such small doses, determines high collective doses and the number of years at risk. In this case, further decrease of even small doses can be justified. Alongside with this, in order to use the well-known principles of radiation protection, risk coefficients for chronic exposure in low doses should be specified. We are not to exclude the fact that radioepidemiological studies of the effect of chronic low dose exposure of people born after the Chernobyl accident and those who receiver small doses during a long period of time, will make it possible to receive in the future actual risk coefficients for chronic exposure in small doses. This will also provide the scientific justification for conducting of long-term intervention under conditions of low dose exposure.

Absence of actual risk coefficients of the consequences of chronic exposure in small doses and the necessity of using the values of coefficients obtained during the analysis of the consequences of high dose exposure, leads to certain speculations about, supposedly, more harmful effect of small doses which increases the phychoemotional tension in the society and forces the Government to make decisions about different kinds of intervention without their proper scientific justification. Nevertheless, the present situation cannot be changed abruptly, and it's necessary to take it into consideration. This requires the conducting of at least some protective measures aimed at decreasing of phychoemotional tension which by itself is harmful to the health of the population residing at the contaminated territories.

SMALL DOSES OF IONIZING RADIATION AND POSSIBLE GENETIC CONSEQUENCES FOR THE RESIDENTS OF THE REPUBLIC OF BELARUS

Lazjuk G I , Nikolaev D.L., Novikova I.V.
Belarus Institute for Hereditary Diseases, Minsk, Republic of Belarus

ABSTRACT

In the Republic of Belarus National Genetic Monitoring for Congenital Malformations and Regional Monitoring for the Anomalies Found in Embryos and Fetuses showed an increased anomaly frequency in embryos and fetuses. The increase correlated with Cs-137 contamination density , but no linear dependence on collective and average individual doses for the individuals of reproductive age has been found. No direct teratogenic effect of Chernobyl accident has been revealed, but the effect through mutations in gamets is possible

National Genetic Monitoring for Congenital Malformations (CM) and Regional Monitoring for anomalies found in embryos and fetuses were used to carry out epidemiological study of the frequencies of the anomalies for the period from 1982 to 1995 National Monitoring covered about 80,000 births a year The congenital malformations diagnosed by a physician at the maternity house during the first 7 days of babies' life were accounted The list of the registered CMs and their frequencies in relation to the Cs-137 contamination density are presented in Table 1

All anomalies found in embryos and fetuses, 5 -12 week legal medical abortuses, by embryologists of Belarus Institute for Hereditary Diseases, the Ministry of Public Health, have been recorded at pathological examination The abortuses were obtained from the women, the residents of Minsk-city (control) and from the areas with Cs-137 contamination density of 15 Ci/km^2 (555kBq/m^2) and more. In total, 33376 abortuses were examined, including 2701 abortuses obtained from the areas contaminated with radiation.

Collective and cumulative doses for the individuals of reproductive age, the residents of Gomel and Mogilev regions (excepting large industrial cities) were calculated at the Institute of Radiation Medicine, the Ministry of Public Health The data from Vitebsk region, which is considered the most safe for radioactive contamination, was taken as a control

The following conclusions have been made from the studies

1 For the period from 1986 to 1995 in the areas with radioactive Cs-137 contamination of 555 kBq/m^2 and more, an average frequency of anomalies found in embryos and fetuses has been registered as 7 91, in the control it was 4 90 per 100 examined abortuses or it was recorded as 4.62 and 2.55 per 1000 examined organs, respectively.
2 Throughout the whole territory of Belarus Republic increased anomaly frequency has been registered in embryos and fetuses, it was manifestered as increased frequency of children, born with congenital malformations (Table 1) For nine post-Chernobyl years (1987-1995) the coefficient of the increase in the control was found as 0 50, it was 0 83 in the areas with Cs-137 contamination density of 555kBq/m^2 (15 Ci/km^2) and more, and in the areas with Cs 137 contamination of more than 37 kBq/m^2 (1 0 Ci/km^2) the increase was recorded as 0 51
3 The increase was mainly due to congenital malformations with great contribution of de novo mutations (multiple CMs, polydactyly, reduction limb defects)
4 Increased frequency of the Down's syndrome has not been found in the contaminated areas
5 Teratogenic effect has not been registered in the cases of in utero exposure due to Chernobyl accident The registered increase of frequencies found in embryos and fetuses can be the result of a combined (teratogenic and mutagenic) effect
6 Increased frequency of CMs correlated with collective and individual exposure doses, which were calculated for the population of reproductive age (Table 2) The higher the dose, the higher was CM frequency However, no linear dependence of a collective dose on an increase of CM frequency has been recorded Per 1 unit increase of CM frequency in Gomel region there was 216 p/Sv and in Mogilev region it was 116 p/Sv

7. In Belarus a thorough international study is required to reveal the true causes of increased anomaly frequency found in embryos and fetuses.

Table 1

Incidence of Obligatory Registered Malformations in Belarus for 1982 to 1995 (per 1000 neonates)

Malformation	Areas contaminated with Cs-137				Control (30 regions)	
	>15 Ci/km^2 17 regions		>1 Ci/km^2 54 regions			
	1982-1985	1987-1995	1982-1985	1987-1995	1982-1985	1987-1995
Anencephaly	0.28 11	0.44 26	0.24 48	0.64* 226	0.35 23	0.49 63
Spina bifida	0.58 23	0.89 53	0.67 132	0.95* 335	0.64 42	0.94* 120
Cleft lip and/or palate	0.63 25	0.94 56	0.70 137	0.92* 324	0.50 33	0.95* 121
Polydactyly	0.10 4	1.02* 61	0.30 60	0.66* 232	0.26 17	0.52* 66
Limb reduction defects	0.15 6	0.49* 29	0.18 36	0.35* 123	0.20 13	0.20 26
Oesophageal atresia	0.08 3	0.08 5	0.12 23	0.15 53	0.11 7	0.14 18
Anorectal atresia	0.05 2	0.08 5	0.08 16	0.10 35	0.03 2	0.06 8
Down's syndrome	0.91 36	0.84 50	0.86 170	1.03 362	0.63 41	0.92* 117
Multiple malformations	1.04 41	2.30* 137	1.41 277	2.09* 733	1.18 77	1.61* 205
Total	3.87 151	7.07* 422	4.57 899	6.90* 2423	3.90 255	5.84* 744
Per cent increase before and after Chernobyl	83		51		50	

*Significant difference (p - 0.95) between the values for 1982-1985 and for 1987-1995.

Table 2

Comparasion of CM frequencies with additional radiation doses obtained by rural population of Belarus at the age of 18 years and older

The region under observation	Frequency per births	of CM 1000	Average accumu-lated doses for a group (mSv)	Collective dose of radiation (person/Sv)
	1982-85	1987-95	1986 - 1994	
Gomel region	4.06±0.39 Growth Dose	7.45±0.24 82% Effect	13.40 (55.8n) 46	6276 (66.1m) 216.4
Mogilev region	3.50± 0.53 Growth Dose	6.41±0.30 78% Effect	8.82 (36.7n) 0.35	2909 (30.6m) 116.4
Vitebsk region	3.60±0.63 Growth	5.04±0.27 53%	0.24 (n)	95 (m)

CELL INACTIVATION BY ULTRASOFT X-RAYS : ROLE OF INNER SHELL IONIZATION

F.ABEL[1], M.A HERVE DU PENHOAT[1] , I.DESPINEY-BAILLY[2] , A. TOUATI[1], B.FAYARD[1], A.LHOIR[1], L.SABATIER[3] , A.CHETIOUI[1] , D.STEVENS[4] , M.HILL[4] , D.T.GOODHEAD[4].

(1) Groupe de Physique des Solides, Universités Paris 7 et Paris 6,(CNRS URA 017, CEA LRC N° 6), Tour 23, 2 place Jussieu, 75251 Paris cedex 05.

(2) CEA/DSV/DRR/, Lab de Radiotoxicologie, BP.1291680 Bruyères le Chatel, France.

(3) CEA/DSV/DRR/, Lab de Radiobiologie et Oncologie, BP.6, 92265 Fontenay aux Roses cedex, France.

(4) Radiation and Genome Stability Unit, Medical Research Council, Harwell, Didcot,Oxfordshire, OX11 0RD, U.K.

Abstract

The biological effect of K-electron removal in C, N, O atoms of the DNA needs to be systematicly studied. A calculation of the RBE of X-rays around K-edges was performed to test experimental feasibility. Results obtained motivated an experimental study of the lethal effectiveness of C-K ionizations and experiments were performed with monochronized synchrotron radiation. Cell survival was studied with a V79 chinese hamster cell line, using cells grown as monolayers on mylar foil. The linear quadratic shape survival curves obtained for 250 eV and 340 eV radiation are discussed.

INTRODUCTION.

Recent questions on the possible role of K-ionization in the biological effect of heavy ions (Chetioui *et al* , 1994) show that there is a strong need of a systematic study of the biological effect of a K-electron removal in C,N,O atoms of the DNA.

A method to study selectively the effect of a K-ionization, consists in comparing biological effects of X-ray irradiations at energies before and after the K-ionization threshold. X-ray induced K-ionizations have probably a less severe effect than ion-induced ones since the latter are usually accompanied by multiple outer shell ionizations in the same atom and additional ionizations along the ion-track. Nevertheless, the lethal effectiveness of X-induced K-ionizations provides a lower limit of that of ion-induced ones.

To test the feasibility of experiments at the K-threshold of the various atoms and to determine an appropriate range of irradiation energies, we have performed a simple calculation of the RBE of X-rays around K-edges, assuming the same lethal effectiveness for the K-ionizations of C,N and O atoms of DNA.(For a first trial a uniform 1% value has been chosen) This calculation is performed in the framework of the model of critical size events of Goodhead *et al* (1979) : track clusters (clusters of more than 100 eV in 2nm-size volumes occuring at the track end of secondary electrons) and clusters from K-ionization are both considered to contribute to the lethal effect.

The results of the calculation (Du Penhoat *et al*, submitted to Radiation Research -1997) display a strong increase of RBE (by a factor of ~ 2) just above the C-K threshold , followed by a less pronounced increase above the N-K threshold and then a decrease above the O-K threshold since O-K ionizations occur mostly outside the DNA.These results have motivated an experimental study of the lethal effectiveness of s C-K ionizations (Threshold energy : 284 eV)

EXPERIMENT and METHODS.

Because of the strong absorption of ultrasoft X-rays, a comparison of the effect of two radiations at different energies can only be significant if their attenuation in the cell is the same. The isoattenuation criteria has been fullfilled by using radiations of well defined energies: 250 and 340 eV respectively. The experiment was performed with monochromatized synchrotron radiation at the LURE facility in Orsay close to the super ACO storage ring.

The entrance dose to a cell was evaluated from the X-ray fluence. Two separate measurements of the intensity were performed by an X-ray Si photodiode with a 20 mm^2 active area, and by a commercial parallel plate extrapolation chamber with modified window.

When comparing radiations with isoattenuation, the mean dose within the cell nucleus is an appropriate parameter to correlate with the cell survival. Consequently the attenuation within the cell must be known. For this purpose measurements of the thickness of cytoplasm and nucleus of cells under study have been performed using confocal microscopy.

Study of cell survival was performed with a V79 chinese hamster cell line. Cells were grown as monolayers on 0.9 μm thick mylar foil and allowed to attach to the film and flatten for 48 hours. In these conditions, the mean dose inside the nucleus was about 15% of the entrance dose

RESULTS and DISCUSSION.

The survival curve for the 250 eV radiation display a linear quadratic shape. When plotted against the average dose, the coefficients of the quadratic fit are : $\alpha = 0.40\ Gy^{-1}$, $\beta = 0.54\ Gy^{-2}$,very near those obtained in the experiment of Goodhead *et al* (1979) with carbon K-X rays (278 eV) : $\alpha = 0.43\ Gy^{-1}$, $\beta = 0.62\ Gy^{-2}$.

At 340 eV, the survival curve present a much steeper decrease as a function of dose: at 250 eV, the dose for 10% survival is about twice the one at 340 eV. This enhanced lethality is the consequence of the production of **concentrated energy depositions around the C-K ionizations which mostly take place on the DNA.**

In the framework of the calculation described in the introduction, one can extract from the survival curve at 250 eV a 1.8% value for the lethal yield of track clusters overlapping DNA, close to that -1.9%- which can be extracted from the survival curve of Goodhead *et al* (1979). From the survival curve at 340 eV, a lethal yield of the order of 2% is obtained for C-K ionization clusters overlapping DNA.

This value is high since it is comparable to the yields measured for major events such as K disintegrations of incorporated ^{125}I nuclides .

The knowledge of the RBE of X-rays at various energies provides - in the frame of the above model- some information about the lethal yield of C,N,O K-vacancies generated by heavy ions and their role on the overall ion lethality.

Acknowledgements

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IAEA-CN-67/89

DEPENDENCE OF RADIATION EFFECTS IN THE PROGENY OF THE FIRST AND SECOND GENERATION ON STAGES OF THE DEVELOPMENT OF GERM CELLS OF BOTH PARENTS AT THE TIME OF IRRADIATION : EXPERIMENTAL STUDIES

I. Nefyodov, I. Nefyodova and G. Palyga, Medical Radiological Research Centre RAMS, Russia

Abstract

Studies of 35199 offspring of Wistar rats showed that after irradiation of both parents (P) with doses of 0.25-4 Gy the manifestation of radiation effects in the descendants of the first (F1) and second (F2) generations in ontogenesis depended upon radiation dose and the stage of development of P germ cells at the moment of radiation exposure. After irradiation of the matured oocytes, spermatids and spermatozoids the consequences for F1 are mainly determined by a female or their aggravation takes place. After irradiation of the maturing oocytes, spermatocytes and spermatogonia the effects for F1 are mainly determined by the male. The death of F1 occurs chiefly in embryogenesis and F2 in early postnatal ontogenesis. It is more marked by the father's line (the descendants of F1 males and intact females) than by mother's line (the descendants of F1 females and intact males).

1. INTRODUCTION

The parent study has investigated radiation effects in progeny of the first and second generations of Wistar rats after irradiation of one and/or both parents with doses of 0.25-4 Gy. Attention was focused on the relationship between stages of gametogenesis in parents at the moment of radiation exposure and death of progeny in embryogenesis and early postnatal ontogenesis.

2. MATERIALS AND METHODS

Totals of 4207 mature males and females Wistar rats, 17465 offspring of the first generation (F1) and 17734 offspring of the second generation (F2) were the subjects of investigation. Male and female rat parents (P) of 220-250 g were exposed to an external single irradiation by gamma rays to doses of 0,25, 0,5, 1, 2, 3 and 4 Gy at a dose rate of 0.003 $Gy.s^{-1}$ (^{60}Co source). Following irradiation they were mated with each other and also with non-irradiated intact individuals. The animals were mated at different times after irradiation so that different stages in gametogenesis were studied [1]. The stages were for males spermatozoids, spermatids, spermatocytes, and spermatogonia; and for females metaphase I to metaphase of the II^{nd} division of maturity and maturing (late dictyothena) oocytes. The beginning of the pregnancy was registered cytologically by the presence of sperm in vaginal smears. Experimental groups were formed depending on the stages of spermato- and oogenesis of P gametes at the moment of irradiation and radiation dose. Each consisted of 30-50 first-pregnant females. Embryogenesis F1 was studied after euthanasia of some females by ether on the 20th day of pregnancy. The fetuses were scored for size and mass, pathology of viscera and skeleton and the total, pre- and post-implantation death of embryos was calculated. In addition development of young rats was observed for 30 days after the birth. The numbers surviving on the 1st and 30th days after the birth were calculated, giving the death rate for this period of time. When F1 sexual maturity was achieved, F1 males of each experimental group were mated with intact females to produce F2 descendants from the father's line and convercely F1 females use mated with intact males to produce F2 descendants from the mother's line. Embryogenesis and early postnatal development F2 were studied in the same way as F1. All animals were kept in the standard conditions of the vivarium. The uncertanties in the resultant data was considered reliable at $p \leq 0.05$.

3. RESULTS

3.1. Radiation effects in embryogenesis and early postnatal ontogenesis F1 after irradiationa of one or both parents with doses of 0.25-4 Gy

The embryonic death F1 changed from 10.8 ± 1.9% to 83.1 ± 2.8% (in control 13.1 ± 2.2%) depending of radiation dose, stage of gametogenesis at radiation and whether one or two irradiated parents participated in the mating. The embryonic death was highest levels after irradiation of germ cells of parents at stages of spermatids, spermatozoids and matured oocytes. Following irradiation of both parents with doses of 0.25, 0.5 and 1 Gy at these stages of gametogenesis and 4 Gy at the stage of

spermatids and matured oocytes there was a trend of increasing radiation effects caused by the participation of two irradiated germ cells (Fig.1). After irradiation of both parents with doses of 2, 3 and 4 Gy (for spermatozoids and matured oocytes) the embryonic death F1 was essentially the same as rates for irradiated females and non-irradiated males. There was no dependence of F1 embryonic death, with respect to parental doses, on germ cells exposed as spermatogonia, spermatocytes or maturing oocytes. This is shown in Fig.2 where it is also interesting to note that for irradiated mature oocytes universal death rate in F1 embryos followed irradiation of the female that was unaffected by whether or not the male parent was also exposed. However following irradiation of the maturing oocytes the F1 death rate from both irradiated parents is very similar to that observed when only males were irradiated (except for the care of irradiated spermatocytes + maturing oocytes). Therefore one may postulate that the F1 embryonic consequences were determined by the female parent if the irradiation occurs to the mature oocytes, but by the male if the oocyte was still maturing.

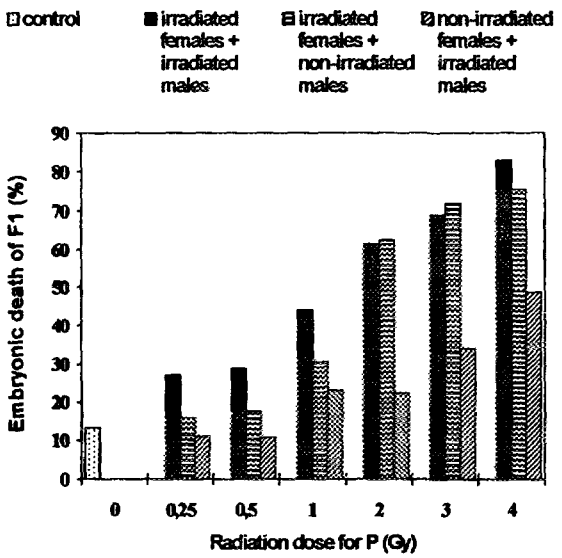

Figure 1. Embryonic death of the first generation (F1) after irradiation of germ cells of parents (P) with doses of 0.25-4 Gy at the stages of spermatozoids and matured oocytes.

The F1 death rate in early postnatal development exceeded the control (9.9 ± 3.1%) only after irradiation with doses of 2, 3 and 4 Gy. It changed from 9.6 ± 3.5% to 33.5 ± 3.5% and depended to a greater degree on development stages of parent's germ cells at the time of irradiation (Fig.3) than on radiation doses. F1 death reached maximum values usually after irradiation of germ cells of both parents at the stage of spermatids, spermatozoids and matured oocytes. Following irradiation of germ cells with a dose of 2 Gy at the stage of spermatozoids and the matured or maturing oocytes an increase in radation effects was noted when two irradiated rats were mated (Fig.3). In some cases deviations occurred in late development. But cases of F1 death in the period 1-3 months post natal when the animals were reaching maturity were rare.

Overall the results lead to a conclusion that the production of radiation effects in F1 depends on both radiation dose and stage of the development of germ cells at the moment of irradiation and occurs mainly in embryogenesis. In the particular situation of both parents having been irradiated, hereditary effects may be dominated by dose to one or other of the parents depending on the particular stage of germ cell maturation when the exposure occurred. From these results we may draw up a list of gamete irradiations in the following order of decreasing effect: matured oocytes + spermatids /spermatozoids/ spermatocytes/ spermatogonia and maturing oocytes + spermatids/ spermatozoids/ spermatocytes/ spermatogonia.

3.2. Radiation effects in embroygenesis and early postnatal ontogenesis F2 after irradiation of both grandparents with doses of 2-4 Gy

F2 death in embryogenesis did not exceed the control (12.9 ± 1.9%) if both parents were irradiated with doses of 2 and 3 Gy, but it rose up to 47.8 ± 4.0% following irradiation of fathers with a dose of 4 Gy. The frequency of visceral abnormalities in 20-day F2 embryos did not differ from the control, but disorders in the rate of skeleton ossification occurred in all experimental groups. In this case no dependence on radiation doses and stages of gametogenesis at the time of parental irradiation was found. In early postnatal development the F2 death from both irradiated parents had practically no dependence on exposure over the range of doses. Studied death of F2 by father's line was higher than by mother's line and reached maximum values after the irradiation of germ cells of male-parents at the stages of spermatogonia and spermatocytes (Fig.4). Irradiation of the parents'mature oocytes resulted

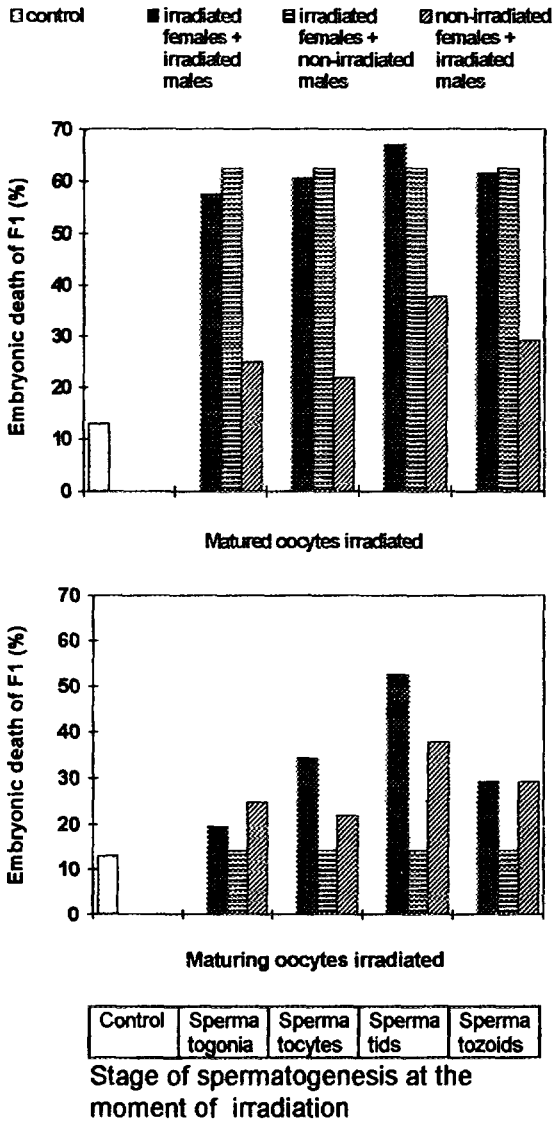

Figure 2. Embryonic death of the first generation (F1) after irradiation of germ cells of parents (P) with dose of 2 Gy at the different stages of gametogenesis.

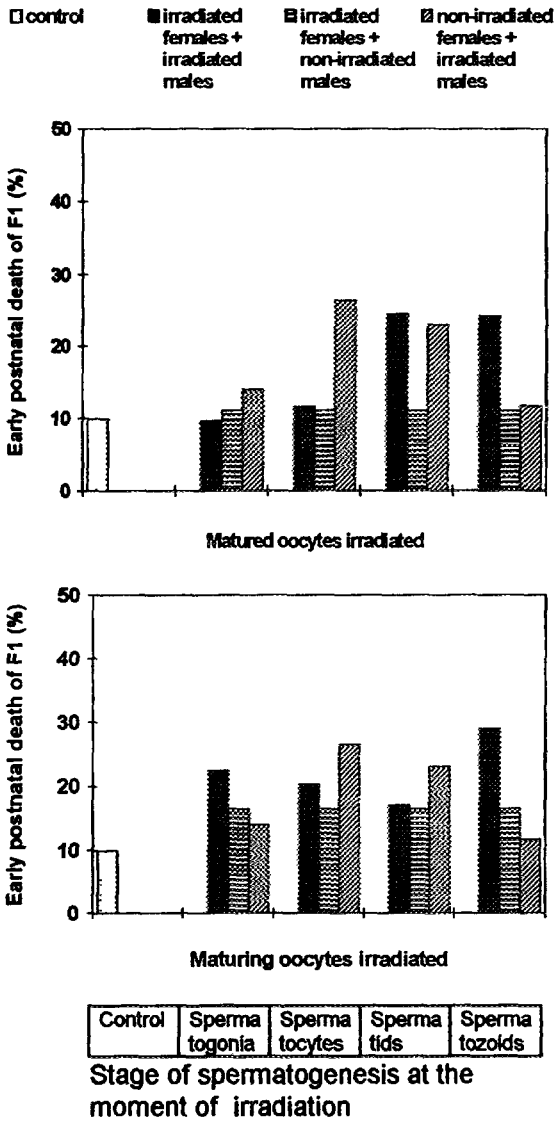

Figure 3. Early postnatal death of the first generation (F1) after irradiation of germ cells of parents (P) with dose of 2 Gy at the different stages of gametogenesis.

either in a higher F2 death rate, or a rate equal to that which was observed following irradiation of the maturing oocytes. F2 death in early postnatal development depended more on stage of parents at the time of irradiation than on radiation dose. The total F2 death (without subdivision into specific experimental groups) after irradiation of both parents by a dose of 2 Gy was 26.7 ± 0.6% (1 517 of 5 679 subjects died) and in control 9.2 ± 1.8%.

In general, these results lead to a conclusion that radiation effects in F2 depend, to a greater degree, on the stages of gametogenesis of both parents at the time of irradiation than on radiation dose. Radiation effects in F2 mainly occur in the early post natal period and they were more expressed through the father's line than the mother's. Gametes of puberscent F2 males of both irradiated parents have a higher radiosensitivity compared to F2 of non-irradiated parents. Based on these observed radiation effects in F2 one may draw up a list of parental germ cells, irradiated at different stages of maturation, in the following decreasing order of effect: matured/maturing oocytes + spermatocytes/ spermatogonium/ spermatids/ spermatozoids.

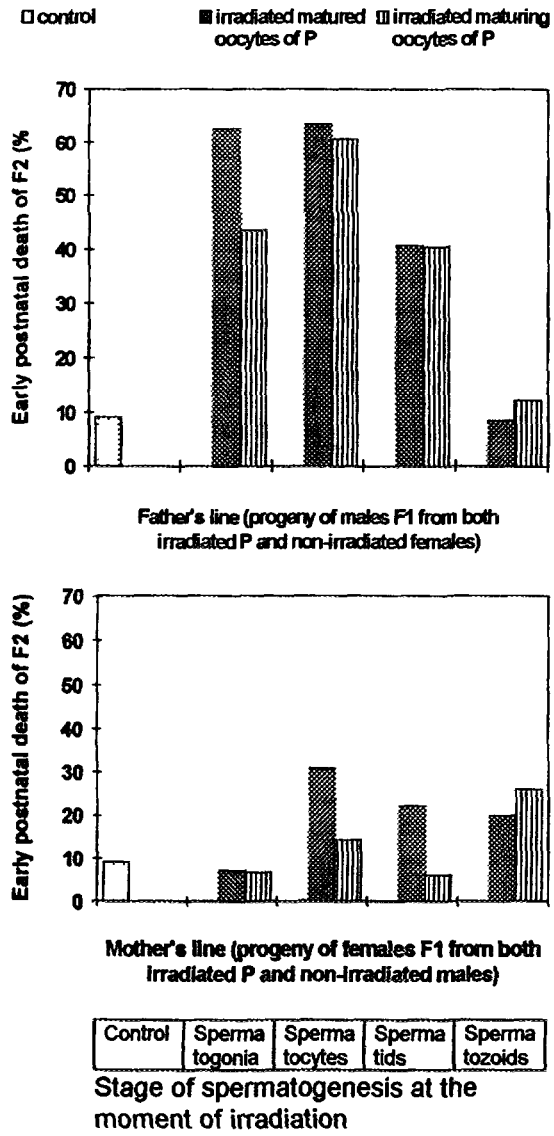

Figure 4. Early postnatal death of the second generation (F2) after irradiation of germ cells of both parents (P) with dose 2 Gy at the different stages of gametogenesis.

4. DISCUSSION

The studies of the casual relationship between the stages of development of parents'germ cells at the time of irradiation and effects in development over 2 following generations showed certain trends which have led to suggestions of possible mechanisms. The increase in radiation effects in the F1 from the mating of two irradiated parents appears to be associated with a mechanism demonstrating additivity or synergism. The outcome in the F1 of mating between one or both irradiated P is influenced by variations in genetic radiosensitivity of both male and female germ cells at different stages in their maturation.

The mature oocytes are more radiosensitive than the maturing oocytes or male gametes at any stage of spermatogenesis. The high death rate of F1 during embryonic development is likely to be associated with gross chromosomal and genomic abnormalities, whiest the death of F2 after the birth is connected with non-repaired point DNA mutations induced by radiation in gametes P. The point DNA mutations in germ cells may lead to the allowance of DNA instability of the somatic cells in organisms developed from irradiated gametes [2]. This process may results in the reduction of the specific effects, or altered sensitivity of individuals to various pathogens. It may not manifest phenotypically but rather appears as a latent characteristic "physiological inferiority" [3] against some specific pathogen or environmental pressure. Taking into account the universal nature of the biological effect of ionizing radiation on mammals, it is reasonable to assume that the same mechanisms as shown here in rats would also operate in humans. It is, however, not possible to predict how the actual numerical results presented here would apply human species.

ACKNOWLEDGEMENTS

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MEDICAL AND SOCIAL CONSEQUENCES OF LOW DOSES OF RADIATION FOR THE POPULATION OF LATVIA

XA9745617

V. TSOI
Department of Radiology Latvian Cancer Center,
Riga, Latvia

Abstract

About 6000 people involved in the elimination of the consequences of the Chernobyl accident and family members evacuated from Pripyat settled in Latvia. Although exposed to doses not exceeding 25cGy, an increasing number of diseases leading to invalidity and mortality of liquidators is noted. The symptoms of the various medical disorders being observed are described.

In Latvia a new small independent country on Baltic sea-side (former USSR) with a population of about 2.5 millions. There lived approximately 6000 people which took part in the elimination of consequences of the Chernobyl catastrophe in 1986 and, according to the State Register, including also the members of about 200 families which had been evacuated from Pripyat (Ukraine) and settled in Latvia.

In the Chernobyl region during 1986-1989 our liquidators worked as decontaminators, drivers, building workers etc. some of them were on the roof of the Nuclear Power Station (NPS).

Officially (by the temporary rules and instruction of former USSR-86) each liquidator was exposed to doses not exceeding 25 cGy without taking into account the incorporation of radionuclides. But in reality we don't know precisely about absorbed doses (external and internal exposure).

The medical, social and psychological situation among our liquidators is characterised by a long-term tendency of increasing diseases of invalidity level and still increasing mortality level.

The analysis of our data allowed us to accept next main reasons: first it is necessary to note that behind the fate of a lot of liquidators there is hidden an enormous personal tragedy. There were many cases when liquidators were dismissed from work and lost employment, working ability, divorced, committed suicide etc. These all was caused by a lot of unsolved social and economical problems.

About 2,5% liquidators have died during 1987-1997 (30% of those during first 5 years). Among them are about 35% cases of mortality in different accidents (at work, home, street etc.).

About 20% cases of mortality are suicides and other cases of complex diseases induced by radiation and radiophobia. Among our liquidators about 15% are invalids (with woking disability). The main reasons of invalidity are complication of health disorders. We should mention the following dominating syndromes:

1. One of the most specific syndromes of our liquidators is osteoalgetic syndrome (muscule-sceletal disorders). About 58% of patients have suffered from diseases expressed as osteoarthropathy, arthritis, polyradiculitis, osteoporosis etc.
2. Cerebro-vascular disorders with cephalgia (suffer by about 52% of patients) expressed as vegetative disorder and neurocirculatery disorder.
3. Digestive and endokrinological disorder (suffer by about 45% of invalids) which leads to chronical gastroduodenitis, hepatitis, diabetes, etc .
4. Among cardiac -vascular disorder (suffer by about 25% of invalids) prevailed ishemic heart diseases, hypersonic diseases, etc.

5. Neurological and psychiatric disorder (suffer by about 25% of invalids) which expresses as asteno-neurological syndromes, astenodepressive syndromes, encephalopathy and psychiatric, etc.

We observed also some cases of thyroid cancer and malignant neoplasmas.

All liquidator invalids have the combination of 3-4 and more diseases.

In conclusion it is necessary to note that in reality now medical, social and psychological consequences for liquidators turn out more dramatically than it was expected from taking official exposure doses (25 cGy by former USSR-86 y. Rules) into account.

RELATION BETWEEN POST-CHERNOBYL LOW LEVEL THYROID IRRADIATION, STABLE IODINE DEFICIENCY AND THYROID DISORDERS IN LITHUANIA (EPIDEMIOLOGICAL STUDY:1992-1996)

T. Nedveckaite, V. Filistovic
Institute of Physic, Radiation Protection Department
Savanoriu 231, Vilnius 2028, Lithuania
A. Krasauskiene
Lithuanian Institute of Endocrinology, Laboratory of Thyroid Disorders
Eiveniu 2, Kaunas 3007
K. Kadziauskiene
Ministry of Health Republic of Lithuania, National Nutrition Center
Kalvariju 153, Vilnius 2048

Abstract

RELATION BETWEEN POST-CHERNOBYL LOW LEWEL THYROID IRRADIATION, STABLE IODINE DEFFICIENCY AND THYROID DISORDERS IN LITHUANIA (EPIDEMIOLOGICAL STUDY:1992-1996)
The volatile radioiodine was detected in Lithuania in the very first day after the Chernobyl accident. Aim of the study was to perform the epidemiological investigation of thyroid disorders among Lithuanian inhabitants and to compare the data with thyroid radioiodine doses and stable iodine deficiency (urinary iodine excreation) results. Thyroid equivalent doses were estimated using the modified ICRP three-compartment cyclic model. These calculations applied Monte Carlo methods and consideration of regional iodine deficiency. The adult thyroid doses range up to about 50 mSv and the infant's and children's doses amounted to 200 mSv. High prevalence of thyroid abnormalities (up to 48%) are attributable to deleterious effect of ionising radiation as well as stable iodine deficiency for geological and socio-economical reasons. These data may be useful for estimating health effects that could develop in the future among Lithuanian inhabitants as a result of stable iodine deficiency and radioiodine exposure following the Chernobyl accident, especially amongst those who were infants at the time of accident
Key words: ^{131}I; Chernobyl; stable iodine; thyroid disorders

1.. INTRODUCTION.

After the Chernobyl accident Southeast wind transported radioactive materials over the Western part of Belarus, Southern and Western part of Lithuania toward Scandinavian countries. The measurements of airborne and milk radioiodine were performed in Lithuania during the period 30 April to 20 May 1986 and there were defined three area with different contamination levels: the mean ^{131}I activity concentration in milk over 1000 Bq/L (A), 370 Bq/L to 1000 Bq/L (B) and up to 370 Bq/L [1,2].
A rapid increase of thyroid disorders in Lithuania made physicians and scientists of various fields unit in solving this problem. The joint project was initiated in 1992. The present stage of scientific investigations is being focused on thyroid dose and stable iodine deficiency assessment as well as epidemiological studies of the few thousands of Lithuanian inhabitants.

2. MATERIALS AND METHODS

Thyroid doses were calculated using the post-Chernobyl airborne and milk radioiodine activity data and ICRP three-compartment cyclic mathematical model. This model was modified to include the effect of stable iodine intakes on radioiodine intakes explicity [3]. Stable iodine deficiency was evaluated by Ceric arsenite method in casual urine samples [4].
Thyroid doses in the same age group and in the same region are extremely variable due to significant variability in human metabolic characteristics, regional prevalence of stable iodine deficiency, errors in the measured radioiodine activity, etc.. For these reasons Monte Carlo procedure has been used for numerical solution of equations. External exposure added a negligible thyroid dose.
The screening of thyroid disorder (798 11-year school-children and 1711 adult) has been performed by endocrinologist and pediatrian-endocrinologist in three areas of Lithuania with different radioiodine contamination after the Chernobyl accident. Collection, accumulation and evaluation of medical data has been performed according WHO standards by mean of WHO type questionnaire including the data on thyroid gland state (inspection, palpation, ultrasound examination with the help of sonography system, immunological state, thyroid hormones assays, TSH radioimmune assays, etc.).
Advanced software has been created for the purpose of Data Base and evaluating the statistical data of thyroid disorders, stable iodine deficiency and thyroid dose assessment.

3. RESULTS AND DISCUSSIONS

The results of stable iodine deficiency and thyroid dose evaluations are presented in Fig.1 and Fig. 2. As is evident present-day stable iodine deficiency is of moderate degree. The highest adult doses range up to about 50 mSv and infant's and children's doses amounted to 200 mSv in the most contaminated area of Lithuania
The results of adult thyroid examination are presented in Table. It is necessary to stress high abnormal thyroid (up to 30 %) and thyroid with nodes (up to 20%) amongst adult Lithuanian inhabitants.

Table I. Prevalence of adult thyroid gland pathology in three areas of Lithuania with different radioiodine contamination (epidemiological study:1992-1996)

Region and contamination area	Persons examin.	Abnormal thyroid, %	Nodules / cancer	Hypoth., %	Hyperth., %	Microsom. antibod., %	Iodine in urine's, $\mu g\ dl^{-1}$	Terioidit. autoimun.
Kaisiadorys (B)	239	25.6	12 / 0	10.3	7.1	15.8	6.6±1.0	-
Varena (A)	336	26.8	15 / 2	7.3	6.2	15.0	6.5±0.8	22
Kretinga (A)	294	27.5	10 / 0	2.1	2.6	22.5	6.3±0.8	34
Salcininkai (B)	242	25	21 / 2	5.4	3.1	22.3	5.3±1.2	24
Joniskis (C)	338	29.8	16 / 3	3.9	4.3	21.7	8.3±0.9	31
Druskininkai (A)	266	27.1	20 / 1	2.6	2.6	18.1	-	23
Mean	1715	26.9	94 / 8	4.3	4.4	19.2	6.5±0.9	146

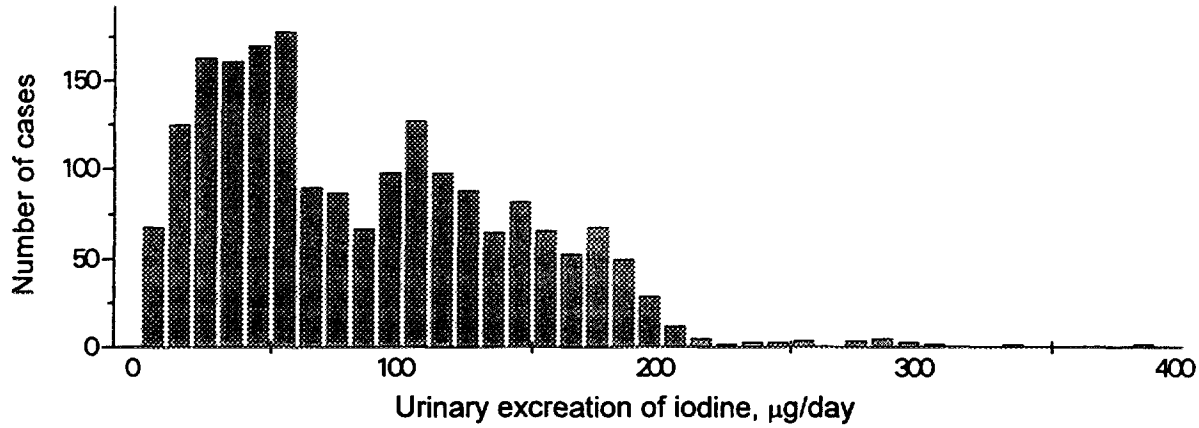

Fig. 1. Daily urinary excreation of stable iodine

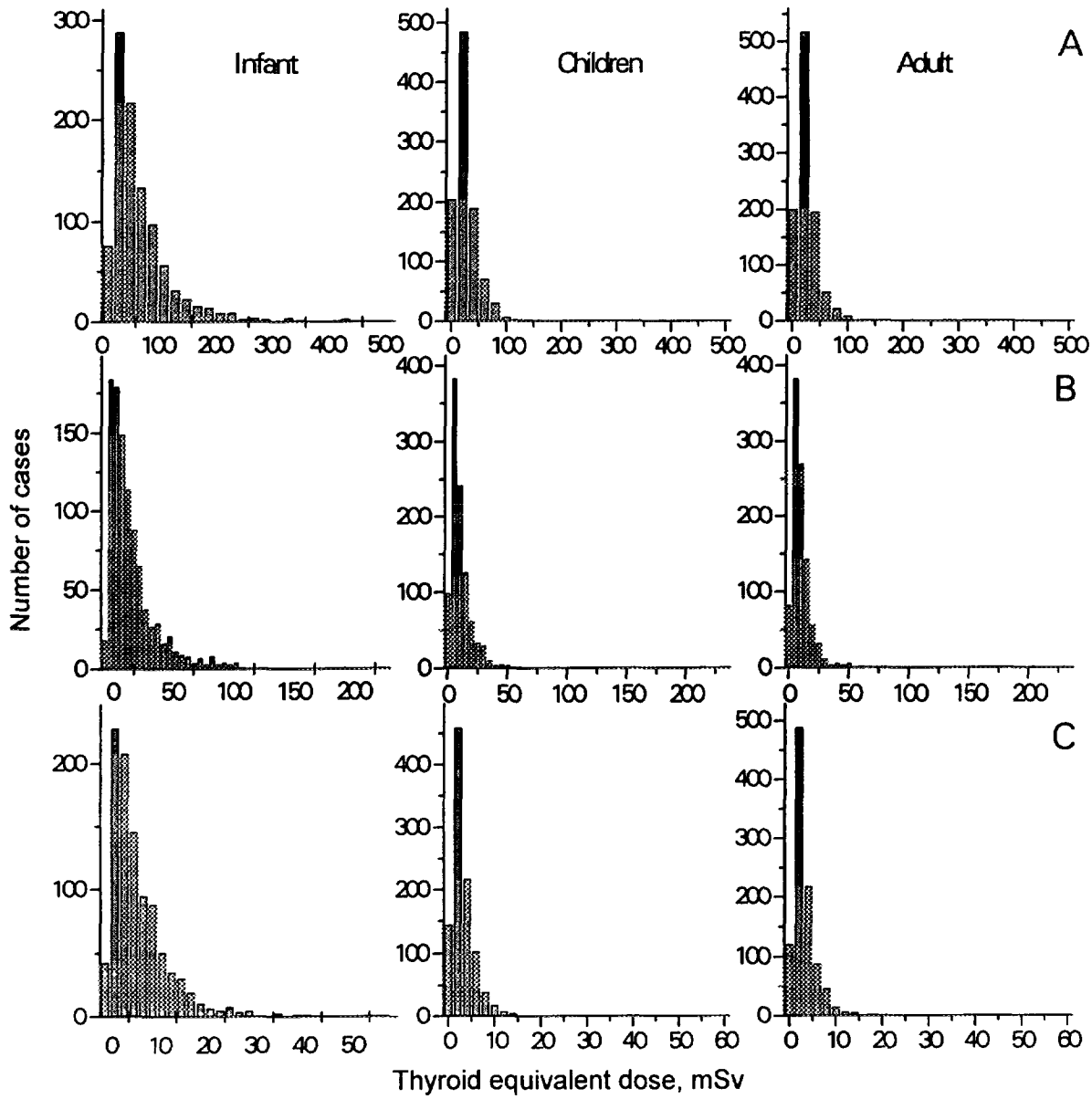

Fig. 2. Infant , children and adult thyroid equivalent dose distribution in three areas of Lithuania with different radioiodine contamination levels after the Chernobyl accident

In 798 cases of examined schoolchildren (the juvenile population of Lithuania who were born before or within six months of the accident) thyroid disorders had 48% whereas nodular thyroid had no more than 1% of examinated.

CONCLUSIONS

Risk of radiation at low doses have been increasingly studied in recent year. The consequences of Chernobyl accident in Lithuania have presented evidence on the relationship of thyroid disorders at low thyroid irradiation doses and moderate degree of stable iodine deficiency. In an explicit form the increase of induction of thyroid diseases over the spontaneous rate can not be demonstrated during one decade after the Chernobyl accident. The project is underway and progressing satisfactorily in accordance with expectations. Our current activities are concentrated on the further epidemiological investigation of thyroid disorders. High prevalence of thyroid abnormalities (up to 48%) suggests that radiation exposure is not unique environmental agent adversely affecting the thyroid. Amongst other adversely factors which will bound to be investigated in the nearest future, are disorders of dietary iodine consumption, exposure to polyhalogenated biphenyls, other environmental, social and economical factors. These data may be useful for estimating health effects that could develop in the future among Lithuanian inhabitants as a result of stable iodine deficiency and radioiodine exposure following the Chernobyl accident, especially amongst those who were infants at the time of accident

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Determination of Thoron (^{220} Rn) Short-Lived Decay Products in Surface Air by Gamma-ray Spectrometery inTripoli

XA9745619

M. A. Shenber

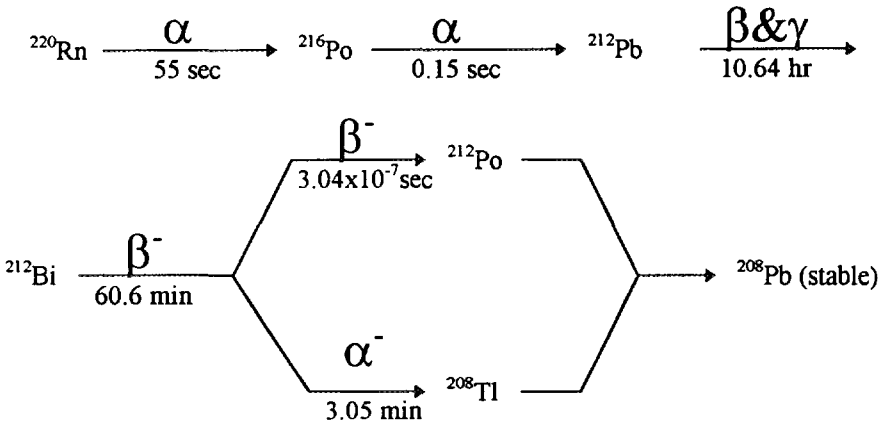
Radiation Protection and Health Physics Department
Environmental Radiation Measurements Division
Tajoura Nuclear Research Centre
P. O. Box, 84326 Tripoli, Libya

ABSTRACT

The activity concentration of thoron (^{220}Rn) short-lived decay products in surface air around Tripoli meteopolitan area have been measured using gamma-ray spectrometry.
Average morning activity concentrations of thoron short-lived decay products in Tripoli, are reported. Averages ranged from 10 to 75 mBq m^{-3} . The average activity concentrations of thoron short-lived decay products were 60 for ^{212} Pb, and 12 (mBqm^{-3}) for ^{212}Bi. The annual effective dose from thoron short-lived decay products outdoor air is found to be 4.11 μSv .

INTRODUCTION

Thorium in the soil is the main source of thoron in the global atmosphere. The activity concentrations of short-lived thoron decay products have been measured at Tajoura on the East coast of Libya.
The decay of ^{220}Rn occurs according to:



^{216}Po will be presented in atmospheric air mainly in the form of unattached atoms and its activity concentration on the filter will be very low due to very short half-life. The contribution of ^{216}Po to the activity concentration of ^{212}Pb and ^{212}Bi on the filter during sampling, delay and time interval can be neglected due to the same reason. Thus, the filter activity will be practically consisting of ^{212}Pb and ^{212}Bi. Besides, taking into account the fact that the total thoron and its progenies potential alpha energy (4.72×10^5 MeV Bq^{-1}) a part of ^{212}Pb and ^{212}Bi is equal to 4.72×10^5 MeV Bq^{-1} , it becomes apparent that these two radionuclides really control the inhalation pathways dose to man for thoron short-lived decay products (Tammer, 1980; NRE, 1964; NRE II, 1975; NRE III, 1980; Postendrfer et al., 1980 and UNSCAER, 1982 & 1988).

MATERIALS AND METHODS

Site description

The sampling station is located at Tajoura (North 13^0-14^0, and West 31.5^0-33^0), about 30 km east of Tripoli. The location is in the east of Libya. The natural environment, mostly woodland, is uncultivated and the soil is a loamy sand. To the south, at a distance of about 500 m, is agricultural land.

Sampling procedure

The air was sampled at a height of 1.5 m above the ground. The samples were collected on a PVC fibre filter, type FPP-15-1.5, 0.36 m^{-2} (Russian made) and using a high-volume sampler with on air-flow of rate 600 m^{-3} h^{-1}. The filters are compressed by means of a hydraulic press at up to 3 tons to give a cylinder of 40 mm diameter and 15 mm height. This procedure assures a highly reproducible geometry.

Measurement of radioactivity

All activity concentrations of these samples were measured using a (SEN-ELECTRONICS) low-level gamma counting system consisting of a high-resolution, HPGe detector coupled to a 8192-channel analyzer with built-in microprocessor. The energy resolution of the 1332 KeV line from ^{60}Co was found to be 2.1 KeV at full width

of half maximum (FWHM) with the relative efficiency of 30 %. Standard source of ^{152}Eu of known activities were prepared at the laboratory.

Calculation of Equilibrium equivalent concentration (EEC) for ^{220}Rn short-lived decay products.

The formula given by Shenber, M. A. et, al., 1985 thecnical report was use to estimatethe equilibrium equivalent concentration of ^{220}Rn short-lived decay productsin outdoorair:

$$EEC = 0.212\ (4.31\ C_{Pb} + 0.41\ C_{bi})$$

C_{Pb} and C_{Bi} are respectively the average activity concentrations of ^{212}Pb and ^{212}Bi in air.
The detectable level of the methodology is $0.45X10^{-3}$ and $3X10^{-3}$ for ^{212}Pb and ^{212}Bi respectively.

RESULTS AND DISCUSSION

^{220} Rn short-lived daughter products

Table 1 shows the activity concentrations for ^{220}Rn short-lived decay products in mBq m^{-3} for approximatly 30 outdoor air samples collected around Tajoura nuclear research center.

Table 1. Average morning activity concentrations of thoron short-lived decay products and equilibrium equivalent concentration.

Radionuclide	Activity concentration (mBq m^{-3})
^{212}Pb	60
^{212}Bi	12
EEC	56

For the ^{212}Pb activity concentration, each values was an average of three values obtained from the 238 keV photopeak. The results ranged from 56-82 (mBq m^{-3}) , with an average of 60 $mBqm^{-3}$.

For the ^{212}Bi activity concentration, each values was an average of three values obtained from the 727 keV photopeak. The results ranged from 10 -18 (mBq m^{-3}) , with an average of 12 $mBqm^{-3}$.

As it seen from Table 1 data, activity concentration of ^{212}Pb approximately 7.5 times higher than obtained value by Blifford, J. H et., al. 1956 for North Africa. Table 1 also gives the average equilibrium equivalent concentration (56 mBq m^{-3}) in outdoor air.

Table 2. Activity concentrations of ^{220}Rn short-lived decy products and effective dose from inhalation (outdoors).

Radionuclides	Average activity concentration	Effective dose
^{212}Pb	60 mBq m^{-3}	4 $\mu Sv\ y^{-1}$
^{212}Bi	12 mBq m^{-3}	0.11 $\mu Sv\ y^{-1}$

Inhalation dose

Taking into account the observed equilibrium equivalent concentrations in air, the breathing rate (20 m^{-3} air inhaled per day) and the dose conversion factors for inhalation, in Sv Bq^{-1} (ICRP, 1979), the annual effective dose is found to be 4.11 uSv fromμ^{220} Rn short-lived decay products in outdoor air (Table 2). The annual effective dose arising from inhalation (outdoors) in Tripoli metropolitan area from Thoron short-lived dacay products is found to be approximately 4.8 times lower than the world averages data (UNSCEAR, 1982).

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XA9745620

REGULATORY CONTROL OF LOW LEVEL RADIATION EXPOSURE IN TANZANIA

A.M.Nyanda and W.E.Muhogora
National Radiation Commission
P.O.Box 743 Arusha, United Republic of Tanzania

Abstract

REGULATORY CONTROL OF LOW RADIATION EXPOSURE IN TANZANIA

In Tanzania, the radiation protection law was issued in 1983. Under this law, the National Radiation Commission is responsible for safe uses of ionizing radiation. The regulatory control of the resulting doses from the uses of radiation sources in medicine, industry, research and teaching is presented. The system of control reflects the existing interactions between the National Radiation Commission and users through the established radiation protection infrastructure. From the national dose registry data, it is found that the highest annual individual doses over 10 years ago, came from less than 5% of total monitored workers and were in the range 10 - 15 mSv y^{-1} . The experienced radiation levels in uncontrolled areas of potential workplaces is less than 1 μSv h^{-1}. The possibility for associating such low dose levels to the effectiveness of the existing regulatory dose control framework is discussed. Despite of this achievement, the need to improve further the radiation protection and safety programs is found necessary.

1. INTRODUCTION

The National Radiation Commission (NRC) was established by the "Protection from Radiation Act 5, 1983" of the United Republic of Tanzania. Under this law, the NRC is responsible for the safe uses of ionizing radiation. The law enables the promulgation of codes of practice as approved by the responsible minister to ensure that appropriate standards of radiation protection and safety are met. The recent code of practice was approved and put into force in 1990 and is based on the Basic Safety Standards [1]. Currently, regulations on radioactive waste management and control of radiation contamination to food stuffs are being prepared.

In Tanzania the major practices where radiation exposure to workers and members of the public is possible, are found in medicine, industry, research and teaching. More than 90% of these applications are medical; of which nearly 99% involve diagnostic radiology. The increasing uses of ionizing radiation in Tanzania, have demanded an effective system of control in order to keep the potential radiation exposures as low as practically achievable. This paper discusses the regulatory control methods undertaken by NRC to achieve this demand.

2. METHODS

2.1. Legislation and Licensing

The legislation requires that all ionizing radiation users be registered and licensed annually. The activities requiring licensing include possession and use of radioactive materials

with activities above 3.7 kBq or 74 Bq g^{-1} ; or any ionizing radiation emitting device capable of giving a dose rate not exceeding 1 mSv h^{-1} at 1 m. The import and export of all sources of ionizing radiation as well as the disposal of radioactive waste is also subject to licensing. The issue of the licenses depend mainly on the adequacy of radiation shielding of premises, availability of qualified operating personnel; standard performance of equipment and good radioactive waste management as is applicable. The radiation safety program at each centre is supervised by a Radiation Safety Officer (RSO) who is appointed by NRC.

2.2. Radiation safety inspections and radiation surveillance of workplaces

The validity of the issued licenses is further subject to the verification of continuing good radiation safety status at the centres through a planned quality audit program based on recommended standards [2,3]. Particular attention focuses the assessment of radiation levels in uncontrolled areas. Essentially all centres are supposed to be inspected annually in order to update relevant records before the issuance of the following year license.

2.3. Personnel monitoring service and standardization of dose measurements

The NRC operates a centralized Personnel Radiation Monitoring Service using LiF thermoluminescent dosimeters (TLDs) to about 1000 radiation workers. The dose limit of 50 mSv y^{-1} [1] is applicable pending the review of the law for the adoption of new dose limits [4]. In order to ensure traceability of the dosimetry to the international measurement system, the National Calibration Laboratory (NCL) for ionizing radiation was established and became operational in 1995. The laboratory is a member of IAEA/WHO network of Secondary Standard Dosimetry Laboratories (SSDLs).

2.4. Radioactivity and ambient radiation monitoring

This program is based on geological surveys indicating the existence of uranium, coal and phosphate bearing minerals. The aim is to collect scientific data on safety aspects of the practice on the basis of which decisions or measures can be taken to limit the radiation doses. Some collaboration on the subject exists with the IAEA, SateilTurvaKeskus (STUK) and the Global Environment Monitoring Network (GERMON).

2.5. Education and Training

The NRC undertakes a training program to radiation workers and safety officers in the country in order to ensure that appropriate knowledge of radiation protection and safety is imparted to them. The training is provided through the IAEA training program and also through regular annual national seminars. The seminars are offered to radiation workers and customs control, clearing and forwarding officials. There is also a plan to extend the seminars to the police officers following two recent incidents on illicit trafficking of spent industrial radioactive devices. A wide range of topics on radiation protection and safety are covered in the seminars and also in public media.

3. EXPERIENCES

Since the legislation on control of ionizing radiation sources and practices, considerable experience has been acquired.The legislation is now familiar to the majority of ionizing radiation users. Currently, about 300 radiation work places and installations have been

licensed and their compliance with license conditions is satisfactory. Less than 40% centres, majority being diagnostic radiology facilities do not comply fully. Most of the centres which do not comply, lack adequate radiation shielding, satisfactory performing equipment and/or qualified operating personnel. These centres fail to implement the usually recommended remedial measures due to financial constraints. Frequent malfunctioning of diagnostic x-ray machines in most of these centres is still significant the situation which has forced NRC to provide quality control checks and maintenance services.

The positive impact of the education and training program in making the radiation protection programs successful is clearly evident. Even more evident is the good cooperation received by NRC from users and members of the public. The direct reporting of RSOs to NRC on matters concerning radiation protection and safety and the recent arrests of illicit spent radioactive devise traffickers signifies this good will.

The introduced dose control measures has resulted into low dose levels to radiation workers and members of public. For example the maximum individual doses in the period 1986-1996 were in the range 10 - 15 mSv y^{-1} and were received by less than 5% of total workers. It is also interesting to note that during this period, there were no over exposures recorded. Table I summarizes the data from the national dose registry.

TABLE I. THE RELATIVE DISTRIBUTION OF OCCUPATIONAL DOSE FROM 1986 TO 1996

Annual dose range (mSv y^{-1})	Relative distribution of individual doses (%)
less than 5	75.8
5 - 10	20
10 - 15	4.2

With respect to members of the public, the situation of radiation exposure is also encouraging. Radiation survey measurements around radiation workplaces show that the radiation exposures in uncontrolled areas do not exceed 1 μSv h^{-1} . However, the program on radioactivity and ambient radiation level monitoring has revealed significant levels in some places which call for attention. Typical radioactivity and ambient radiation levels are given in table II .

TABLE II. SOME RADIOACTIVITY AND AMBIENT RADIATION LEVELS IN TANZANIA

Sampling site	average radioactivity level of ^{238}U (Bq kg^{-1})			average ambient radiation (nGy h^{-1})	
	NRC	IAEA	STUK	NRC	GERMON
Phosphate mine	5339 [1]	6720 [1]	6600 [1]	1380 [2]	-
Coal mine	72 [1]	-	-	-	-
Cement industry	52 [1]	-	-	-	-
NRC premises	-	-	-	140 [2]	87 [2]

[1] as measured in 1992

[2] as determined in 1996

Despite the success of the existing radiation protection infrastructure, some constraints have also been experienced. The law needs revision particularly on some administrative and technical issues. For instance the application of the present law is restricted only to mainland Tanzania and does not cover the Zanzibar isles. Further to this, the law does not address some of technical issues such as the sale or lease of the radioactive materials or radioactive devices; and the more uptodate International Basic Safety Standards. Equally important, the monetary penalties for offenses need also be updated for inflationary trends.

4. CONCLUSIONS

The experience gathered in controlling low radiation doses from ionizing radiation exposures has been so far encouraging. Generally, Tanzania has experienced low dose levels to the workers and members of public which are well below the recommended dose limits. The present radiation exposure status suggests that the regulatory system of dose control is fairly effective. Despite of this achievement, the need for further improvements as already been mentioned is still required. Behind this achievement has been the generous technical assistance of IAEA given to NRC in the upgrading of national radiation protection infrastructure.

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In vitro and in vivo effects of low dose HTO contamination modulated by dose rate

Ileana Petcu[a], Diana Savu[a], Nicoleta Moisoi[a], G. J. Köteles[b]
([a])Institute of Physics and Nuclear Engineering-"Horia Hulubei", P.O.Box MG-6, R-76900 Bucharest, Romania; ([b])"Frederic Joliot-Curie" National Research Institute for Radiobiology and Radiohygiene, P.O. Box101, H-1775 Budapest, Hungary.

Abstract
The experiment performed *in vitro* intended to examine whether an adaptive response could be elicited on lymphocytes by low-level contamination of whole blood with tritiated water and if the modification of the dose rate has any influence on it. Lymphocytes pre-exposed to ^{3}HOH (0.2 - 6.6 MBq/ml) and subsequently irradiated with 1 Gy γ-rays showed micronuclei frequency significantly lower (40% - 45%) than the expected number (sum of the yields induced by ^{3}HOH and γ-rays separately). The degree of the radioresistance induced by HTO pre-treatments became higher with decreasing dose-rate for a rather similar total adapting dose.
In vivo, the aim of the study was to investigate if different dose rates are inducing modulation of the lipid peroxidation level and of the thymidine uptake in different tissues of animals contaminated by HTO ingestion. The total doses varied between 5 and 20 cGy and were delivered as chronic (100 days) or acute contamination (5 days). It was observed that only doses about 20 cGy caused a dose-rate dependent increase of the lipid peroxidation level in the tissues of small intestine, kidney and spleen.
Both chronic and acute contamination did produce reduced incorporation of thymidine in the cells of bone marrow. The most effective decrease of thymidine uptake was induced by the acute contamination in the lower dose domain (≅ 5 cGy). Our hypothesis is that in this dose domain the modification of thymidine uptake could be due to changes at the level of membrane transport.

Introduction

The interest about possible ^{3}H induced health detriments corresponding to low dose irradiation domain is justified by the use of nuclear power as well as by the ongoing research on fusion reactor technology. During the past decade a large number of radiobiological studies have become available for ^{3}H - most of them focusing on the RBE of tritium beta rays [1]. A point of interest concerning the tritium induced low-level effects came from the research on the adaptive response of mitogen stimulated human lymphocytes to low-LET radiation exposure [2].

The present paper reports the results of two different types of experiments: one is referring to *in vitro* induced effects on human lymphocytes while the other one is referring to *in vivo* effects observed on internally contaminated animals.

The experiment performed *in vitro* examined the question whether adaptive response can be elicited by low-level irradiation from tritiated water (HTO) and can be influenced by the modification of the dose rate. The response induced by the pre-treatment of the human lymphocytes with HTO of different specific ^{3}H activities and for different time intervals was subsequently provoked by acute gamma irradiation of the cells. The frequency of micronucleus induction, used as biological end-point, was evaluated after culturing the whole blood.

The aim of the *in vivo* study was to investigate if different dose rates are inducing any modulation in the lipid peroxidation level or in the thymidine intake level in some tissues of animals contaminated by HTO ingestion.

Materials and methods

Part of the work, i.e. the experiment performed in vitro, has used human blood samples, taken from healthy young male donors. HTO diluted with RPMI-1640 medium was added to whole blood samples to achieve final ^{3}H levels ranging from 0.2 to 6.6 MBq/ml of plasma, which correspond to irradiation dose rates from 0.05 to 1.7 cGy/h. The incubation times varied between 1-24 h in order to obtain similar total doses, with different dose rates. Exposure doses were evaluated by measuring the

^3H in the supernatant of the first centrifugation for washing the cells and by taking also into account the incubation time and a value of 0.8 for the correction factor for the water content of the cells [3].
The cells were subsequently irradiated with 1 Gy of γ-rays (0.476 Gy/min) from a Gammatron-3 equipment. Immediately after the challenging irradiation, microcultures were set up and 72h later cytokinesis-blocked (CB) binucleated lymphocytes [4] were scored for micronucleus frequency [5]. The results were expressed as the average number ± SD of micronucleated cells per thousand of CB-cells.
The experiment designed to evaluate in vivo effects of tritium low dose contamination was conducted on Dowley-Sprague rats, devised in 5 groups of 10 animals each; on the whole duration of the experiment (100 days) they received standard food and as drinking water, some groups received tap water (groups M, C and D), while the other groups received tritiated water (groups A and B), with specific activity in the range of 9.25 kBq/ml and 37 kBq/ml. Group M were used as nonirradiated controls. Animals from groups C and D were subjected to acute irradiation by single intraperitoneal injection with HTO (41.6 MBq/animal and respectively 166.5 MBq/animal), and sacrificed 5 days later.
The dose evaluation was made by a combined procedure, using an equation reported in the literature for tritium retention in rats [6] and also using experimental values for the final tritium specific activity, measured by us in the blood plasma of the animals.
At the end of the exposure. the animals have been sacrificed, collecting liver, kidney, spleen, small intestine and bone marrow samples.
The amount of lipid peroxides was estimated in liver, kidney, spleen and small intestine by the thiobarbituric acid (TBA) reaction [7]; the results have been expressed as quantity of malondialdehyde (MDA) per tissue mass (nmol MDA/g of tissue).
The bone marrow samples were collected in TC-199 culture medium and cell suspensions were prepared
with a cell density of 10^7 cells/ml. After repeated washings of cells, the thymidine intake test was performed by incubating the cells (normal or pre-treated with KCN) at 37°C for 15 min with ^{3}HTdR with specific activity of 0.4 μCi/ml. The uptake in whole cell material was evaluated by liquid scintillator measurements and it was expressed as dps/10^7 cells. In order to compare the modifications observed in our experiment for the different aspects under investigation, a normalisation of the data have been operated; there were calculated for each type of treatment ratios relative to the unirradiated control, denominated as "arbitrary units".
The statistical significance of the differences observed between irradiated and nonirradiated groups was assessed by Student's *t* test.

Results

Lymphocytes exposed in vitro to ^{3}HOH, to doses in the range of 1-10 cGy (intervals of 1-24 hours and specific activities of 0.2-6.6 MBq/ml) and subsequently irradiated with 1 Gy γ-rays (in the G_0 phase of their cellular cycle) showed micronuclei frequency significantly lower than the sum of the yield induced by ^{3}HOH and γ-rays separately. The frequency of micronuclei induced by ^{3}HOH alone remained similar to that of the non-irradiated control within the whole range of specific activities used in this experiment (Fig.1). Even doses of 10 cGy received by lymphocytes exposed for 24 hours to ^{3}H specific activity of 2 MBq/ml (0.5 cGy/h) were proved to be statistically ineffective for micronucleus induction The reduction of micronuclei induction appears to decrease with the increase in ^{3}H specific activity, for total conditioning doses between 1 - 2 cGy (Fig.1). We did observe individual variability in the responses of micronucleus induction either after HTO treatments, after 1 Gy γ-irradiation or concerning the amplitude of the adaptive reduction of micronucleus frequency. However, adaptive responses were positively observed for all 4 investigated donors .

The results obtained in the evaluation of the malondialdehyde content in tissues homogenates are summarised in Table I for both types (chronic or acute) of in vivo contamination with tritium.
In the case of liver and kidney, significant increase of lipoperoxides content was observed for contamination situations corresponding to total exposure doses of 20 cGy. The amplitude of the effect was higher at higher dose-rate. The spleen did respond the most sensitively to the investigated dose domain. A significant increase of the peroxide level was induced by very low dose rates (0.04 cGy/day), for total doses of 5 cGy; the same type of modification was observed for the other contamination situations and a dose-rate dependency was

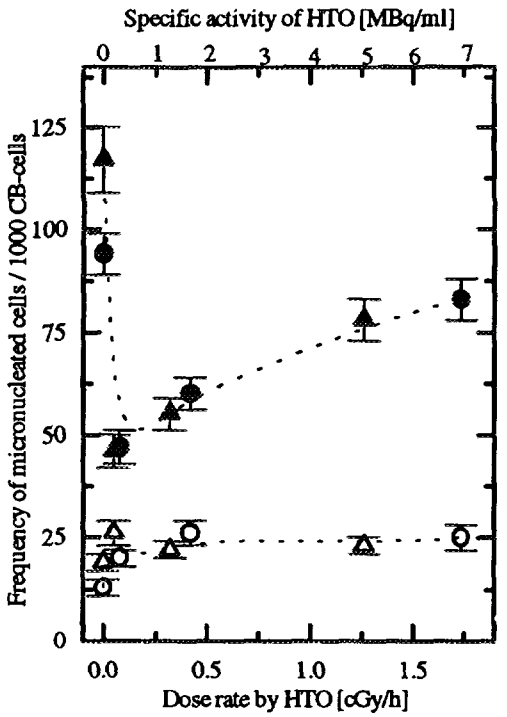

Fig. 1: Adaptive response: The relationship between the frequency of micronucleus induction and the dose-rate of the priming irradiation by HTO: o, Δ - HTO; o, Δ - HTO + 1 Gy γ - ray

noticed at doses of 20 cGy, the increase of the peroxide level reaching 300%. Similar sensitive response was observed in the case of the small intestine but the addition of a dose-rate dependency on the radioinduced effect was less pregnant

The results of the ^{3}HTdR incorporation assay, performed in vitro on bone marrow cells previously irradiated in vivo by HTO, are presented in Table II.

A significant decrease of TdR incorporation in KCN treated cells was shown for low total doses as 5 cGy; this decrease is larger at the higher dose rate. For larger dose, at 20 cGy, the decrease of the thymidine uptake is no more observed.

Alternatively, on normal cells (non-treated with KCN), a modification in the level of the ^{3}HTdR incorporation is observed for all the dose range. This parameter is also sensitive to the dose rate.

The decrease of thymidine uptake in the cell could be due to the radiation induced modifications of membranes, of enzymes which catalyse the subsequent steps until thymidine enters into DNA or to the modification of the mechanism of DNA synthesis.

Table I. Effect of chronic and acute irradiation by HTO contamination on peroxide content of different tissues (nmol MDA/g tissue)

Exp. group Tissue	M (control)	A (4.2 cGy) 0.04 cGy/day	B (19.4 cGy) 0.19 cGy/day	C (5 cGy) ~1 cGy/day	D (20 cGy) ~ 4 cGy/day
Liver	8.01 ± 0.74	9.32 ± 0.86	15.69 ± 1.43 p_M=0.0004	10.30 ± 1.56	17.58 ± 1.12 p_M=0.00001
Kidney	16.52 ± 1.54	20.47 ± 3.15	22.19 ± 0.94 p_M=0.002	21.53 ± 2.39	31.94 ± 3.17 p_M=0.0009
Spleen	32.97 ± 1.59	50.58 ± 4.17 p_M=0.002	53.34 ± 4.48 p_M=0.001	52.94 ± 4.14 p_M=0.0007	108.95 ± 8.80 p_M=1*10^{-6}
Small intestine	20.43 ± 2.91	31.45 ± 3.86 p_M=0.04	26.72 ± 2.42	31.26 ± 1.99 p_M=0.001	35.10 ± 4.07 p_M=0.01

Table II. Effect of chronic and acute irradiation by HTO contamination on ^{3}HTdR uptake in bone marrow cells (the data expressed as "arbitrary units")

Exp. group	M (control)	A (4.2 cGy) 0.04 cGy/day	B (19.4 cGy) 0.19 cGy/day	C (5 cGy) ~1 cGy/day	D (20 cGy) ~4 cGy/day
KCN treated cells	1.00 ± 0.14	0.50 ± 0.10 p_M=0.018	0.91 ± 0.13	0.36 ± 0.12 p_M=0.007	0.92 ± 0.04
Normal cells	1.00 ± 0.07	0.73 ± 0.06 p_M=0.014	0.62 ± 0.05 p_M=0.001	0.53 ± 0.05 p_M=0.0003	0.75 ± 0.06 p_M=0.026

Discussion

The present results are sustaining the assumption that the micronucleus test, which represent a suitable indicator of the frequency of chromosomal aberration induced by ionising radiation, can be used also for the adaptive response assay, in good agreement with some previous reported results [8].Our experimental observations seem to demonstrate the possibility of inducing the adaptive response by small doses of β-irradiation delivered on G_0 lymphocytes, as long as the exposure occurred in the whole blood environment.

An important observation of our study is that the dose rate of the adapting irradiation, modulated by the level of tritium specific activity have some influence on the yield of micronuclei induction. The degree of the radioresistance induced by HTO pre-treatments became higher with decreasing dose-rate for a rather similar total adapting dose. However, the relative yield between observed and expected number of micronuclei decreased only until 40%-45%. This limit is already reached at dose rate of 0.3 cGy/h.

The interest of the peroxide level evaluation in the spleen and small intestine was suggested by their sensibility for the expression of radiological effects especially in the low dose domain [9]. Indeed our results showed a significant increase of the peroxide level for the lowest dose used (5cGy) only for the tissue homogenates of spleen and small intestine.. For doses of 20 cGy the effects were observed to occur for all the studied tissues and also to be dose-rate dependent: at higher dose rates the level of peroxides is significantly additionally increased.

Summing up, our study put into evidence only an increase of the lipoperoxide level due to HTO contamination., for the dose domain of 5 - 20 cGy and for dose rate range of 0.04 - 4 cGy/day. In most of the cases the effect is monotonically associated with the dose and the dose rate increase.

The test of DNA precursors incorporation in bone marrow was already previously used to characterise the biological response to low dose irradiation, by Feinendegen research group [10]. Our results showed that for chronic irradiation by HTO contamination in the low dose domain, the modification of the thymidine uptake could be due to changes at the level of membrane transport.
For the higher dose, the inhibition of the uptake could be due to a decreased activity of the thymidine-kinase, as it was suggested in the literature. Both phenomena are, most probably part of the same process of metabolic defence, triggered in the hit cells by low dose and low dose-rate irradiations. This mechanism might involve different steps, and their triggering could require different intensities of irradiation stress.

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DOSIMETRIC MONITORING BY THERMOLUMINESCENT DOSEMETERS OF EMPLOYERS WORKING IN IONISING RADIATION FIELDS

L. QAFMOLLA
Institute of Nuclear Physics,
Tirana, Albania

ABSTRACT

Radiation Protection Commission was established in the Ministry of Health and Environment as Regulatory Authority, organises and supervises all activities related with radiation protection, as the licensing, inspection, dosemetric personal control, medical examination,radioactive waste management,etc.

Actually in our country are exerting some activities,which intend to covert the principal tasks in the field of radiation protection. Such activities are dosemetric personnel control based on TLD, radioactive environmental monitoring, radioactive waste management, calibration of dosemetric equipment's etc.

This paper describes the realisation of personnel monitoring by thermoluminescent dosemeters TLD -100 chips and cards were furnished by IAEA some years ago. Various experiments to determine the dependence of the response of dosemeters versus dose and versus orientation, the fading and lower detectable dose. The personnel monitoring of workers that work in ionising radiation field were in charge o f Institute of Nuclear Physics (INP). Actually in Albania was established the personnel monitoring service for employers of INP, Oncological Centre, Nuclear Medicine Centre and some other nuclear units in Tirana city.On the near future year exists the possibility to extend personnel monitoring for all physicians and technicians of rontgendiagnostic units of Durres,Shkodra,Elbasan cities.

RADIATION PROTECTION ORGANISATION

Albania is a small country, with no nuclear power industry and also not involved in a large scale with ionising radiation's.

The establishment of a proper radiation protection system requires following elements: legislation, administrative mechanism, qualified personnel and dosemetric equipments.All these elements exist actually in our country, but their efficiency is not fully sufficient.

Radiation Protection activities started at the same time with the beginning of use of radiodiagnostic devices in health field,but realistic conditions were created after setting up of some nuclear units in medicine,industry,agriculture and finally with INP in 1971 year.

The first Law on Radiation Protection in Albania has been set out 26 years ago by a special Ordinance of Ministers Council Law No. 83, date27.05.1971.In the new Law No.8025, date 9.11.1995 defines radiation protection terms for all activities, performed with radioactive materials and radiation devices, providing safety of the workers professionally exposed, population and environment as a whole from eventual detriments of ionising radiation[1]. Other act in this law describes also the general rules for production, use, transport, storage and disposal of the radioactive wastes and spent radiation sources.

A Radiation Protection Commission was established in the Ministry of Health and Environment as Regulatory Authority for the organisation and supervision of the all activities related with Radiation Protection problems[1].

In collaboration with the Institute of Public Health (Office of Radiation Protection), Institute of Nuclear Physics the Commission of Radiation Protection control all activities in Radiation Protection field.

The Institute of Nuclear Physics (INP) in Tirana is the focal point for the transfer,uses and implementation of nuclear techniques in the country, including research activities in different fields: radiation protection service, radiological environmental monitoring etc.

ASSESSMENT OF INDIVIDUAL EXPOSURES

a- Control of doses of the workers by TLD.

The Radiation Protection Division in INP, carries out all the personnel monitoring activities for our country, Albania. Actually this control fulfilled for about 300 workers, based on TLD (LiF, TLD-100 cards) furnished by IAEA. Nearly half of the monitored persons are employers in the medical field in Tirana and Durres cities.

TLD-100 is produced by homogeneous melting of lithium fluoride,magnesium fluoride, lithiumcryolite and lithium titanium fluoride, resulting in a phosphor containing 300 ppm magnesium and 20 ppm titanium. A single crystal is solidified from the melt, then pulverised, and the powder grains sieved and separeted.Personal dosimeters TLD are worn on the trunk of the body at chest level where the dose is likely to have its maximum value while the reading of the dosimeters is taken to correspond to whole-body dose with assumption that the body is uniformly irradiated. Actually we haven't made any correction for non-uniform exposure or to apply convertation factors[2]. We have tried to use extremity dosimeters to a small proportion of workers in the Oncological Hospital to determine the value of dose exposure there. Plastic sachets in ring form with a solid TLD worn on a finger supplied by IAEA after being exposed during work in a month period.Neutron dosimeters are worn by a small group workers of the Neutron Physics Division in our Institute and Oil Enterprise in Fier city. In all cases dosimeters were issued regularly for a period of one month[2].

The TLD system is based on a HARSHAW-4500 reader now in operation one year. 7 years ago we have used a HARSHAW-2000 reader and during this period, the maximum annual individual dose was below 4.25 mSv. Some of the monitored employers have received month dose below the lower detection limit (0.1 mSv). These doses are quoted as zero.The record of data regarding with individual monitoring are kept regularly and we have made a Regional Worker Dose Registry,which contains information relevant to radiation protection for each employer that works in ionising radiation field.

Albania meets a difficult problem related with medical exposure of the populations a result of the old age of X-ray units in the country, a great concern exists for radiation of both categories of practitioners and technicians and population in whole related to high level of exposure during different radiodiagnostic procedures.For improvement of this problem it is foreseen a QA programme in medical field as well as the reviewing of the possibilities for gradual replacement of old X-ray units for medical purposes.

b. Environmental Monitoring

An important problem is the monitoring of environmental radioactivity.The control of environment fulfilled for two motive: radiation protection of environment from different radioactive contamination and estimation of doses of the population. The Basic Safety Standards define permissible levels of exposure and derived limits.There are three categories of people according to the levels of exposure:

Category A- a personnel,temporary or permanently working in field of external and/or internal exposure 50 mSv.

Category B- some part of population older than 18 years with limit of 5 mSv,(people that live near the nuclear facilities).

Category C- the whole population of the country with limit of 0.5 mSv [1].

Some Institutions and Centres in a national network co-operate together for realisation of the environmental monitoring.This monitoring is done through the sampling of atmospheric fall-out and air filtration,taken from three small stations that cover all territory of our country.

Samples of soil from a depth of 10 cm and from surface ground are taken every quarter in the vicinity of INP for four direction of horizon.For all the samples a total beta measurement is done. All values are registered and are comparable with those published elsewhere.INP also performs the control of eventual radioactive contamination of certain foodstuffs [3].

With the increasing application of the thermoluminescent dosemeter (TLD) in environmental monitoring, some attempts have been made in our country to establish minimum acceptable performance criteria for TLD systems. In addition to the use of TLD for personal dosimeter and for radiation-area monitoring , since radiation from man-made sources is superimposed upon the natural environmental radiation,thermoluminiscence dosimeter is also attractive for surveying the radiation levels in the vicinity of nuclear facilities.From six years the monitoring of environmental radioactivity near the INP is done on a routine basis. Crystals of CaF_2-Dy (TLD-200 chips) are used with the HARSHAW reader[4].

Data from the control samples collected at the surroundings of INP have shown that the general radioactivity level and the content of radionuclides are within the limits of tolerance and tent to decrease.

MATERIALS AND METHODS

In our country the individual monitoring of external exposure was carried out by using film badge dosemeters until 1990. Actually the individual monitoring to be performed with TLD-100 cards,given by IAEA, was established.Every month the Dosemeters Service Division on INP distributes around 250-300 pieces TLD badge dosemeters for measurement of effective dose, of nuclear units in Tirana and Durres .The characteristics of commercial "whole-body" dosemeters utilized,such as the procedures of calibration and methods for dose assessment are presented. Two reference methods for determination of the dose were applied,one in which

TABLE 1 Mean Annual Effective Dose for workers of Tirana city

No.	Occupational Practices	Mean Annual Effective Doses (mSv)		
		1995	1996	1997
1	Military Hospit.	0.25	0.35	0.95
2	Hospital No.1	0.45	0.5	0.35
3	Hospital No.2	0.45	0.82	0.55
4	Hospital No.3	0.3	0.5	0.45
5	Hospital No.4	0.3	0.35	0.3
6	Hospital No.5	0.35	0.3	1.5
7	Ptisio-Pneum. Hos.	0.4	0.45	-
8	Disp. anti TBC	0.6	0.55	0.3
9	Nuclear Medicine	0.39	0.65	0.45
10	Reg.Polyclin.No.2	3.5	1.9	1.3
11	Reg.Polyclin.No.3	0.45	0.45	0.35

TABLE II Number of persons working with Ionising Radiation in Albania.

Medical	Research/Teach.	Veterin/Agricult.	Industry	Total
600	150	100	150	1.000

dosemeters for calibration,irradiated with Cs-137 (activity A=30 mCi) are used, and another in which two sets of dosemeters were employed for calibration, one irradiated with Cs-137 source and other one with a Am-241 source (activity A=100 mCi) [1].In table I are given mean annual effective dose, mSv for workers of nuclear units of Tirana city.

RESULTS

In the Dosemeters Service Division on INP, values of annual mean effective dose for occupational practice (Table I) evidence that practices with largest mean doses for external irradiation are those of Regional Polyclinic No.2, Hospital No.5,and Military Hospital,but underline that in no case exceeds 5 mSv.

During the last year (1997) the higher value of annual effective dose was registered for Military Hospital,Hospital No.5, and Regional Polyclinic No.2 (1995,1996,1997)

The percentage of workers which received doses lower than that value,is in all practices,around 95%.

The frequency of cases above 5 mSv oscillate between 3-5 workers,but underline,these situations are negligence of workers,after they have forgot dosemeters on the ionising fields. It results that technicians of Regional Polyclinic No.2 with high level of exposure doses,as a result of the old age of X-ray units and bad conditions on work places.

CONCLUSIONS

For all occupational practices the current system of dose limitation established in Albania with 50 mSv as limit of annual dose is satisfied.

To extend personnel monitoring with TLD-dosemeters for all physicians and technicians of rentgennodiagnostic units of Durres,Shkodra,Elbasan,Fieri cities.

To create the Radiation Dose Registration Centre and National Worker Dose Register for workers designated by CRP near the INP,extending personnel monitoring all over country (about 1000 workers), IAEA has supplied our Institute with 1500 pieces TLD-cards and badges.Table II given number of persons working with ionising Radiations in Albania.

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THE BIOLOGICAL EFFECTS OF LOW DOSES OF IONIZING RADIATION ON ADAPTIVE POSSIBILITIES OF THE ORGANISM

G. Bulbuc
Oncological Institute of Moldova, Chisinau, Moldova

Abstract

The study of adaptive possibilities and cancer risk in animals exposed at low doses of ionizing radiation was the object of the present work. The action of immunostimulating treatment on these processes was studied as well.

In previously irradiated animals the diminution of adaptive possibilities and of the antitumoral resistance of the organism was observed. The stimulating action of Bufostimulin on these processes in irradiated animals was less pronounced than in unirradiated ones.

The evaluation of the adaptive possibilities and cancer risk in persons at low doses of ionizing radiation remains an important problem of scientific investigations [1, 2]. The study of the adaptive possibilities of enterocytes and antitumoral resistance of the organism in animals exposed at low doses of ionizing radiation was the object of the present work. The action of Bufostimulin (BS) application on these processes was studied as well.

Materials and methods

70 white inbred female rats weighing 160-170 gm and 200 white inbred female mice weighing 22-23 gm were taken in experiment. In rats beforehand exposed at 25R whole-body x-irradiation the adaptive possibilities of enterocytes were tested. The following groups of animals were distinguished: 1) control-10; 2) unirradiated + carbo-hydrates diet - 10; 3-4) irradiated - 20 (by 10 within 30 and 60 days after irradiation accordingly); 5-6) irradiated irradiated + diet - 20; 7-8) irradiated + BS + diet - 20. The carbo-hydrates diet consisted of substitution of drinking - water by 5% solution of sugar and addition of sugar beet in ratio (by 10 gm of beet daily for each animal). The administration of diet lasted for 7 days before the experiment.

In mice irradiated at the same conditions the appearance of skin cancer after application of DMBA (Flaka AC, Bucha SG) was studied. DMBA was applied twice weekly during 3,5 months, beginning 2 weeks after irradiation. The following groups were followed: 1) control - 50; 2) unirradiated + BS -50; 3) irradiated - 50; 4) irradiated + BS - 50.

BS is an immunostimulant which is obtained from the secretion of suprascapular glands of Bufo viridis L.

Results

The received data demonstrate after the administration of carbo-hydrates diet the membrane digestion is modified considerably (table I). The invertase activity on the intestinal micosa (membrane digestion of sucrose) and the tissular homogenates (the common content of this enzyme into enterocytes) in experimental animals (group 2) was increased by 36.6% ($p<0.001$) and 90.1% ($p<0.002$) accordingly. In irradiated rats the adaptive possibilities of enterocytes were altered both after 30 and 60 days. In 5th group in comparison with 3rd group the indices of invertase activity were not different, in the 6th group the modifications of enzymatic activity in comparison with the 4th group were less pronounced. BS in animals irradiated by 1 month before the experiment was ineffective, in irradiated by 2 months before the experiment the application of BS results in the enhancement of invertase activity only on the mucosal surface.

Table 1. The modifications of adaptive possibilities of enterocytes after whole-body X- irradiation at dose 25 R.

Test	Control	Unirradiated + diet	Days after irradiation					
			30			60		
			Irradiated	Irradiated +diet	Irradiated+diet + BS	Irradiated	Irradiated + diet	Irradiated+diet + BS
Invertase activity on intestinal mucosa	40.7 ± 1.9	55.6* ± 2.1	43.3 ± 2.7	41.4 ± 1.7	42.8 ± 2.7	41.6 ± 1.1	46.7* ± 1.5	53.5* ± 2.7
Invertase activity in the tissular homogenates	92.8 ± 5.0	176.4* ± 24.4	87.5 ± 3.5	95.4 ± 6.2	95.6 ± 7.6	85.7 ± 4.0	120.7* ± 7.8	140.9 ±9.9

* $p<0.05$

The appearance of benign tumors in all groups of animals was likewise (table 2). The first papillomas appeared in a month after beginning of DMBA application. During all period of the experiment the papillomas appeared in 43 mice of I group, 44 - II group, 42 - III group

Table 2. The action of BS on benignant tumors appearance in unirradiated and irradiated mice after application of DMBA

Group	Weeks after beginning of DMBA applications					
	4	6	8	10	12	13
Control	12	12	29	36	39	44
Unirradiated + BS	8	14	20	30	37	43
Irradiated	8	14	32	37	39	43
Irradiated + BS	11	15	24	33	38	42

Table 3. The action of BS on malignant tumors appearance in unirradiated and irradiated mice after application of DMBA

Group	Weeks after beginning of DMBA applications							
	10	13	15	17	20	22	24	26
Control	3	4	8	11	18	35	35	35
Unirradiated + BS	-	-	4	6	12	22	23	26
Irradiated	4	7	11	21	28	31	34	35
Irradiated + BS	2	3	8	14	26	30	36	36

and 43 - IV group. The dynamics of malignant tumors appearance in mentioned groups of animals was different. In irradiated mice the appearance of skin cancer was established in 9 weeks after beginning of DMBA applications, in unirradiated mice in 10 weeks.(table 3)

Further on in irradiated mice the number of animals with skin cancer was greater than in unirradiated ones. The administration of BS in unirradiated mice was more efficient than in irradiated ones. Thus 18 weeks after beginning the DMBA application in I group were 14 cancer, in II - 8, in III - 28 and in IV - 16. Further on this difference remains. But at the end of the experiment the skin cancers appeared in all survived animals.

Discussion

The adaptive possibilities of the organism after low doses of ionizing irradiation are disturbed. This is confirmed by the diminution of adaptive possibilities of enterocytes to functional tests (loading) of the digestive tract with easy assimilated carbo-hydrates and by speeding up of malignant tumors appearance after carcinogens application. About cancer risk increase in persons irradiated at low doses of ionizing irradiation has related J.Gofman [3].

The immunomodulating treatment with BS in previously irradiated animals at low doses is less pronounced. In unirradiated mice the administration of BS resulted in a considerable increase of antitumoral resistance of the organism which was expressed in a latest appearance of malignant tumors. In irradiated ones this action of BS was less. The stimulating action of BS on adaptive possibilities of enterocytes after application of diet containing easy assimilated carbo-hydrates was diminished as well.

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THE BIOLOGICAL EFFECTS OF LOW DOSES OF IONIZING RADIATION: CHERNOBYL NUCLEAR ACCIDENT AND SPREADING OF HEMOBLASTOSES IN MOLDOVA

G. Bulbuc, I. Corcimaru, I. Bahnarel, A. Buzdugan, V. Holban, O. Bragoi, S. Garaev

Oncological Institute of Moldova, Chisinau, Moldova

XA9745624

Abstract

The study of morbidity by hematologic neoplasms before and after the Chernobyl Nuclear Accident in regions of Moldova differently affected by radiation and some immuno-metabolic disturbances in people from these regions was the object of the present work.

An increase of standardized (world) incidence of hemoblastoses during the 10 years after the Accident, especially in children under 10 years old and in persons over 60 years old, was registered. A decrease of immunologic indices and the alterations of the amino acids content in blood serum and erythrocytes of healthy persons from the regions with higher radioactive impact after the Accident were established as well. A possible correlation between mentioned modifications are discussed.

The exposure of a lot of persons to long-term external and internal radiation, as well as relatively small doses of different radio-nuclides (iodine, caesium, strontium and others) as a result of Chernobyl nuclear accident (26.04.96) motivate the assessment of carcinogenic risks and disorders of the reactivity of the organism in inhabitants from the differently affected by radiation territories. The first results of the accident impact on human health were related [I,2].

The study of some immuno-metabolic disturbances in people from certain regions of Moldova and spreading of hemoblastoses in these regions before and after the accident was the object of the present work.

Materials and methods

The highest background radiation levels found during the first days after the accident were registered in the eastern and northern districts of Moldova. During the period from 29 April 1986 to 9 May 1986, average values on the territory of Moldova ranged from 60 μR/h to 100 μR/h.

The same features of food-stuff radioactive contamination and radioactive pollution of environment objects was registered as well.

Continuous study of morbidity by hematologic neoplasms was realized throughout the country. Information of patients is based on complex examination of medical documentation, concerning data about the patient's addresses for medical assistance and causes of death. In all cases the diagnosis was confirmed morphologically. All patients were treated in the National Hematological Centre.

The quantitative and qualitative amino acids analysis in blood serum and erythrocytes was performed by the ion changing chromatography at ionites with amino acid analyzator AAA-339 (Chehia). The obtained results were settled accounts by means of special formulas at computer. The amount of blood T-lymphocytes was estimated by our modification of method [3], the seric immunoglobulines - by Mancini method.

Results

Because of the insufficient number of persons investigated concerning the immune tests and amino acids content in blood serum and erythrocytes from some mentioned regions the data from the regions with radioactive level >80 μR/h and <80 μR/h during the period 29 April - 9 May 1986 were evaluated. Immunologic assessments of apparently healthy contingents of population from the mentioned region have established a difference of immune functions in investigated persons (table I). In people from the first region (high level) the amount of blood T-lymphocytes spontaneously established and maximum traced out and of seric IgG were smaller than from the second region.

Table I. The immunological indices in blood of donors from different regions of Moldova

Test	Region		P
	North - East	Center - South	
T_{spont}(%)	49.6±1.0	58.0±1.8	<0.02
T_{max} (%)	53.0±1.0	64.0±1.6	<0.01
IgA(mg/ml)	1.6±0.1	1.5±0.1	>0.05
IgM (mg/ml)	0.9±0.1	0.8±0.1	>0.05
IgG (mg/ml)	1.4±1.1	10.7±0.4	<0.01

In blood serum of investigated persons from the first region the amount of taurine, proline, leucine, ornithine, ethanolamine and α-aminobutyric acid was greater than in those from the second region. The amount of phenylalanine and γ-aminobutyric acid, on the contrary, in persons from the second regions was greater. In erythrocytes of these persons (from the second region) the amount of citruline,ornithine, α-aminobutyric acid and urea was greater than in those from the first region.

An increase of the standardized (world) incidence of hemoblastoses during the 10 years after the accident in comparison with the same period before the accident was registered both in males and in females (table 2). The most considerable increase of morbidity by hematologic neoplasms was established in age-groups under 10 years old and over 60 years old. Thus in males 0-9 years old the standardized incidence of hemoblastoses after accident in comparison with the indices before the accident in the Ist region was by 2.6, in II - by 2.5, in III - by 2.1 and in IV - by 1.9 times higher. In females the increase of indices was accordingly by 2.2, 2.2, 1.4 and 1.1 times. In persons over 60 years old the correlation of morbidity increase with radioactive fund and radioactive pollution during first 10 days after accident was less pronounced.

Table 2. The standardized incidence per year of hemoblastoses in different regions of Moldova before and after Chernobyl nuclear accident

The radioactive fund during first days after accident (μR/h)	Males (per 100000)		Females (per 100000)	
	1976 - 1985	1986 - 1995	1976 - 1985	1986 - 1995
>100	9.0	12.4	5.1	8.2
80 - 100	10.9	13.2	6.2	8.9
60 - 80	9.2	12.1	6.0	8.6
<60	8.9	12.1	7.2	8.6

Discussion

The decrease of immunologic indices in healthy persons from the regions with higher radioactive impact after Chernobyl Nuclear Accident may facilitate the occurrence of hematologic neoplasms in persons of advanced age. But the increase of morbidity in children under 10 years old could be influenced by other factors as well, particularly by radiation impact on genetic mechanisms.

The alteration of the amino acids content in blood serum and erythrocytes of apparently healthy persons from the regions more intensely affected by radiation are typical of patients with degenerative diseases. These modifications may appear because of harmful action of some carcinogenic agents, inclusively, of low doses of radiation.

The increase of morbidity by hematologic neoplasms during the mentioned period among the population of Moldova may be tied not only by radiation impact but also by concomitant action of much more harmful factors.

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Estimation of health effects of long-term chronic exposure of the low level radiation among children exposed in consequence of the disaster at the Chernobyl nuclear power plant

E. I. Bomko, A. E. Romanenko, A. A. Bomko

Scientific Centre for Radiation Medicine, Academy of Medical Science of Ukraine
Address: 53, Melnikov St., 252051, Kiev, Ukraine

Abstract

The low level dose effects have been studied for a long time within a framework of biological effects of radiation exposure. The estimation of the dose level of Ukrainian people who have been exposed in consequence of the Chernobyl accident allowed to consider that one of the critical populations which had been exposed to the low level radiation were children residing on the areas contaminated with radionuclides.

The purpose of this work is – to reveal a regularity in morbidity and mortality of the critical populations having been exposed to long-term chronic exposure of the low level doses of radiation in consequence of the Chernobyl accident.

The prospective cohort investigation was organised. Total amount of the children was 12000 persons born in 1972-1986 (0-14 years old at the moment of the accident). The cohort consists of four subcohorts. Each of the samples has specific level of the individual dose accumulated for 10 years and different character of exposition (chronic or acute exposure). The results of the profound medical examinations of the selected people were analysed. The accumulated morbidity, frequency of a new incidents, their weight comparatively to the total amount of the diseases, the risk indexes were estimated.

It was revealed that:

- There were not any differences in morbidity distributions (by range) of the subcohorts with different levels of the average accumulated doses.
- The subcohort with the highest level of the average accumulated dose and a subcohort of the evacuated from 30-km zone had a higher morbidity indexes than another ones.
- The biggest amount of the cases of "Endocrine system diseases" were revealed during several first year after the accident and then the amount of the newly revealed cases were decreasing from year to year.
- The frequency of the cases of blood diseases were increasing during the period of the investigation.
- The subcohort 2 had the highest value of the attributive risk in such classes of the diseases as "Blood and hemopoietic organs diseases", "Mental disorders".

To make knowledge about health effects of the low level doses of radiation more precise it is necessary to follow up the selected people and their descendants during 30-50 years and also the personal doses should be known.

The obtained data will be added to our knowledge about the health status of civil people exposed to the low level radiation in consequence of their residing in zone of a nuclear accident.

Key words: the Chernobyl accident, children, chronic exposition to low level radiation.

Existing works on estimation of the population dose level [1-3] allow to consider that those of Ukrainian child population who are residing on the areas contaminated with radionuclides in consequence of the Chernobyl accident are being exposed to long-term chronic exposure of the low level radiation.

The purpose of this work is – to reveal a regularity in morbidity and mortality of the critical populations having been exposed to long-term chronic exposure of the low level doses of radiation in consequence of the Chernobyl accident.

The prospective cohort investigation was organised. Total amount of the children was 12000 persons born in 1972-1986 (0-14 years old at the time of the accident). The cohort was divided into four subcohorts. The subcohorts 2, 3, 4 correspond to the residents of areas with different level of the radioactive contamination. The areas is officially named zone 2, 3, 4 in Ukrainian law "About the status and social protection of citizens suffered in consequence of the accident at the Chernobyl nuclear power plant" [4, 5]. The subcohort 1 corresponds to the evacuated from 30-km zone (excepting town Prypiat) because they were exposed to the acute dose of radiation (some of them lived in 30-km zone after the accident up to 10 days). Average individual doses accumulated for 10 years were calculated by the Dosimetry department of NCRM for each populated area.

Distribution of the children with corresponding doses inside the cohort is presented in Table I.

Table I. The cohort of person born in 1972-1986 (0-14 years old at the moment of the accident) in 10 years after the accident and corresponding doses.

Zone (subcohort)	Level of contamination, kBq/m^2	Number children in the study	Dose range, mSv	Collective dose, person-Sv
2	555	1000	50	55
3	185 - 555	5436	10-50	106
4	185	3713	10	55
1 (the evacuated from 30-km zone excepting town Prypiat)	<37	1800	2-120	
Total		11949		

The subcohorts are distinguished by levels of the average individual doses and levels of the soil contamination of the residence and by the character of exposition. Interference were minimised:

- the cohort consists of children 0-14 years old at the moment of the accident;
- the children live in the countryside of the same administrative and ethnic region;
- the cohort is homogeneous in sex distribution 51-52%% – boys, 48-49%% – girls.

It was noticed that members of the subcohorts having the highest dose of Cs have the highest thyroid dose. Every year some children achieve age of 14 year old and leave the cohort.

The results of annual profound medical examinations of the cohort members were analysed.

Comparative estimations of the morbidity in the subcohorts were carried out by first revealed cases of the chronic diseases having occurred after the accident. Some indexes of the morbidity (absolute increment, rate of increment, rate of growth, weight of first revealed diseases, risks) were calculated and grouped into time series. Reliable difference was checked with chi-square method.

The accumulated morbidity was estimated in two ways:

- frequency of a newly revealed cases per 100000 person-year;
- morbidity accumulated from the moment of the accident (the moment of exposition) to a moment of revealing of case per 1000 person-year.

It was revealed that distribution of the somatic morbidity accumulated for 10 years was identical for all zones, which are different in levels of the soil contamination and levels of the average individual accumulated doses. And that morbidity distribution didn't differ from all-Ukrainian one. But it should be pointed that tendency of increasing of morbidity index for class "Neoplasms" among children evacuated from town Prypiat was revealed in our previous investigation [4, 5].

Figure 1 shows charts of the morbidity indexes calculated by newly revealed cases from the time of exposition to the moment of revealing per 1000 person-year.

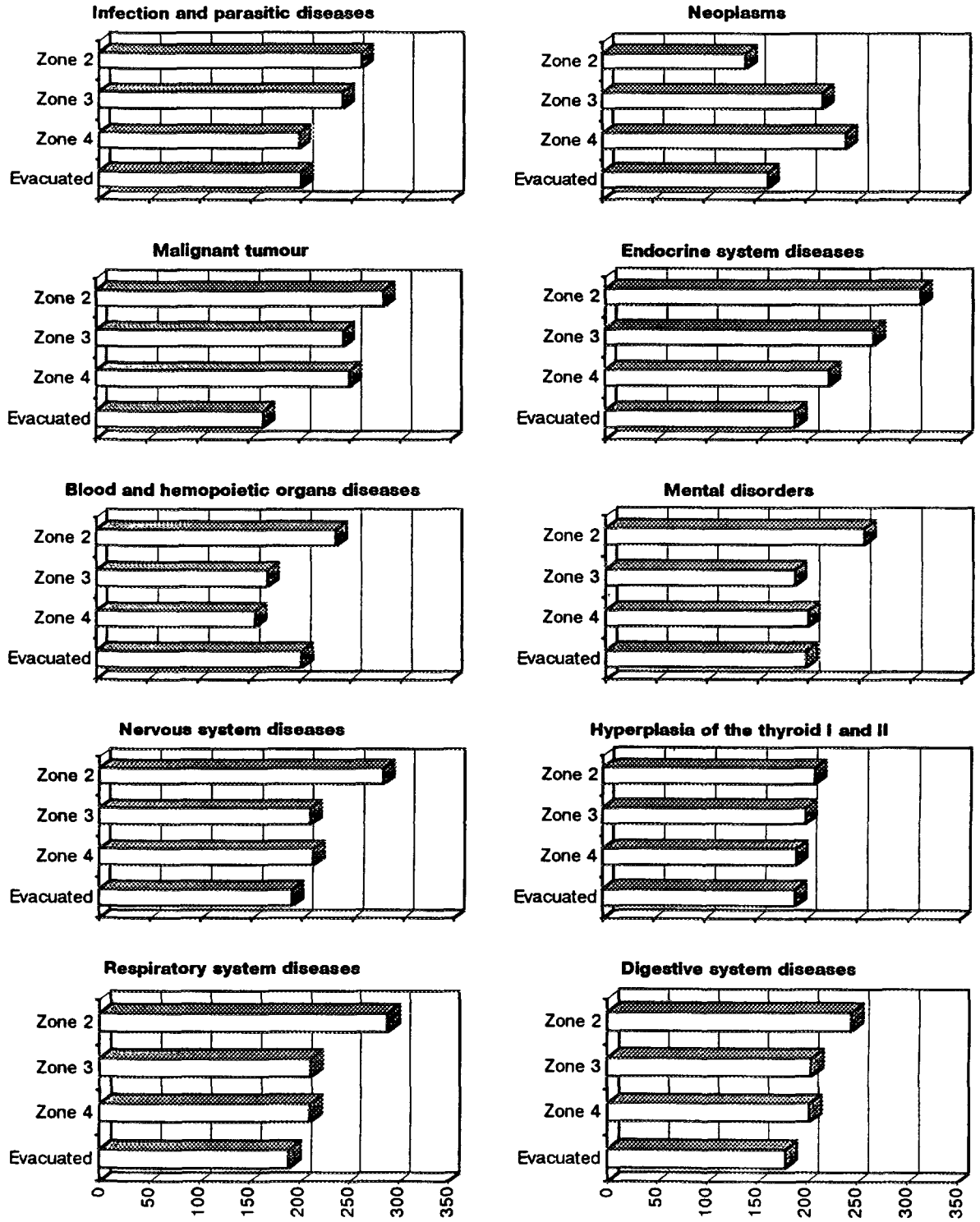

Figure 1. Charts of the morbidity frequencies of the newly revealed cases from the moment of the exposition to the moment of revealing (10 year term) for the cohort of person born in 1972-1986.

It was revealed that the indexes of subcohort 2 were higher than ones in subcohorts 1, 3, 4. Also endocrine system's pathology had the highest value of the weight of first revealed cases comparatively to the total amount of the diseases in 1987-88 and then the weight value was decreasing. The weight of first revealed cases of the blood and hemopoietic organs diseases are increasing from year to year up to 1993.

Attributive risk calculations showed that the highest risk for subcohort 2 in comparison with subcohort 4 corresponded to "Blood and hemopoietic organs diseases" and "Mental disorders".

The absolute mortality values are following. 8 children of the cohort living on the contaminated areas (the subcohorts 2, 3, 4) died in 1988-1995 (source: data base of National Register of Ukraine of people who have been exposed in consequence the Chernobyl accident). Distribution of cases of mortality by causes of death: 3 cases of malignant blood diseases (zone 3); 2 cases of respiratory system diseases; 1 case of infection; 1 case of innate malformations of heart and blood circulation system; 1 case of traumas and poisonings. In the subcohort of the evacuated 5 children died. 2 cases of nervous system diseases; 2 cases of traumas and poisonings; 1 case of blood circulation system diseases.

Conclusions:

1. People residing on the areas contaminated with radionuclides in consequence of the Chernobyl disaster are being exposed to long-term chronic exposure of low level doses of radiation.
2. About a subcohort of children born in 1972-1986, residing on the areas with level of contamination $\geq$555kBq/m^2, who has 50mSv of average accumulated individual dose of external and internal exposure we can say that:
   - a reliable increasing of frequency of first revealed cases of "Blood and hemopoietic organs diseases", "Mental disorders", "Digestive system diseases" was brought out;
   - a high level of the weight of endocrine system diseases was in 1987-1988 and it was decreasing later;
   - the weight of newly revealed cases of "Blood and hemopoietic organs diseases" was growing during first 6 years after the accident;
   - during first 10 years after the accident the highest risk (excepting thyroid cancer) corresponds to non-tumour blood and hemopoietic organs diseases and mental disorders.
3. There are no differences in distribution of the accumulated morbidity between the zones with different levels of the soil contamination and average age individual accumulated dose.

We can say about an influence of a group of "the Chernobyl factors", including those which are measures intended to decrease level of radiation effects. For example: It's prohibited to eat a local food-stuffs for the residents of zone 2 (it corresponds to subcohort 2 of this investigation) because of the radioactive contamination of the soil. And those mostly peasant people can't use resources produced by themselves and they are forced to eat bought food. It means that children are limited in fresh natural food and spend a lot of time indoor in monotony of school or kindergarten collectives. So they are in stress for a long time and so on.

To make knowledge about health effects of the low level radiation exposure more precise it is necessary to follow up the selected people and their descendants during 30-50 years and also the personal doses should be known.

The obtained data will be added to our knowledge about the health status of the civil people exposed to the long-term chronic exposition of the low level radiation in consequence of their residing in zone of a nuclear accident.

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XA9745626

REDUCCION DE LAS DOSIS EN EL AMBIENTE DEL IPEN-CNEN/SP

D. L. Rodrigues; M.P.Sanches; G.M.A . A .Sordi.

Instituto de Pesquisas Energéticas e Nucleares - IPEN-CNEN/SP
Travessa R, 400, Butantã, CEP 05508-900, São Paulo, SP, Brasil

RESUMEN

Un trabajo(1) reciente presentó que los niveles de dosis en las vías de circulación del IPEN-CNEN/SP estan arriba de los niveles de dosis para indivíduos del público y segun la legislación brasileña todos los servidores del IPEN-CNEN/SP deberian recibir un adicional de insalubridad de 10% del salário base, además de vacaciones de 20 dias por semestre y jubilación especial después de cumplir 25 años de trabajo.
En el presente trabajo se muestra el estudio realizado para mejorar las condiciones radiológicas de las principales instalaciones que más contribuyem para los niveles de dosis actuales, bien como los costos necesarios para reducir los niveles de dosis abajo de los indivíduos del público. Se hace una comparación entre el costo para la mejoría de las instalaciones y el costo estimado relativo para la concesión del adicional de insalubridad.

INTRODUCCION

Fue hecho un estudio para estimar los niveles de dosis debido a la radiación electromagnética en diferentes puntos de localizaciones dentro del IPEN-CNEN/SP, consideradas como áreas libres, com la finalidad de determinar el background del nivel de dosis. Este estudio fue hecho con el uso de TLD's distribuidos en 29 puntos dentro del IPEN-CNEN/SP, como muestra la figura 1. Las medidas en los 29 puntos seleccionados fueron hechas durante los años de 1993, 1994,1995 y 1996, siendo que los TLD's eran cambiados a cada tres meses. La menor tasa de dosis fue obtenida junto al contador de cuerpo entero y fue de 42 nGy/h. En los demás 28 puntos, la menor y la mayor tasa de dosis fueron de 69 nGy/h y 175 μGy/h respectivamente. Las instalaciones que más contribuyen para estes niveles de dosis son las instalaciones de gestión de residuos radioactivos, el acelerador ciclotron, el irradiador de gran porte y la instalación de producción de radioisótopos.

DISCUSION E CONCLUSIONES

De acuerdo con la legislación brasileña toda persona que estuviere sujeta a la dosis de radiación ionizante arriba del limite para indivíduos del público, durante el desarrollo de sus atribuciones, deberá recibir un adicional de insalubridad de 10% del salário base, además de vacaciones de 20 dias por semestre y jubilación especial después de cumplir 25 años de trabajo. Siendo asin el IPEN-CNEN/SP nos solicitó que hiciésemos un estudio para la implementaçión de mejorias en las instalaciones com la finalidad de reducir los niveles de dosis abajo del limite para el público.
Después de una série de investigaciones y con base en los cálculos se llegó a la conclusión que sería necesario hacer una intervención en las instalaciones, arriba citadas,

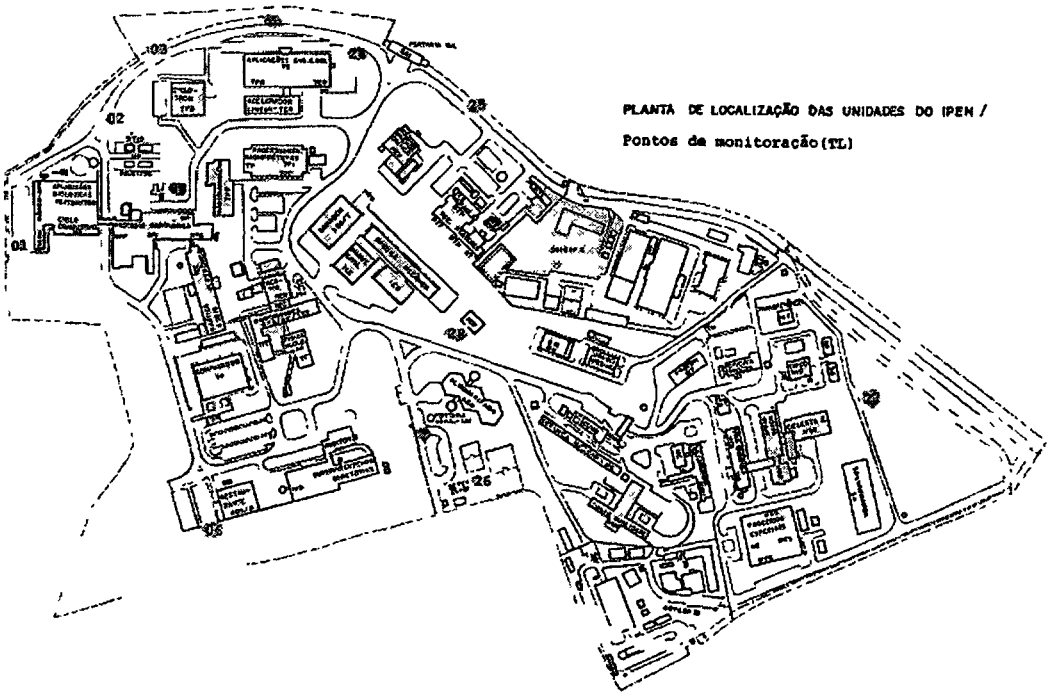

Figura 1: Localização dos Pontos medidos no IPEN-CNEN/SP .

para hacer con que las actividades desarrolladas en ellas se adecuasem de tal manera a cumplir com los limites de dosis para el público. Para esta adecuación sería necesario interrumpir parcialmente las actividades en tales instalaciones com la finalidad de posibilitar las obras necesarias para la reducción de las dosis, siendo necesario para esto invrstir cerca de US$ 800.000,00 para la implementación de las mejorías.

Por otro lado, si no fueren implementadas estas mejorias el IPEN-CNEN/SP tendria que arcar com ciertos encargos tales como pagar el adicional de insalubridad para aproximadamente 500 personas, además de otras ventajas instituídas por la legislación brasileña. Considerando el salário base promedio, recibido por cada trabajador, de US$ 400/mes y que 500 personas tiene derecho a los benefícios concedidos por la legislación, el IPEN-CNEN/SP tendria que arcar anualmente, solamente en salários, com cerca de US$ 260.000,00. Desde este punto de vista, analisando el costo para la implementación de las mejorias, la depreciación referente a la inversión de fondos sería cubierta por medio del valor relativo a tres años de benefícios que deberiam ser concedidos a los trabajadores.

Con la implementación de las mejorias, reduciríamos las dosis en las vías de circulación del IPEN-CNEN/SP, a valores inferiores a los limites para indivíduos del público y con esto evitaríamos gastos con concesiones de benefícios a estes trabajadores.

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ESTIMATION OF HEALTH IN CHERNOBYL NPP ACCIDENT CONSEQUENCES CLEANING-UP PARTICIPANTS

Bebeshko V.G., Kovalenko A.N., Chomazjuk I.N., Klimenko V.I., ChumakA.A., Njagy A.I., Cheban A.K., Jakimenko D.M., Ovsjannikova L.M., Belyi D.A., SushkoV.A., Nosovsky A.V., Ljashenko L.A.
Scientific Center for Radiation Medicine, Kiev, Ukraine

Abstract. Over 11 years period of health observation of Chernobyl Accident's victims permites to make some conclusions. Quantitative changes of peripheral blood and bone marrow cells, changes in ultrastructural organization of hemopoietic cells, disturbance of proliferative activity of hemopoietic and stromal progenitor cells in clean-up workers testify to alterations of functional properties of hemopoiesis. There are high level of T- helpers, early appearance regenerated T-cells, which simultaneously express surface antigens of helpers and supressors, synchronization of proliferative cycle of immunocompetentive cells in these patients. Oppressing of antioxidant protection, stable changes of hormonal maintenance of adoptation and reproduction processes, disturbance of feedback mechanizm between effector glands and hypophysis, significant rise of polyamines were determined. Cardiovascular diseases are the principal cause of health disruptions at victims. Neural and psychological diseases, suicidal cases, trauma, death in automobil accidents are rank second and third in structure of morbidity. In structure of chronic nonspecific pulmonary diseases dominated chronic obstructive bronchitis.The adrenergic tonus of vegetative nervous system was seen. The peculiarity of rehabilitation measures is complexness and continuity in-patients, out-patients service and providing facilities in health resorts.

Over 11 years period of health observation of persons who took part in elimination of consequences of Chernobyl Accident permites to make some conclusions. Ionizing radiation as known alterates various organs. Hemopoietic system is one of the most radiosensitive. As a result of long-term observation we discovered some changes in blood system of victims. No significant differences in indices of peripheral blood and bone marrow of clean-workers, who were irradiated in doses from 0,25 to 1 Zv, in comparison with control in the majority of cases were seen. However, hypercellularity was determined more often than in patients with acute radiation sickness. Blood circulation change and affection of vascular system in majority of trepanobiopsy cases are typical. Quantitative changes of peripheral blood and bone marrow cells, changes in ultrastructural organization of hemopoietic cells, disturbance of proliferative activity of hemopoietic and stromal progenitor cells in clean-up workers 1986-1987 years testify to alterations of functional properties of hemopoiesis. Cultural investigations have shown that no significant differences in colonyformation in the majority of cases in clean-up workers. However, the predominance of eosinophilic and eosinophilic-neutrophilic colonies in culture of 40% of the examined patients was observed as well.

Among clean-up workers disturbance in immune system is more significant than in nonirradiated patients with same pathology or in healthy people with same doses of irradiation. Signs of radioresistance were determined. There are high level of T- helpers, early appearance regenerated T-cells in blood cannel, which simultaneously express surface antigens of helpers and supressors (CD 4+, CD 8+),

synchronization of proliferative cycle of immunocompetentive cells and also presence of main complex of histocompatibility in phenotype in these patients.

Oppressing of antioxidant protection and intesification of processes of lipid peroxidation was determined. Conceptual scheme of metabolic affections of different system in irradiated organism was elaborated.

Stable changes of hormonal maintenance of adoptation and reproduction processes, disturbance of mechanizm of feedback between effector glands and hypophysis, significant rise of polyamines in blood like markers of probability of cancer, athe-rogenic changes of lipid exchange (in half of clean-up workers) were determined.

Long-term monitoring of different parameters of blood circulation system testify that during the whole period after the catastrophe cardiovascular diseases are the principal cause of health disruptions at victims. They are rank first in structure of morbility and mortality (in 30 % of victims) and prevailed over two times in comparison with diseases of organs of digestion and nervous system.

Neural and psychological diseases are rank second and third in structure of morbidity. Combined influence of factors: the radiation, the chronic psychological stress and sickness of population was established. Vegetative dystonia, disturbance of blood circulation in brain and spinal marrow resulting in discirculating encephalopathy and consiquences of small and large hearth insults, nevrological manifistation of bone-muscular paroxysms, neurosis and neurosis-like state were registrated 2-5 times more in patients with doses more than 0,25 Zv. Disturbance of all regulating compartments of vegetative nervous system with predominance of mix visceropathy was determined. In structure of chronic nonspecific pulmonary diseases dominated chronic obstructive bronchitis(80%). Atrophic and catarrhal-sclerotic changes of bronchi's mucous membrane, fibrous-sclerotic changes of lungs with development of obstructive bronchitis and breathing deficiency were observed in clean-up workers 1986-1987 years because of significant inhalation influence of radionuclides. Reliable rise of flat-cellular methaplasia of epithelium with cellular bronchi's atypical characteristics was noted. There is carcinoma in situ in some cases. Frequency of erosive-ulcerated and chronic inflammation of mucous membraneof gastrointestinal tract on the bases of atrophic and hyperplastic processes and significant changes of vegetative status of organism was grown. The adrenergic (sympathetic) tonus of vegetative nervous system instead of cholinergic which inherents in nonirradiated peptic ulcer patients was seen. Results of atropin's test testify to lowering of cholinergic link in pathogenesis of peptic ulcer in 27% clean-up workers with atropinresistant type of secretary reaction (sympaticotony).

We had analysed pathohystological samples of 441 clean-up workers who worked long time at the Chernobyl Nuclear Station and inhabitants of Slavutich.These patients died during 10 after catastrophe. Principal cause of death were diseases of cardiovascular system (35%), basically young persons (31-40 years). It is arouse alarm increase the frequency of suicidal cases (23,08%), trauma (10,66%), automobil accidents because of alcoholism (11,54%).

System of rehabilitation measures was established and improved during post-Chernobyl period of time. The peculiarity of this system is complexness and continuity in-patients, out-patients service and providing facilities in health resorts.

On the stage of hospital service, depending on health and specific diseases of clean-up workers, different combinations of medicines with radioprotective, disintoxicated, membranoprotected, immunomodulated, angioprotected, metabolic and other effects were used. Side by side with them methods of physical and psychoso-

matic rehabilitations, physical therapy aid and methods of nontraditional medicine were used as well.

On the stage of out-patient's service attention was concentrated on supporting therapy, including necessary medicines, physical-balneologic therapy, massage, therapeutic physical training.

Sanatoria's and health resort's stage provides for using of complex of natural climatic factors and nonmedicinal methods of treatment directed on rise of defence activity and nonspecific resistance of organism. Special programmes for improvement and recovery of state in patients with cardiovascular, bronchopulmonal, gastrointestinal, hematoimmune, nervous and for correction of psychoneurological status were proposed side by side with common programme of rehabilitation of victims.

CLINICAL EFFECTS OF CHRONIC LOW DOSES IRRADIATION (11 YEARS AFTER CHERNOBYL ACCIDENT)

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Romanenko A. Y. , Bebeshko V.G.
Scientific Center for Radiation Medicine, Kiev, Ukraine

Abstract. Estimation of clinical effects of influence low doses of irradiation as the result of the Chernobyl accident on the human organizm is presented in this report. The results of the investigations are concerning to changings in different organs and systems of inhabitans of the contamination territories and among clean-up workers. Increasing of morbidity of digestive and nervous systems is notified. Increase of thyroid cancer, chronic thyroidities and hypothyreouses is registed in clean-up workers in dynamic observation. Highly morbidity of bronchopulmonal system and blood circulation system is revealed. High level of compensative and adaptative reactions of immune and hemopoietic systems is notified. Excesses of leukemias and lymphomas in inhabitans of the contamination territories is not demostrated but tendency for increasing quantity cases of oncohematological diseases (leukemias, lymphomas, MDS) among clean-up workers IV-VII 1986 are absent. A dynamic of health state of children injured as a result of Chernobyl accident is characterized with continues negative tendencies.

The total disregulation syndrome (i.e. primary forming of functional declinations on the level of many physiological systems of organism and development of pre-nozological states with transfer to clinical nozology later) is developed due to distabilisation of functional systems activity of an organism at the different levels its integration in personal deficiency of reparative and compensative process in some personals who have been exposed with ionizing radiation in small doses and others accompanied factors of Chernobyl accident (chemical substances and stress).

The primary and initiative disturbances of regulative systems (central nervous, vegetative and hormonal-humoral systems) lie in a fundamental of increasing volume of functional clinations in different organs and tissues of many persons at least measure in region of doses from 0.25 to 1 Gy.

The generalize analysis of the data received from more than 120000 persons irradiated in low doses area is notified the highly morbidity of the all organs and systems in comparison with persons with acute radiation syndrome of 1 and 2 degree. Possibly this fact is connected with forming higher level of trouble among this group patients that undoubtedly has influenced on development chronic disstress and in connecting with it enhancing erosive and ulcerous processes in digestive system last 2-3 years.

Analogical type of frequency arrangements is notified under development of declinations of respiratory system.

First of all it is necessary to study the forming and evolution of changes in the different organs and systems among injureds in dynamic for period after Chernobyl accident.

Characterizing epidemiological situation concerning to development diseases of a blood circulation system should be attracted attention to high expansion of risk factors of this diseases. The risk factors are found out for 78.4% clean-up workers including that for 23.1% there was more than three. For considered ten factors it was prevailing the hereditary predilection, hypertension, cholesteremia, smoking, use alcohol and age.

The reason of 60% cases of deaths is the diseases of blood circulation system render strong influence on the health state of liquidators of consequences of accident and population.

In sphere of medical consequences of the accident the mental-nervous disorders are serios and significant problem.

Last years in spite of decreasing of a frequency of vegetovascular dystonies stability of vegetative disturbances and polymorphism their appearances have been following up definitely and also a tendency to development stability states in view discirculative encephalopathies, paroxysmal forms of vegeto-vascular dystonies and transfer mental-physiological disturbances into psychosomatics.

A development of psychosomatic diseases in persons, suffered as a result of Chernobyl accident, happens with obligated participation of disturbances nonspecific mechanisms of endocrine regulation of adopting system.

Thyroid occupies special place in estimation of medical consiquences of Chernobyl accident.From 1993 it is observed growth expansion of thyroid cancer among adults who are related to cathegories enhancing thyroid risk. It consists of 6.8 cases per 10000 population among evacuated persons from 30-km zone and liquidators of consequences of accident in Chernobyl in April-May 1986. The growth of expension chronic thyroidities and hypothyreouses is notified.

Dynamic observation for a state of immune system evidents of safety humoral link of immunity in general.In this case express individual and temporal violations in concentration of some classes of immunoglobulins it is noted. General types of changings are characterized by being of realized dysplatic, dysregulating syndromes or compensated radiation influence.A compensation of radiation influence is appear in normal expression of differential antigens and in volume of general subpopulations T- and B- lymphocytes. The pointed immunological behaviour is jointed with high expresion of differential CD45 antigen on the lymphocytes and cells of granulocytic number.

As a rule, hematologic effects as the result of influence of low doses for the long temporal period are feebly expressed. Only some persons exposed of irradiation have ones. Hematologic effects appear in qualitative and quantitative changes of hemopoiesis elements although the quantitative indexes of blood are fluctuated in physiological bounds.

High compensative and adaptative posibilities of hemopoietic system are able to demonstrate on decay time of qualitative changings in neutrophiles, lymphocytes, thrombocytes as both in liquidators of consequences of accident in region of doses from 0.25 to 1 Gy as in population living on contamination territories. However, function of cell-predecessors of a hemopoiesis does not reconstruct completely after 11 years from the accident even at full reconstruction their morphological structures especially among the persons of higher radiation risk from the point of view of oncohematology pathology. This fact is a base for appearance in their wrong reply on the influence hemopoietic growth factors.

Dynamic observation for the distribution of leukemias and lymphomas among children and adult population for period after Chernobyl accident is not excited their increase. Although among clean-up workers IV-VII 1986 from 800 m zone in the region of NPP is marked the tendency for increasing of radioinducence oncohematology pathology (leukemias, lymphomas, MDS).

In general, at the comparison of dynamics of changing expansion of general classes of diseases in injureds as a result of Chernobyl accident for period 1986-1996 and analogous data on Ukraine it can noted the authentic increase diseases of digestive and nervous systems.

A dynamic of health changing of children living on the contamination territories for the pointed period is characterized with continues negative tendencies. A percentage children in good health is decreased from 27% in 1986-1987 years to 8% in 1996 and a quantity of children with chronic diseases increases.

At present integral characteristic of the health state of clean-up workers children is few distinguished from control group on the analogous indexes. At the same time increase hematological diseases at the expense of anemias, agranulocytosis, increase of lymphonoduses, nasal hemorrage is notified. Allergic component is the base of chronic inflammation of nasopharynx and respiratory diseases. Mental status of children is decreased at the expense of disorders in perclive sphere. Intellectual and reproductive functions are developed all the better in comparison with control group. It is pointed on the necessary experiences of using ready algorhythms. This dissociation in the health indexes is pointed on the necessary of analytic analyses of qualitative variations of health in clean-up workers with definite doses of irradiation children.

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LEUKEMIAS AND LYMPHOMAS IN UKRAINE POPULATION EXPOSED TO CHRONIC LOW DOSE IRRADIATION

V.G.Bebeshko, E.M.Bruslova, V.I.Klimenko, I.S.Dyagil, V.D.Drozdova
Research Center for Radiation Medicine, Kiev, Ukraine

ABSTRACT. Data about 951 cases of leukemiae and lymphomas appeared at pre- and postaccident period among adult and children population of Kiev and Zhitomir oblasts (regions) is represented in the paper totally for period of 1980-1996. Assessment of cases of diseases has been conducted among inhabitants of controlled areas in oblasts mentioned above with soil contamination with Cs-134 within 1-15 Ci/sq.km and above. Efficient irradiation dose of leukemiae patients deviated within 0.15-15.0 cSv. For period mentioned above analysis of data obtained did not reveal any excessive cases of leukemiae and lymphomas among children and adults residing on territories of radiological control in Kiev and Zhitomir oblasts, and they are similar. Meanwhile, we should point out change in pathomorphosis of the disease with excess of cases of leukemiae with aunfavourable course.

The Chernobyl accident caused number of problems. The most actual among them are issues of assessment of instant and delayed radiobiological effects. Human haemopoietic and lymphoid systems are the most radiosensitive and represent particular indicator of severity of affection of human organism by ionizing irradiation. Preliminary studies have shown that risk of development of acute leukemiae appears mostly at individuals having received high dose loadings (above 100 cSv). Meanwhile, there is some data available about excess of frequency of separate types of leukemiae under influence of ionizing irradiation in doses of up to 50 cSv. Nowadays direct dependence has been proven for development of chronic and acute myeloid leukemia from bone marrow dose. Basic modifying factors have been explained. Data about leukemiae and lymphomas morbidity of population of Zhitomir and Kiev oblasts is represented in the paper totally for period of 1980-1996 and also cases of leukemiae at inhabitants of contaminated areas in these oblasts, where levels of soil contamination with Cs-134 and Cs-137 deviated within 1-15 Ci/sq.km and more. Efficient irradiation dose for leukemiae patients was within 0.15-15.0 cSv. Sex and age indices, structure of leukemiae before and after the Chernobyl NPP accident were estimated. Verification of leukemiae and lymphomas was conducted in haematological and oncological hospital units in appropriate oblasts and the Institutes for Clinical Radiology, Haematology and Oncology. Diagnostics of diseases was based on assessment of clinical symptomatics, investigation of periphery blood, bone marrow with subsequent morphological, cytochemical and immunological identification of blast elements. Data was obtained about 951 cases of leukemiae and lymphomas at population of Kiev and Zhitomir oblasts totally for 1980-1996. At adult population at preaccident period of 1980-1985 (number of population was 2 905 800) 147 cases of leukemiae and lymphomas were revealed: acute myeloleukemia consisted 29.4%; chronic myeloleukemia - 3.4%; chronic lympholeukemia - 25.8%; myeloma - 8.8%; malignant lymphomas - 32.6%. For period of 1992-1996 at the same oblasts (number of population is 2 721 300) 294 cases of leukemiae and lymphomas were revealed: acute leukemia - 23.8%; chronic myeloleukemia - 5.2%; chronic lympholeukemia - 27.8%; myeloma - 9.6%; osteomyelofibrosis - 1.3%; polycytemia - 0.7%; malignant lymphomas - 31.6%. On territories of Kiev oblast contaminated with radionuclides for period of 1992-1996 from number of cases revealed acute leukemia was 25%; chronic myeloleukemia - 2.5%; malignant lymphoma - 40%; polycytemia - 2.5%; osteomyelofibrosis - 2.5%. In similar areas of Zhitomir oblast for period of 1992-1996 acute leukemia was 28.2%; chronic myeloleukemia - 5.9%; chronic lympholeukemia - 20%; osteomyelofibrosis - 4.7%; myeloma - 1.2%. Data obtained testify about excess of number of

malignant lymphomas. It should be pointed out that all the cases of chronic myeloleukemia and majority of malignant lymphomas were revealed at inhabitants of Ivankov raion (district) of Kiev oblast. During period of 1980-1996 on territory of Kiev oblast among children's population 289 cases of malignant diseases of blood system were verified (number of children's population is 435 000). Among children there were 47% of boys, 53% - girls. Different versions of acute lymphoblast leukemia (L1-L3) were established at 83%, myeloblast - 10%; lymphoma - 7% of children. Frequency of diagnostics of leukemiae among children of different age groups was practically similar: children, age below 3, consisted 32.6%, age 3-7 - 31.3%, at individuals of senior age - 36.1%. On territories of Zhitomir oblast for the same period (1980-1996) 187 children with leukemiae and lymphomas were revealed (number of children's population is 349 000). Distribution of patients taking into account sex, age and version of a disease was similar to Kiev oblast. Analysis of morbidity in Kiev and Zhitomir oblasts conducted for 5-years period before the accident and at subsequent first and second five years has not shown excess of number of leukemiae and lymphomas among children at first five postaccident years. Excessive cases of leukemiae were not revealed among children residing on territories contaminated with radionuclides in Kiev and Zhitomir oblasts for period of 1980-1996. Assessment of cases of leukemiae morbidity among children taking into account their age and sex peculiarities, versions of leukemiae and criteria of prognosis conducted in two intervals of 1976-1985 and 1986-1996 by method of interval assessment has shown that number of patients with standard risk group decreased and fraction of children with high risk group exceeded on account of girls, age 10-14. Analysis of data obtained testifies that nowadays among children and adults residing on territories of radioecological control in Kiev and Zhitomir oblasts excessive cases of leukemiae and lymphomas were not revealed. However, change of pathomorphosis of the disease takes place with tendency of excess of versions with unfavourable course.

BIOCHEMICAL AND CELLULAR MECHANISMS RESPONSIBLE FOR EFFECTS OF LOW DOSES OF IONIZING RADIATION

Trebukhina, R.V., Ovchinnikov, V.A., Lashak, L.K., Ledneva, I.O., Petushok,V.G., Petushok, N.E., Motylevich, Zh.V., Kazhyna, M.V.
Institute of Biochemistry National Academy of Sciences of Belarus, Grodno

Abstract - In experiments on white rats influence of small dozes of gamma-exposure on morphological structure of blood and activity of enzymes in blood and thimus was investigated. Short-term reduction of quantity of leucocytes and more long (1 month) reduction of erythrocytes was shown. Accumulation in blood of products of lipid peroxidation correlates with activity of oxidizing enzymes (catalase, lysozyme). Radiation-induced activation of pentose-phosphate pathway of carbohydrates metabolism was established.

The problem of biological effects of small dozes of radiation is one of most disputable. Long-term radioactive exposure in low dozes causes the special form of a radiating defeat. Typical is the slow development of pathologic processes [1]. Blood system as one of the most active proliferative tissue is very sensitive to action of ionising radiations [2]. At exposure in low dozes the expressed infringements in crates of blood can develop not at once. However in remote terms after exposure hematologic changes depends on time and doze of exposure[3]. The least investigated effect of low dozes of radiation on exchange processes is at chronic beam influence. The purpose of research - study biochemical and cellular of effects in blood of rats, subjected chronic gamma-exposure in low dozes.

The experiments was carried out on white rats (females) in weight 140-160 g. All animals were carried on common diet. Chronic exposure in dozes 0.25 Gy at once in week was three-divisible and was carried out on instalation AGAT-C (source of radiation - Co). Decapitation of rats was carried out through 1 hour, 1 day, 1 week and 1 month after 3-rd exposure. Hemogramme was defined on a standard technique. In plasma of blood the toxicity (on kysis of splenocytes), activity of catalase, lysozyme, immune complexes (IC) were determined. In blood the level of malonedialdehyde (MDA), acticity of glucose-6-phosphate dehydrogenase, transketolase and TDP-effect were measured. In thymocytes activity of acid and alkaline phosphatase was defined. The received data were processed statistically with use of Fisher-Student's criterion.

The most sensitive to radiation are the blood cells (Table I). The level of leucocytes already is reduced through 1 hour after exposure. It remains reduced within 24 hours. In the subsequent terms 7 and 30 days the amount of leucocytes restored up to normal values. The reduction of amount of erythrocytes came in a day and gradually reduce on extent of a month. To the end of a month the quantity of erythrocytes reduced by 37%. Endotoxemia in plasma of blood through 1 hour after 3-rd exposure reaches by 25%. IC through 1 hour were reduced by 30%, and trough 24 hours their amount in plasma authentically grows. Repeatedly their level was reduced in a month by 23%. The contents of MDA within the first hours after exposure raises in tissues (liver, brain). In blood the increase of MDA level comes only for 7-th days after the latter exposure by 28%, and in 30 days its level falls by 58%. The activity of all enzymes changes depending on terms of research. Activity of lysozyme and catalase raises through 24 hours after exposure. For 7-th days the lysozyme activity was authentically reduced, and to 30-th day comes back to norm. The activities of glucose-6-phosphate dehydrogenase and transketolase were reduced through 1 hour after exposure. In the subsequent terms the activities of these enzymes raises. The TDP-effect in blood raises through 1 hour and trough 7 days after exposure, that specifies on thiamine insufficiency in erythrocytes [4]. The weigh of thymus changes unsignificantly after exposure of rats by low-doze

irradiation. The activity of phosphatase in thymocytes varies one-directionly. Acid phosphatase in thymocytes was reduced through 1 hour by 24%. In the subsequent terms its activity gradually raises. In 1 month the activity of acid phosphatase was increased by 17%. The activity of alkaline phosphatase through 1 hour after exposure was reduced by 15% and in 30-th day increased by 13%.

Established by us changes of blood composition specify high sensitivity of leucocytes and erythrocytes to small dozes of radiation. Changes in concentration of leucocytes and erythrocytes after exposure mark by other authors too [5,6]. The authors consider that the mechanism of infringement of hemopoesis by radiation is connected with damage of cellular plasmatic membranes. Radiotoxines can change protein spectrum of blood and promote accumulation of toxic products in plasma[7]. Expressed endotoxemia was observed already through 1 hour after 3-rd exposure, and the synthesis of immunoglibulines accrues only through 24 hours. Strengthening og reactions of lipid peroxidation (POL) is one of the first attributes of action of radiation on organism [3]. However, increase of POL secondary products was at first marked in tissues, and in blood the appreciate increase MDA occurs only for 7-th day after exposure. The decrease of MDA level at 1-th hour after exposure is connected to activation of antioxidizing system of organism (catalase, lysozyme). Pronounced changes of enzyme activity in erythrocytes comes through 24 hours after 3-rd exposure. Radiation-induced activation of pentose-phosphate pathway of carbohydrates metabolism some authors consider as "oxidizing explosion" [8] or as enzyming-oxidizing protection [9].

Table I. Effect of low-dose gamma-irradiation on morphological and biochemical characteristics of blood and thymus
Mean±SEM (n=6) *, p<0,05 vs control

	Control	Time after irradiation			
		1 hour	24 hours	7 days	30 days
Plasmatic endotoxemia	0-1%	25%	9%	6%	4%
Leucocytes, 10^9/l	9,0±0,6	7,1±0,5*	6,4±0,2*	8,2±1,0	9,2±1,3
Erythrocytes, 10^{12}/l	5,4±0,3	5,8±0,2	4,8±0,1	4,3±0,2*	3,5±0,3*
MDA, μM	20,9±2,1	16,3±2,2	18,2±0,8	26,7±2,0*	8,9±1,0*
Catalase, nmol/ml/sec	0,98±0,05	1,32±0,12*	0,95±0,1	0,75±0,09	1,18±0,09
Lysozyme, mg/l	1,69±0,12	2,00±0,1	2,20±0,09*	0,76±0,07*	1,46±0,36
IC, g/l	4,4±0,21	3,1±0,29*	5,1±0,16*	4,3±0,24	3,4±0,15*
Glucose-6-P dehydrogenase, μmol/l/sec	36,1±1,1	27,5±0,5*	33,6±2,3	45,2±4,1*	38,3±2,1
Transketolase, μmol/l/sec	1,24±0,06	1,01±0,07*	1,42±0,03*	1,16±0,1	1,38±0,04*
"TDP-effect", %	8±0,12	22±0,81	9±0,27	23±0,51	8±0,13
Acid phosphatase, nmol/l/sec	516±12,1	394±8,1*	570±17,0*	526±13,5	605±24*
Alkaline phosphatase, nmol/l/sec	167±5,4	140±8,1*	151±5,4	154±5,2	189±8,1*

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CONSEQUENCES OF LONG - TERM EFFECTS OF LOW DOSES OF RADIOACTIVE EXPOSURE ON FEMALES WITH ADNEXITIS: HEMATOLOGIC STUDIES

Kazhyna M.

Grodno State Medical Institute. 80, Gorky street, 230015, Grodno, Belarus.

Abstract.

Time cause in changes of haematological indices and Cs radioactivity in females with chronic adnexitis was studied. The significant changes in cellular structure of blood were demonstrated in patients with positive analysis on radioactivity (above 1000 Bq/l). Decelerated blood sedimentation rate, increased erythrocytes' anisocytosis (13-15%), decreased level of lymphocytes (18-25%) were revealed in this group of patients.

Radioactive pollution of the territory of the Republic of Belarus is the problem of great ecological importance. Chernobyl accident caused some medical, ecological, ethical and other problems. One of the most important problem is studying the biological effects of low doses of ionising radiation on human health [1]. Out-patients' examination of females from the territories, exposed to radioactive exposure (5-20 Ci/km^2) defined the relatively high frequency of inflammatory processes of female genitalia. Correlation between the cases and dose of exposure was established [2]. The influence of low doses of radiation on human organism is studied insufficient.

The aim of this work is to examine the influence of low doses of radiation on blood system of females with chronic adnexitis and to evaluate compensatory opportunities of blood system.

We examined 41 patients of reproductive age (age: 20 - 55) with chronic adnexitis. Patients were hospitalised from both the regions exposed to radioactive exposure, and from Grodno, which consider to be the «clean» zone, free of radioactive pollution. We examined morphological blood indices and total radioactivity in patients' blood. Hemogramme was made by haematological autoanalisator «System 9020». Radioactivity (Cs-137 and Cs-134) was studied by gamma-spectrometer NTA-1024 (Hungary). According to revealed radioactivity all patients were divided into 3 groups. Group 1 included patients with chronic adnexitis and negative result on radioactivity (n=17). Two other groups (n=10 and n=14) were differed by the level of radioactive Cs in blood (below 1000 and above 1000 Bq/l). Referent group included donors (n=20).

Results and discussion.

In patients with chronic adnexitis (group 1) the blood sedimentation rate (BSR) was increased by 2.5 times (table I). The amount of leukocytes was elevated by 42%, lymphocytes - by 23%, monocytes - by 25%, trombocytes - by 16% in comparison with control group. In patients of group 2 (positive analysis on blood radioactivity , below 1000 Bq/l) the BSR, amount of leukocytes and lymphocytes were decreased in comparison with group 1. The most significant changes in cellular structure of blood were defined in patients with chronic adnexitis and positive analysis on radioactivity (total Cs-134 and Cs-137 radioactivity above 1000 Bq/l).

In 50% of patients of that group BSR (2-3 mm/hour) and amount of lymphocytes (18-25%) were decreased, whereas grade of erythrocytes' anisocytosis was increased (13-15%).

Table I.

Hemogramme, performed by hematological autoanalysator «System 9020».

Blood indices	Norma (donors)	Patients with adnexitis Specific radioactivity		
		0 first group	<1000 Bq/l second group	>1000 Bq/l third group
BSR mm/hour	5.0 ± 0.16	15.2 ± 0.16	7.3 ± 0.19	6.4 ± 0.22
WBC x 10^9/l	6.2 ± 0.31	8.8 ± 0.28	7.6 ± 017	6.8 ± 0.21
RWC x 10^{12}/l	4.6 ± 0.17	4.7 ± 0.23	4.7 ± 0.31	4.8 ± 0.19
HGB g/l	130 ± 7.8	146 ± 5.3	133 ± 4.3	143 ± 3.2
HCT %	40 ± 1.2	43 ± 1.7	41 ± 0.8	42 ± 1.1
MCV	85 ± 3.4	89 ± 2.7	88 ± 1.8	88 ± 2.3
MCHC %	34 ± 1.7	32 ± 0.9	35 ± 1.6	34 ± 1.2
MCH PG	28 ± 1.4	31 ± 1.6	26 ± 0.9	30 ± 1.5
RDW %	11.0 ± 0.4	12.3 ± 0.72	12.5 ± 0.54	13.5 ± 0.39
PLT x 10^9/l	205 ± 6.5	239 ± 7.8	240 ± 10.1	250 ± 7.3
Lymph %	30 ± 1.8	37.0 ± 0.93	34.2 ± 0.81	25.3 ± 1.25
Gran %	53 ± 2.11	54 ± 1.93	62 ± 2.36	76 ± 3.11
Mono %	6 ± 0.17	7.5 ± 0.25	8.1 ± 0.4	9.2 ± 0.38

Data obtained adjusted with scientific references [3,4]. Authors point the oppression of hemopoesis in condition of long-term influence of low doses of radiation. However, ionising radiation could cause not only the oppression of hemopoesis, but also stimulate the separate components of blood system [5,6]. In patients of group 2 the amount of trombocytes was increased by 17%. In increasing the dose of internal radioactivity (group 3) the level of trombocytes was elevating by 22%, granulocytes - by 43%, monocytes - by 53%.

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STATE OF THE GLUTATHIONE SYSTEM AT DIFFERENT PERIODS AFTER IRRADIATION

Natalia Petushok, Raisa Trebukhina
Institute of Biochemistry National Academy of Sciences of Belarus, Grodno

Abstract - the effect of the 3-fold irradiation on the glutatione system was studied. Activation of these system was shown to take place at early terms (1 hour) after irradiation, then it was exhausted that resulted in accumulation of lipid peroxidation products in blood. This phase changes in glutathione system could be correspond to certain stages of stress-syndrome.

During exposure of the organism to radiation chain free-radical reactions arise, which are accompanied by activation of lipid peroxidation processes (POL), destruction of proteins and nucleic acids [1,2]. Normally, the system of antiperoxide mechanisms (superoxide dismutase, catalase, glutathione peroxidase, glutathione transferase, glyoxalase and formaldehydedehydrogenase) maintains the chain oxidative reactions in a stable state [3]. Reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione transferase (GST), glutathione reductase (GR) and NADPH form a glutathione antiperoxide system. This system, as a rule, effectively protects cells against peroxide stress, and usually only its lack or exhaustion lead to severe damage.

The state of the glutathione system and the content of POL products can characterize the response of the organism to irradiation. In this study the state of the antioxidant system in the blood of low-dose irradiated rats was investigated. Experiment was carried out on female rats initially weighting 140-160 g. The animals were irradiated three times and received a total dose of 0.25 Gy (0.25 Gy per week). Blood was assayed for the activity of GPx, GR, catalase, GST and the content of GSH and malonedialdehyde (MDA). The measurements were made after 1 and 24 hours, 1 and 4 weeks after the last irradiation.

Table I summarizes the results obtained in our experiment. The erytrocyte concentration of low-molecular weight thiols (nearly 90% of which are represent by GSH) was significantly increased (by 21%) one hour after the last irradiation; 24 hours, 1 and 4 weeks later the changes were unsignificant. The activity of the glutathione regenerating enzyme GR was increased (by 34%) after one hour; 24 hours later it was decreased (by 41%); after week it raised to the corresponding control values and after 4 weeks it was decreased again. Increasing of GPx activity was noted 24 hours after irradiation and at other periods this index did not significantly differ from the control values. Besides GPx, catalase is also responsible for H_2O_2 detoxication. Increasing of its activity was noted one hour and 4 weeks after the irradiation. According to the data [4], GPx and catalase function undependendly, however GPx plays a greater role in detoxication of H_2O_2. GPx not only prevents accumulation of organic hidroperoxides by hindering generation of reactive oxygen species, but efficiently reduces them. GST ("nonselenium Gpx") acts in the same way at this site of metabolism. Joint work of these enzymes prevents further progress of peroxidation and accumulation of secondary metabolites. Total GST activity of blood plasma increased (by 43%) by the end of the fourth week after irradiation. It has been suggested that GPx and GST are complementary in organic hydroperoxide metabolism. GPx, by metabolizing of organic hydroperoxides, can prevent accumulation of peroxidation secondary products, but it is unable to detoxicate it. GST successfully metabolizes organic hydroperoxides [5]. This suggestion was proved by MDA level found in our experiment. Its concentration increased by the end of the first week after irradiation and significantly decreased 4 weeks after irradiation.

Thus, in the blood of 3-fold irradiated rats the phase changes in the glutathione system were shown. This changes can be considered either as compensative-adaptational or as stages

of stress-syndrome. At the stage of resistance the organism adapts, mobilizes its defensive forces i.e., the antiperoxide system is activated. Then comes a phase of exhaustion which is corresponded to intensification of free-radical oxidation [6].

The mobilization of defensive forces in our experiment was manifested by increasing of the activities of GR, Gpx, catalase and GSH content at early periods (1 hour) after the irradiation. The phase of exhaustion was noted after 24 hours or one week after the irradiation, when accumulation of POL products in the blood was detected. Four weeks after the irradiation the antiperoxide system was activated again.

Table I. Glutathione system, catalase activity and MDA level in rats blood after irradiation
Mean±SEM (n=6)*, $p<0.05$ vs control

	Control	Time after irradiation			
		1 hour	24 hours	1 week	4 weeks
GSH, mM	2,77±0,11	3,35±0,11*	2,77±0,13	2,95±0,06	2,76±0,18
GR, nmol/l/sec	5,11±0,51	6,83±0,58*	3,03±0,57*	5,58±0,73	1,53±0,14*
GPx, nmol/ml/sec	0,41±0,05	0,44±0,05	0,53±0,055	0,41±0,05	0,45±0,06
GST, nmol/ml/sec	21,67±3,67	17,67±6,67	15,0±2,6	24,5±2,33	31,17±1,5*
Catalase, nmol/ml/sec	0,98±0,05	1,32±0,12*	0,95±0,1	0,75±0,09	1,18±0,09
MDA, μM	20,9±2,1	16,3±2,2	18,2±0,8	26,7±2,0*	8,9±1,0*

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Radio-adaptive Survival Response in Mice
—Hematological Studies on the Acquired Radio-resistance—

Morio Yonezawa* and Jun Misonoh**, *Res. Inst. Advanced Sci. & Technol., Osaka Prefecture Univ., Gakuen-cho, Sakai, Osaka 599-8570, **Bio-Science Dept., Komae Branch, CRIEPI, Iwato-kita, Komae, Tokyo 201, Japan

Abstract

We have reported that X-ray pre-irradiation induced two types of radio-resistance (improved 30-day survival rate after mid-lethal irradiation) in C57BL and ICR strains of mice. The dose-effects were distinguished into the following 4 dose ranges in ICR mice: (1) below 2.5 cGy: no radio-resistance is induced 2 months later, (2) 5 to 10 cGy: significant radio-resistance 2 to 2.5 months later by whole-body pre-irradiation, (3) 15 to 20 cGy: no radio-resistance at any time between 2 weeks to 2 months later, and (4) 30 to 50 cGy: significant radio-resistance 2 weeks later by partial-body pre-irradiation of the trunk as well as whole-body pre-irradiation. We previously reported that the recovery of blood cell counts of erythrocytes, leukocytes and thrombocytes was enhanced by the pre-irradiation in C57BL, but not in ICR mice.

In the present study, hematological changes were examined on blood coagulation time and hemorrhaging tendency in case of pre-irradiation with 45 cGy in ICR mice. Blood coagulation time prolonged on day 12 after sub-lethal irradiation, but it was not restored by the pre-irradiation, while occult blood appearance in feces collected on days 10 to 12 after sub-lethal irradiation was decreased by the pre-irradiation in ICR mice.

Introduction

Radio-adaptive response on chromosomal damages [1,2] and gene mutation [3] has been extensively studied in cells. In animals, Maisin et al. [4] first reported an increase in the 30-day survival rate after mid-lethal exposure in rats pre-irradiated with as low as 5 R about 2.5 months before. Daquisto [5] made a review and a confirmatory experiment on the induction of radioresistance with 50 R. We confirmed in the previous study that ICR mice acquire radio-resistance 2 months after exposure to 5-10 cGy [6] and 2 weeks after exposure to 30-50 cGy [7]. Partial-body pre-irradiation experiment was planned to distinguish the two types of radio-resistance, since Miyachi et al. [8] reported that mouse brain is sensitive to very low dose irradiation. The partial-body pre-irradiation showed that the former radio-resistance needs whole-body pre-irradiation but the latter was induced by pre-irradiation of the trunk as well as whole-body [9]. Last year we reported that C57BL mice also acquires the two types of radio-resistance, but Balb/c and BDF1 do not [10]. Recovery of the peripheral blood cell counts after challenging irradiation was enhanced in C57BL pre-irradiated with 50 cGy, but not in ICR [10]. It seemed likely that the induction mechanism might be different between the two strains of mice.

In the present study, the effect of priming irradiation on hemorrhaging tendency and blood coagulation time after challenging exposure was examined to get information about the mechanism of the induction of radio-resistance in ICR mice after pre-irradiation with 50 cGy

Materials and Methods

Six-week old male ICR mice, free from contamination with *Pseudomonas* bacteria, were irradiated with the priming irradiation with 50 cGy of X-rays Sham-irradiated controls were run concurrently with the pre-irradiated groups The mice were exposed to the challenging dose two weeks after the priming irradiation Hemorrhaging tendency was estimated by determining occult blood appearance in feces collected on days 10 to 12 after challenging irradiation with 6 12, 6 3 or 6 48 Gy two weeks after the priming irradiation, during the period when the hemorrhage is mostly marked after irradiation [11] The feces were dried, powdered, and hematin content was determined as reported elsewhere [11] The powder (40 mg) was extracted with 4 ml of 30% acetic acid, and centrifuged The supernatant (2 ml) was extracted with 5 ml of ice-cold ether The ethereal layer (1 ml) was mixed with a mixture of 0 7 ml of 1% ortho-dianisidine ethanol solution, 1 4 ml of 50% acetic acid, and 0 4 ml of 3% hydrogen peroxide After 20 (or 10) minutes, the absorbance at 459 nm was measured Hematin (or hemoglobin, Hb) content was estimated from the standard curve obtained with a pure hemoglobin Blood coagulation time was measured with KC 1A coagulometer (Amerung Co , Germany) The blood was collected by decapitation of mice on day 12 after challenging exposure to 5 2 Gy

Results

1 Preirradiation decreased hemorrhaging tendency

Fig 1 shows that hemorrhaging tendency measured by occult blood appearance in feces of mice (ten per group) collected on days 10-12 Hemoglobin content was low in both groups of mice exposed to 6 12 Gy Hemorrhage became marked in control groups exposed to 6 3 and 6 48 Gy The pre-irradiation resulted in a decrease in occult blood appearance after these challenging doses

2 Pre-irradiation did not restore blood coagulation

Blood coagulation time was measured on day 12 after the challenging dose of 5 2 Gy in mice of three groups unirradiated intact (10 animals), sham-5 2 Gy (control, 11 animals), and 45 cGy-5 2 Gy (experimental, 10 animals) The challenging irradiation elongated the coagulation time (mean $\pm$ SE), from 87 1 $\pm$ 4 6 sec to 112 9 $\pm$ 8 0 sec, but the pre-irradiation did not restore the coagulation time (111 4 $\pm$ 5 9 sec)

Discussion

Pre-irradiation of mice of both C57BL and ICR strains with 30 to 50 cGy induced radio-resistance (decrease in bone-marrow death after mid-lethal exposure) two weeks thereafter [10]

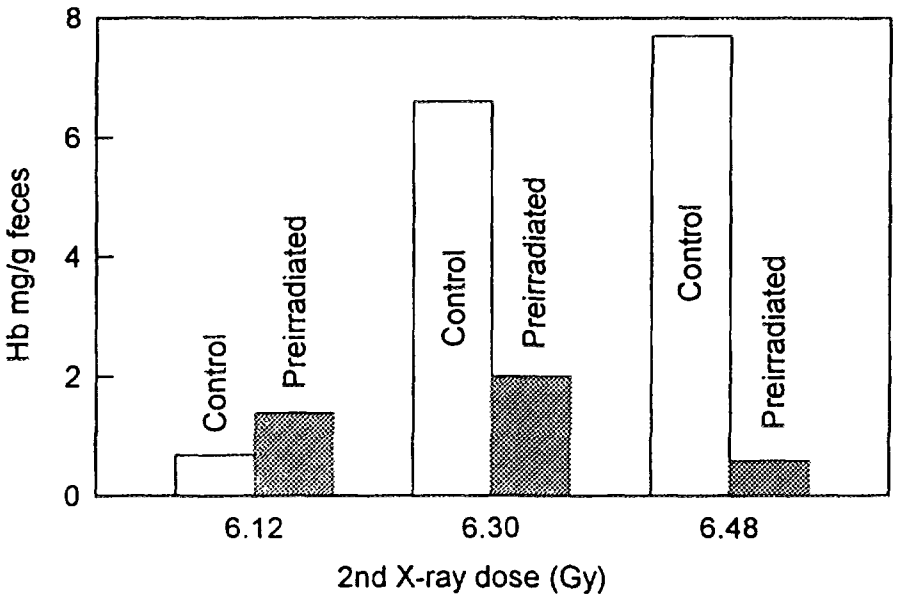

Fig. 1. Decreased hemorrhage by the pre-irradiation.

Recovery of blood cell counts of erythrocytes, leukocytes, and thrombocytes after sub-lethal irradiation was enhanced by pre-irradiation with 50 cGy in C57BL, but not in ICR [10]. In other words, the pre-irradiation decreased bone-marrow death without increasing blood cell counts in ICR mice. Nakamura et al. [12,13] reported that radiation-induced hematopoietic death in mice is caused by the cerebello-medulla oblongata hemorrhage and is closely related to thrombocytopenia. In the present experiments in ICR mice, hemorrhaging tendency was decreased by the pre-irradiation, though there seemed little relation within thrombocytopenia and the death rate. Blood coagulation time, elongated by the challenging irradiation, was not recovered by the pre-irradiaton. Blood clotting system may not be concerned in the acquired radio-resistance. We therefore imagine that production of some factors which relate to repair or strengthen blood vessels not to leak blood cells might be increased by the pre-irradiation.

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Practical Aspects of Occupational Exposure Monitoring During Management of Radioactive Waste

Agrinenko S D., Prokasova L.M., Sobolev I.A., Shurkus A.E.
SIA"Radon", 2/14,7th Rostovsky Lane Moscow Russia 119121

Abstract

From the time of setting up since 1961 the SIA "Radon" as a centre of collection, treatment and disposal of non-nuclear radioactive waste, large experience in the field of radiation monitoring of occupational exposure is gained. Some aspects of personnel monitoring and some dose statistics are presented in the paper

The radiation monitoring at SIA"Radon" is based on the principles written in International and National Standards of Radiation Safety [1,2] and also on the number of Acts [3,4,5] and Regulatory Texts [6]

According to the requirements of these documents. radiation protection is based on the three groups of Norms basic dose limits, permissible levels and reference levels.

The main characteristic feature of radiation monitoring at SIA"Radon" is the following. "Radon" deals with the waste of various chemical and radiochemical compositions. As a rule they are liquid and solid low active waste and spent sources from medical institutions, industrial enterprises and scientific-research institutes from central region of Russia Radioactive composition of waste is mainly presented by long lived radionuclides. the larger part of which comes in the open form

Personnel dosimetry is a fractional part of radiation safety control, which is carried out as an occupational hygiene estimation of labor condition of workers exposured to ionizing radiation.

The amount of staff , undergoing monitoring , reading intervals, list of personnel and method of dosimetry is determined from standard requirements [1,2.6] and approved by the administration of the enterprise on consultation with the units of State Sanitary Supervision.

Depending on character of work the personnel monitoring includes individual dose control of external β-irradiation, x-ray and γ-ray, on the one hand. and a dose control of radionuclides intakes and internal irradiation, on the other hand It also includes collection and analysis of personnel dose data in order to optimize radiation protection

During estimation of occupational exposure. we take into consideration all the radiation sources, effecting the workers at working place during operation time

The main task of external dosimetry at SIA"Radon" is chronic exposure monitoring. which in its turn. includes a daily monitoring with a quarter reading and operative one, as required At the first stage, for daily monitoring we used film dosimeters ИФКУ type, sensitivity, metrologic characteristics and labour consumption of which were worth being better. Since 1986 we have applied thermoluminescent dosimeters and now SIA"Radon" uses automatic TLD-system DOSACUS of Finnish firm "RADOS" The TLD-system provides individual calibration of each personnel dosimeter. automatic tracing of the system working parameters stability and storage of reading results.

At first for operative monitoring of workers involved in operations with higher risk of exposure we used ionizing dosimeters of condenser type КИД-2. ИД-02 with one week reading cycle Now for operative dosimetry we use a set of semiconductor dosimeters RAD-101S.

For monitoring of internal effective dose in practice. we use three basic methods estimated. direct and indirect By estimated method we calculated the committed effective dose from annual average intake of radionuclides by the body of workers The estimated method is based on the conditional person concept, which was elaborated in publications 30, 66 ICRP [7,8] The intakes can be traced on radioactivity aerosols concentrations in the air of working places. which were measured with stationary or portable samplers and also, in individual cases, on radioactivity of biosubstrates During calculation of committed effective dose we take into account only inhalation way of intake The preliminary calculation is made in terms of dose factors. given at [2] for conventional, the most rigid estimated parameters (median diameter- 1μm. conventional scheme of metabolism, predominantly slow class of transportability of nuclide compounds. conditional person- 70kg) If derived dose does

not exceed the dose limit quota of internal exposure, which as fixed at SIA"Radon" amounts to 1/2 dose limit = 10mSv/year, this value is included into data archive If this dose limit is exceeded we make the more detailed calculation and particularize all the parameters, including the moment of intake, radionuclide and dispersion composition of aerosols, chemical class of compounds, metabolism scheme and so on If required, we sent the person for examination to the Institute of Biophysics (Moscow)

For routine monitoring all the workers are examined with the body counter twice a year Critical group of workers involved in the most dangerous works is examined every quarter If necessary any worker is examined without schedule

Many years of observation show that β-active radionuclides (as a rule ^{137}Cs, ^{134}Cs, ^{90}Sr, ^{60}Co, ^{144}Ce and some others) account for not more then 2% of committed effective dose, in spite of the fact, that their content in the air of premises amounts to in average 80 - 90 % of total aerosol activity So the main internal dose is governed by α-emitters (mainly ^{239}Pu, ^{238}Pu, ^{242}Pu, ^{241}Am, ^{226}Ra, ^{210}Po, ^{233}U, ^{235}U, ^{238}U and some others) Fig 1 represents average annual committed effective doses of personnel determined on aerosol concentration in the air of working places One should emphasize that data given at fig 1 are the results calculated for the most severe conditions, the real committed effective doses are smaller, the uncertainty factor we estimate as 3

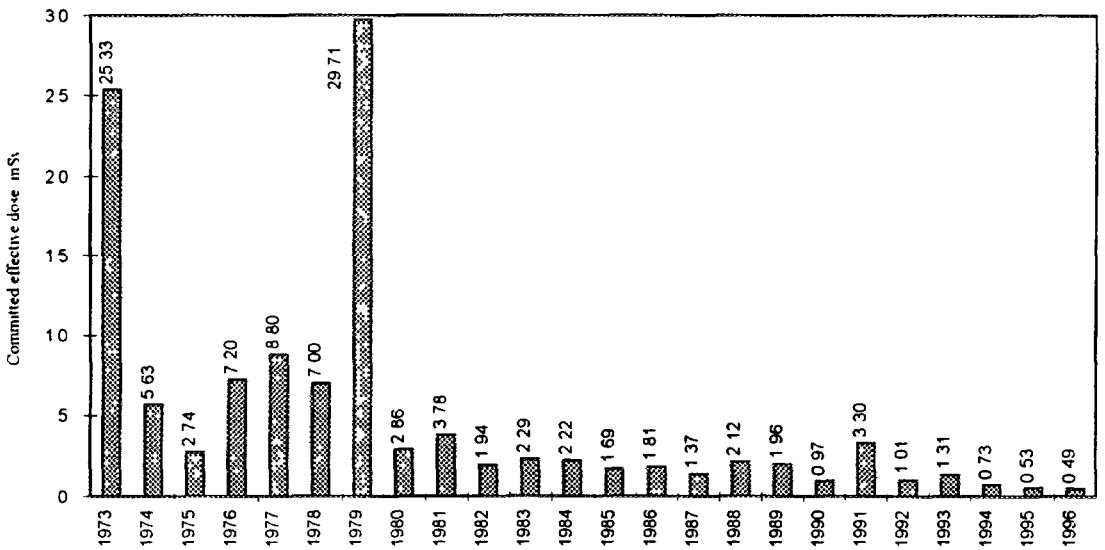

Fig 1 Committed effective dose

The monitoring results of external occupational exposure of workers of some professions are given at fig 2 Up to 1986 the personnel monitoring at SIA"Radon" was performed with photodosimeters and ionizing detectors which had high error and did not meet the requirements of standard [6] Further we changed these dosimeters for more precise thermoluminescent ones For the last three years average annual dose of external exposure does not exceed 1 3 mSv Fig 3 shows median and quartile values of annual dose distribution of external exposures for the personnel of SIA"Radon" The mid-point in fig 3 denotes the median of the frequency dose distribution, the box is 27% and 75% percentiles respectively, whiskers denote the non outlier values, which meet the condition

$$D_{25}-1.5(D_{75}-D_{25}) < D < D_{75}+1.5(D_{75}-D_{25}).$$

D_{25} - 25%-quartile, D_{75} - 75%-quartile of annual dose distribution The circles symbolize the outlier cases Fig 3 gives dynamic optimization of both metrologic tools and system of radiation protection in general As it can be seen, the unpredictable outliers have been excluded since 1977 Putting the more precise TLD into operation in 1987 led to reduction of monitoring results variability

Frequency analysis of personnel doses confirms lognormal character of distribution mentioned above in a number of papers [9 10] Study of dose frequency distribution for workers who operate at

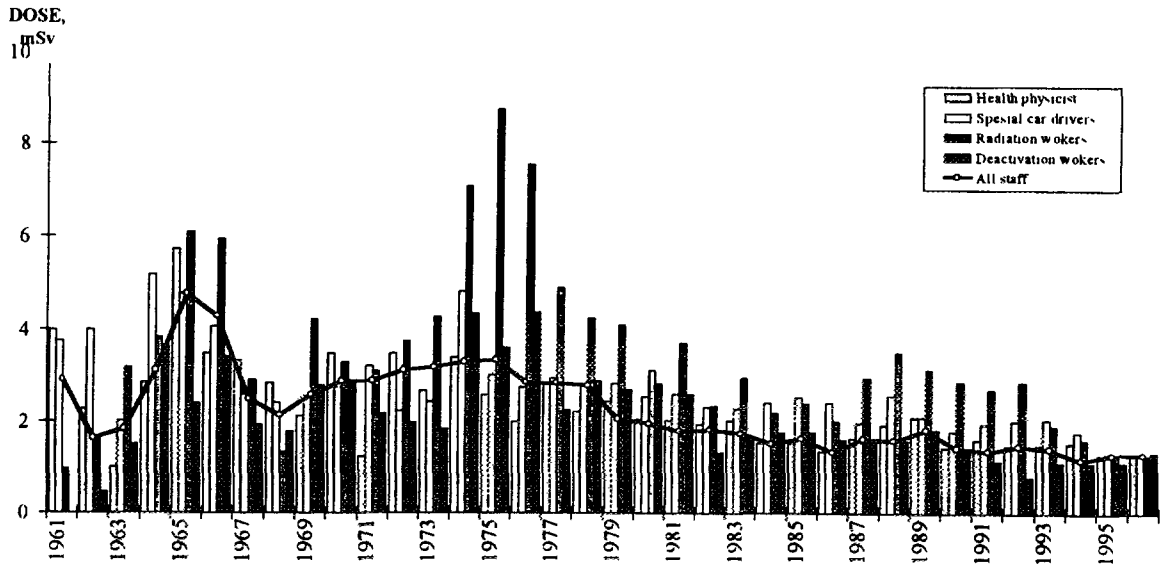

Fig.2. The results of personnel external dosimetry in SIA"RADON"

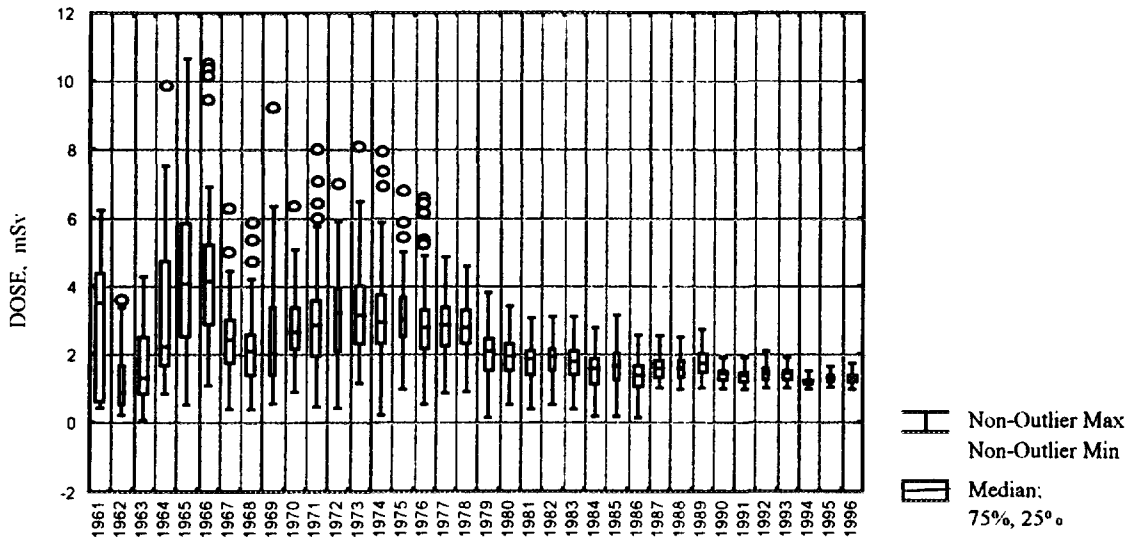

Fig.3. Personnel monitoring statistics.

SIA"Radon" for a longer period of time demonstrated that the character of personal dose distribution was also close to lognormal. At any rate, in the sample of case 76 persons the criterion of conformity by Kolmogorov-Smirnov did not exceed 0.06 at significance level $p<0.1$. It gives reason for introduction of the personal reference level determined for some years of individual observation. While depending on the character of works the personal reference level can alter dynamically.

We introduced the complex parameter for estimation of radiation danger of the SIA"Radon" activity, as average annual collective effective dose of workers related to the unit of treated waste radioactivity - man*mSv/GBq. Fig.4 gives dynamic variation of this parameter according to years. Abrupt change in the parameter in 1996 can be explained, on the one hand, by the reduction of the treated waste volume, and, on the other hand, by the recent growth of science contribution at the enterprise. As a result, lately total average effective dose of occupational exposure at SIA"Radon" has amounted to 1.7-1.9 mSv/year, while the dose limit according to the norms, amounts to 20mSv [2].

Table 1 gives the value of probable overdose and risk of unfavorable consequences for the workers of basic professions.

Every quarter the results of personnel monitoring are introduced into the database for further processing and storage. At the same time, data of personnel monitoring are registered into the personal

cards The dose data read are kept for 50 years more after moving the worker to the other enterprise or his retirement

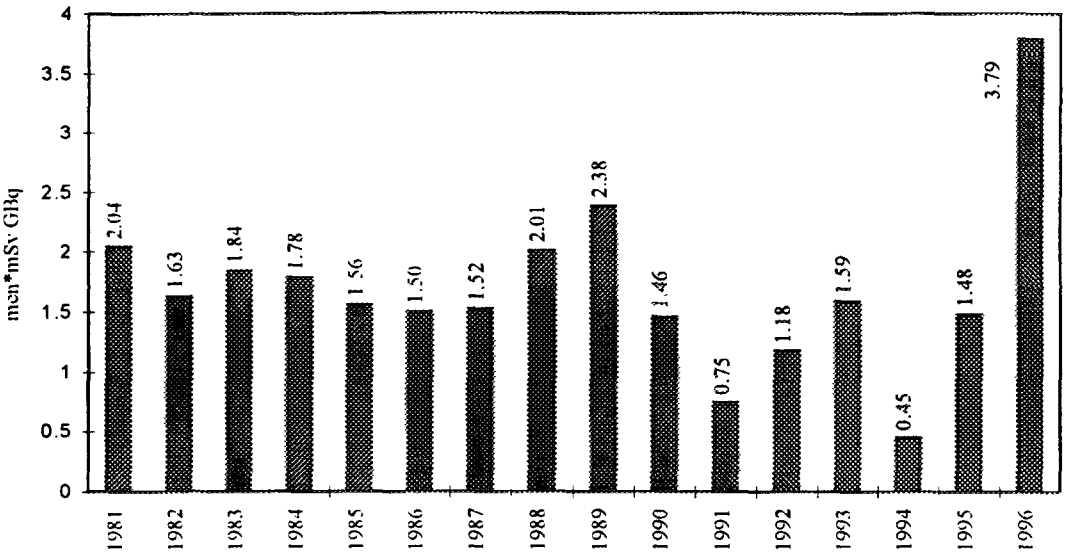

Fig.4. Specific collective dose.

Table 1

Profession	Dose limit, mSv	Probability p(>D)	Collect. dose man*mSv	Average dose, mSv	Individ. Risk
Health physicist	10	1.1E-08	82.15	1.83	3.02E-04
	3	1.0E-03			
Radiation worker	10	1.0E-08	86.45	2.06	3.40E-04
	3	4.2E-02			
Radioactive decontamination worker	10	1.9E-13	109.98	1.75	2.89E-04
	3	5.0E-05			
Engineer, science and technical staff	10	1.0E-10	667.26	1.79	2.95E-04
	3	1.2E-04			
All staff	10	4.0E-10	1824	1.78	2.94E-04
	3	5.3E-05			

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CONDITION OF ORGAN OF VISION AND FREE RADICAL PROCESS PARAMETERS IN LIQIDATORS OF THE CHERNOBYL ACCIDENT

Sosnovsky S., Danilicnev V., Nikiforov A.*, Zybina N.*, Nesteruk L.**

Military Medical Academy, Saint-Petersburg, Russia
*All-Russian Center of emergency and radiation medicine, Saint-Petersburg, Russia
**Helmholtz Institute of Eyes Diseases, Moscow, Russia

XA9745635

ABSTRACT

84 liquidators of consequences of Chernobyl APS accident from the age of 28 to 58 were examined. The control group was made with 22 men from the age of 28 to 52. A certain increase of infringement of a transparency of lens without typical attributes of radiating cataract is revealed in the experimental group. Electrophysiological investigation (EPI) shows a certain reduction of amplitude of a wave "a" of macular electroretinogram (ERG) on green stimulus, amplitude of a main component and lengthening of an interpeak time interval of flicker ERG 10 Hz is revealed. These changes indicate the tendency to reduction of functional activity of a retina (first of all at a level of photoreceptors) in paramacular and in a smaller degree in peripheral zones among liquidators. The parameters of contrast sensitivity are definitely reduced in the experimental group for all stimuli on all spatial frequencies. Luminous and colour sensitivity to stimuli of different colour in the experimental group is definitely reduced in all central field of sight, but in paracentral zone the degree of reduction is higher. We investigated the parameters of oxidative stress in both groups. Definite increase of production of the reactive oxygen species and disbalance of a glutathione link of antioxidant protection are revealed. Authentic correlation dependences are revealed: moderate direct correlation - between a level of glutathione reductase and amplitude of a main component of flicker ERG 10 Hz, between a level of oxidized glutathione and interpeak time interval of flicker ERG 10 Hz, inverse correlation - between the level of oxidized glutathione and amplitude of a main component of flicker ERG 10 Hz. In view of large spontaneous activity of free radical processes in a retina in norm the received results can explain revealed changes of an organ of vision.

INTRODUCTION

The medical rehabilitation of people, who had taken part in the liquidation of consequences of accident of Chernobyl APS occupies a very important place today. A big number of publications is devoted to the investigation of organ of vision among the mentioned categories. The analysis of literature shows that the majority of authors used first of all the methods of evaluation of morphological condition of the eyeball structures (ophthalmoscopy, skiascopy, biomicroscopy and others). To evaluate the functions of organ of vision, as a rule, there were used classical, but at the same time sufficiently rough methods of the diagnostics (visomerty, perymetry and others) [1].

At the same time, within the last years the leading Russia's specialists in radio biology, clinical radiology and radiation hygiene formed the new outlook on pathogenesis of post-Chernobyl pathology. The factor of increased radiation load is not the only one in shaping of pathological conditions, observed among the liquidators [2]. The liquidators were subjected to the influence of the unique complex of extreme stress-producing factors: physical and chemical, informative, semantic. Aggravating circumstances are the impossibility of sensory control and retrospective

estimation of the damaging radiation degree, as well as the chronic character of the long term psycho traumatic factor in post accident period. The rehabilitation period coincided in time with radial social transformation in the country, with also become an aggravating factor [2]. Combination of mentioned factors leads to infringement of some important regulation systems in the organism; it forms the negative background for the somatic pathology development. One of the universal mechanisms of forming such pathology are free radical processes, initiated in the organism by so called reactive oxygen species [3]. Free radicals are constantly generated in the human body and are necessary for some biological processes. Hyperproduction of free radicals or antioxidant depletion, however, may be a reason of oxidative cell damaging. All cell components lipids, proteins, carbohydrates can be damaged by free radicals. It provokes serious disorders in their structure and functions. The liquidators even 10 years after the accident demonstrate free radicals hyperproduction and high level of oxidative destruction of macromolecules [4].Thus, the reason for pathogenesis of various diseases among the liquidators is the influence of the whole complex of unfavorable factors of the radiation accident, including the joint radiation and non-radiation components. As a result there develop pre-clinical, pre-morbid functional disorders of organs and systems in the organism. A lot of material on that was published in the literature of non-ophthalmological subject. Concerning the organ of vision, we must mention that no research in this respect was found in the literature available to us. In this connection, besides generally accepted diagnostics methods for examining liquidator's organ of vision we included into a complex of examination a number of functional, objective and newest psycho physiological methods notable for high sensitivity. In the organ of vision the risk of free radicals damage is extremely great [5]. The eye tissues are uninterruptedly subjected to the action of light, capable of provoking free radical processes. Membranes of retina are rich in unsaturated lipids and thiol-containing proteins receptive to the free radicals attack. Retina is a tissue intensively supplied with air and blood, which creates the particular prerequisites for activations of free radical processes. In connection with obvious significance of free radical processes in the development of pathology among the liquidators and particularities of retina molecular structure we defined a number of parameters of oxidative stress among patients.

MATERIAL AND METHODS

We examined 71 liquidators in 1986-1989 at the age from 28 to 53, who did not produce any complaints about vision. Control group consisted of 22 sound persons at the age from 28 to 50 We included only men in both groups. Individual absorbed dose by dose registration cards in the experimental group was within the limits of 0,56 to 125 cGr. We used the following diagnostic methods: table visometry, classical perymetry, table color sensitivity testing, refractometry, biomicroscopy, ophthalmoscopy, EPI: hanz-field ERG, macular ERG on the red and green stimulus, flicker ERG to frequency 10 Hz and 30 Hz; computer tangent screen perymetry of central eyeshot (IBM-based program «Ocular»): luminous and color sensitivity testing; contrast sensitivity to achromatic and color stimuli (IBM-based program «Zebra»); parameters of free radicals system in blood: levels of superoxide, hydrogen peroxide, reduced and oxidized glutathione, glutathione reductase, superoxide dismutase.

RESULTS

Visual acuity with correction in both groups was not below 40/50. Ametropia was not over 5 diopters. Neither in the experimental, nor in the control group was revealed any changes of eyeshot, pathology on the eyeground, infringement of color vision. Infringement of vitreous transparency in shape of initial or moderate destruction was revealed equally often in both groups. Infringement of lens transparency had the most initial nature and did not influence

visual functions. But change frequency in lens among liquidators was definitely higher, than in the control group ($p<0,001$).

At the analysis of EPI we estimated 18 parameters. The liquidators had authentic reduced wave A amplitude of macular ERG to green stimulus ($P<0,001$), reduced wave B amplitude ($P<0,01$) and prolonged interpeak interval between A and B waves ($P<0,01$) of flicker ERG 10 Hz.

Program «Ocular» allows to study topography of sensitivity of retina in the central area (20 degrees from the fixing point). Study is conducted monoculary. Colour stimulus of increasing brightness is presented behind gray background in different points of screen. While determining thresholds of luminous sensitivity a patient fixes a moment of finding of stimulus. While determining thresholds of color sensitivity a patient fixes a moment of making out the stimulus color. We used three stimulus colours: red, green and blue. We estimated differential thresholds of physical brightness of stimulus in different areas of central eyeshot: Thresholds in the group of liquidators are definitely higher while presenting all color stimuli in all areas, but in the paracentral zone in greater degree. Gray screen background with brightness 1 cd/m^2 ensures mesopic conditions for suppressing functions of rode system. Various differential thresholds while presenting different color stimuli both in experimental, and in control groups confirm a three different cones systems participation (red, green and blue) in the perception of chromatic objects brightness. Thresholds of color sensitivity are definitely higher among the liquidators to red and blue stimuli. Difference between experimental and control groups while presenting a green stimulus is unauthentic.

Achromatic and color contrast sensitivity we study by means of program "Zebra". Sinusoidal grids with the frequency of 0,5 to 22 cycles/degree were presented on the monitors screen. Totally 12 spatial frequencies were researched. The program allows to close pattern by the screen rising from below. Patient fixes a moment, when he stops making out a structure of the grids. Contrast sensitivity among liquidators is definitely reduced on all spatial frequencies while presenting red and blue patterns. Maximum reduction is observed in the field of medium and low spatial frequencies. In the field of high spatial frequencies reduction is smaller, but authentic. While presenting achromatic and green patterns the reduction of contrast sensitivity had the same character, but in the field of high spatial frequencies a difference was unauthentic. Correlation analysis did not reveal dependence of investigated parameters of organ of vision from individual doze load.

Estimation of free radical parameters shows, that liquidators have a considerably increased level of basal production of reactive oxygen species (level of basal superoxide ($p<0,001$) and of basal hydrogen peroxide ($p<0,01$)), exhausted reserves of their generations (level of stimulated superoxide ($p<0,001$) and of stimulated hydrogen peroxide ($p<0,001$)) and disbalance antioxidant system in the first place on the level of thiol-disulfide metabolism (increased level of oxidized glutathione ($p<0,05$), reduced level of reduced glutathione ($p<0,001$) and of glutathione reductase ($p<0,05$)).

DISCUSSION

Analysis of results of EPI allows to draw a conclusion on authentic reduction of electrobiological activity of retina among liquidators first of all in paramacular zone. To a lesser extent is oppress the activity of retina on peripheral zone. The changes of electrogenesis are revealed on the level of photoreceptors in paramacular zone (reduction of wave A amplitude of macular ERG to the green stimulus), on the level of bipolars in paramacular and peripheral zones of retina (reduction of wave B amplitude of flicker ERG 10 Hz), as well as on the stage of interneuronal interactions between photoreceptors and bipolars (a prolonging of interpeak time of flicker ERG 10 Hz). Infringement of retina activity in macular zone by means

of EPI is not revealed.
Methods of threshold sensitivity estimation by means of program "Ocular" reveal an oppression of retina functions both in macular, and in paramacular zones. But in paramacula degree of oppression is considerably higher.
Oppression of contrast sensitivity in the field of medium and low frequencies is typical for dysfunction of retina in paramacular and peripheral zones accordingly. These data correlate with results of preceding methods.
Correlation analysis of functional infringement of vision with changes of free radical processes has shown the following definite moderate correlation ties:

- direct ties - between the level of glutathione reductase and wave B amplitude of flicker ERG 10 Hz (correlation coefficient 0,57, significance level 0,004);
- inverse ties - between the level of oxidized glutathione and wave B amplitude of flicker ERG 10 Hz (correlation coefficient -0,58, significance level 0,008);
- direct ties - between the level oxidized glutathione and interpeak interval A-B of flicker ERG 10 Hz (correlation coefficient 0,63, significance level 0,003).

Increase in contents of oxidized glutathione and shortage of glutathione reductase tell of exhaust in the glutathione metabolism mechanisms. Reduced glutathione is a donor of thiol (-SH) groups for reparations of protein structure, damaged by the free radicals influence. Rhodopsin in retina is one of protein, containing SH-groups. Changes in glutathione metabolism and correlation ties, found by us, can be among the possible reasons of infringement of the functions of organ of vision, which we revealed in liquidators. Finding out other reasons requires further deep studies of this problem and is a perspective goal of our research.

CONCLUSIONS:

1. Sub-clinical reduction of functional of organ of vision is revealed among the liquidators.
2. Reduction of functional parameters of organ of vision is stipulated by oppression of activity in paramacular and to a lesser degree in peripheral retina zones.
3. Reduction of functions of retina among liquidators has no dose dependence.
4. Reduction of some functional parameters of organ of vision among liquidators correlate with parameters of free radical processes of organism. Disbalance of glutathione link of antioxidant system in blood, revealed among liquidators, can be one of the reasons of changes of the visual functions.
5. It is possible to suppose that revealed shifts of functional parameters of organ of vision among the liquidators appear as a resulte of influence of complex of unfavorable factors of Chernobyl accident, which have both radiation, and non- radiation nature.

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THE WEAKENING OF CELL PROTECTION AS A RESULT OF THE CHERNOBYL NPP ACCIDENT RECOVERY FACTORS AFFECT ON LIQUIDATOR'S ORGANISM

Zybina N., Dryguina L., Katashkova G.
ALL-RUSSIAN CENTER OF EMERGENCY AND RADIATION MEDICINE,
SAINT- PETERSBURG, RUSSIA

XA9745636

ABSTRACT

The markers of oxidative stress as well as intracellular antioxidants (enzymatic and non-enzymatic) were studied in 100 Chernobyl accident recovery workers(liquidators). Hormone screening tests were carried out in 250 liquidators. All persons (mean age - 35 years) have got external irradiation dose from 2 to 30 cGr. Control group was selected from persons of same age having not participated in accident liquidation.

The significant antioxidant imbalance was found. ROS inactivating enzymes deficiency was revealed in neutrofils, lymphocytes and alveolar macrophages (AM). For instance, superoxide dismutase(SOD) activity in liquidator's AM was 2,8±0,3 U/mg protein (4,1-±1,8 U/mg protein in controls, P<0,05). Catalase activity was also lower than in control group (P<0,05). The significant disorder of the thiol-disulfide turnover was revealed: depression of reduced glutathione by 1,71-±0,46 μmol/l (control: 3,15±-0,34 μmol/l, P<0,05). . The oxidative stress destructive action realized in the conditions of excessive production of ROS, while the antioxidant potential was diminished(P<0,05). The oxidative destruction of lipids and proteins was found to be induced by free radical action. TBARS level in alveolar macrophages of liquidators was more than three times higher compared to controls. Enhanced levels of protein carbonyl groups were found as well.

The decrease of TT3 in liquidators was detected most frequently. In 19% liqudators examined, TT3 was below the reference value (0,8 ng/ml). The TT3 level was registered at the low limit of the reference range (0,8 ng/ml) in 18% of liquidators."Low T3" syndrome may be considered as a cell protection weakening.

All the cellular protective mechanisms take part in processes of DNA synthesis and repair, transcription and translation, cell respiration and metabolism. Significant impairment of the cellular protective systems in liquidators could be regarded as a base of persistent "chromosomal pathology" and imbalance of metabolism complicated by the various diseases including oncology.

INTRODUCTION

Physical and biological consequences of liquidation of accidents at nuclear power stations are generally considered as a result of damage to genome. It is the genomic damage that is believed to increase morbility and lethality in the liquidators. It may cause not only oncologic diseases but some other clinical disorders as well. At the same time, genomic damage itself may result from both radiation and significant cell metabolism imbalance, including defects of DNA repair and cellular defense systems.

One of such defense systems, the antioxidant system, carries out extremely important function of cell protection from destruction by free radicals. Components of this system prevent biomacromolecules from oxidative damage by reactive oxygen species (ROS). Besides that, some antioxidants, e.g. reduced glutathione, are required for DNA repairing enzymes. Thyroid hormones are known to possess antioxidant properties and able to accelerate DNA repair. Hence, they also participate in cellular protection.

MATERIALS AND METHODS

The markers of oxidative stress as well as intracellular antioxidants (enzymatic and non-enzymatic) were studied in 100 liquidators. Hormone screening tests were carried out in 250 liquidators. All persons (mean age - 35 years) have got external irradiation dose from 2 to 30 cGr. Control group was selected from persons of same age having not participated in accident liquidation.

The following parameters were chosen for the assessment of the antioxidant system: reduced and oxidized glutathione levels of red blood cells [1], plasma protein thiol groups content [2], antioxidant enzymes - superoxide dismutase (SOD) [3], catalase (C)[4], glutathione peroxidase (GP) [5], glutathione reductase(GR) [6] of blood cells and alveolar macrophages. total T3 (TT3), total T4 (TT4), free T3 (FT3), free T4 (FT4) and thyroid stimulating hormone (TSH) levels of plasma (commercial enzyme immunoassays by Hoffmann- La Roche, Switzerland). The oxidative stress was asessed by superoxide and hydroperoxide generation by neutrophils and mononuclear leukocytes of blood and by alveolar macrophages [7]. The degree of protein and lipid oxidative destruction were determined by thiobarbituric acid-reactive substances (TBARS) and carbonyl groups contents of plasma [8,9].

RESULTS

The significant antioxidant imbalance was found. ROS inactivating enzymes deficiency was revealed in neutrofils, lymphocytes and alveolar macrophages (AM). For instance. SOD activity in liquidator's AM was 2,8±0,3 U/mg protein (4,1-±1,8 U/mg protein in controls, $P<0,05$). Catalase activity was also lower than in control group ($P<0,05$). The significant disorder of the thiol-disulfide turnover was revealed: depression of reduced glutathione by 1,71-±0,46 μmol/l (control: 3,15±-0,34 μmol/l, $P<0,05$). Actvity of antioxidant enzymes such as GP and GR was higher in liquidators than in controls ($P<0,05$). The oxidative stress destructive action realized in the conditions of excessive production of ROS, while the antioxidant potential was diminished. Significantly increased superoxide baseline level was detected in liquidators (68,7±-9,0 nmol/10^6 cells per 10 min,$P<0,01$) compared to control (20,1-±9,1 nmol/10^6 cells per 10 min).The same pattern was detected in hydrogen peroxide (controls: 39,8-±5,6 nmol/10^6 cells per 10 min, liquidators: 78,5-±22,2 nmol/10^6 cells per 10 min, $P<0,01$). The oxidative destruction of lipids and proteins was found to be induced by free radical action. TBARS level in alveolar macrophages of liquidators was more than three times higher compared to controls. The differences in TBARS in plasma were not significant. Enhanced levels of protein carbonyl groups were found as well.

Average concentrations of thyroid hormones TT3 were found to be 0.9±0.11ng/ml: TT4 - 83,5±8,63ng/ml; TSH - 1,45±0,5 mIU/l. The decrease of TT3 in liquidators was detected most frequently. In 19% liqudators examined, TT3 was below the reference value (0,8 ng/ml). The TT3 level was registered at the low limit of the reference range (0,8 ng/ml) in 18% of liquidators. TSH concentration was raised in 12% cases (> 3,2 mIU/l). Moreover, in a half of those cases the impairment of the negative feed-back relationship (TT3-TSH) was detected.

DISCUSSION

Reduction of TT3 in liquidators may be considered as a latent hypothyroid state. possibly due to both direct influence of accident factors and the imbalance of thyroid hormones conversion. Therefore, "low T3" syndrome may be considered as a cell protection weakening.

The TT3 reduction was not accompanied by changes of FT3 and FT4. Hence, an impairment of hormone transport mechanisms could be supposed. It is evidenced by decrease of the T3/FT4 ratio.

It is known that thyroid hormones possess an ability to modify free radical damage to lipids, proteins and nucleic acids by regulation of cellular metabolism. They therefore act as antioxidants and cell protective agents.

All the cellular protective mechanisms take part in processes of DNA synthesis and repair, transcription and translation, cell respiration and metabolism. Significant impairment of the cellular protective systems in liquidators could be regarded as a base of persistent "chromosomal pathology" and imbalance of metabolism complicated by the various diseases including oncology.

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TUMOUR MARKERS IN CHERNOBYL ACCIDENT RECOVERY WORKERS IN THE LATE POST-ACCIDENT PERIOD

L. DRYGUINA, E. STRUCOV, A. NIKIFOROV
ALL-RUSSIA CENTER OF EMERGENCY AND RADIATION MEDICINE
SAINT-PETERSBURG, RUSSIA

ABSTRACT

Tumour markers (TM) are base plasma proteins with a carbohydrate component, produced by various types of tumor cells.

84 male liquidators aged from 30 to 50 y.o. were examined in the clinic of All-Russian Center of Emergency and Radiation Medicine in September 1994-April 1995. External irradiation exposure amongst liquidators varied from 2 to 30 sGr. TM concentration in serum and plasma were determined by conventional ELISA methods (CEA, AFP, CA19-9, PSA, NSE).

The first (control) group was composed of liquidators with no GI tract pathology. The second group consisted of 28 liquidators with irradiation - induced cytogenetical disturbances in peripheral blood lymphocytes. The third group consisted included 28 liquidators with chronic GI tract deseases.

In control group, levels of CA 19-9, CEA and AFP amounted to 4.7± 0..4 U/ml, 2.4± 0.8mg/ml, 2.1± 0.2 IU/ml, correspondingly. The CA 19-9 level has been shown to increase statistically significantly in the second (14.5±1.5 U/ml) and in the third group (17.8± 1.2 U/ml). A simultaneous elevation of CA 19-9 and CEA was found in 7.1% of the liquidators of the third group, the CA 19-9 level changes ranging from 63 to 708 U/ml. The mean value of PSA in all three groups remained within the discrimination concentration limits and amounted to 2.5± 0.4 U/ml. Concentration of NSE was equal to 29.9± 7.2 mg/ml in all three groups.

Based on the data on frequencies of the tumour marker elevation, a group of 6 was selected.This group required a detailed dynamic examination because of the problem of remote consequences of the effect of complex factors of the Chernobyl Atomic Station accident upon its victims.

INTRODUCTION

Tumour markers (TM) are base plasma proteins with a carbohydrate component, produced by various types of tumor cells. Numerous data [1,2,11] show that presence and concentration of TM in blood correlate with the presence and growth of malignant tumours in the individual concerned. Chronic disease and benign conditions can also affect TM concentration. The problem of discrimination between benign and malignant conditions by TM concentration is not yet solved.

Two oncofetal markers - AFP and CEA and carbohydrate antigen CA 19-9 are used for digestive system organs monitoring. In healthy individuals AFP concentration does not exceed 10 IU/ml [5,6], CEA - 5 ng/ml [8], CA 19-9 - 37 U/ml [5,6]. In case of primary hepatocellular, germ cell [12], gastric, colorectal carcinoma those levels could be increased ten-fold and more. Elevated serum levels of AFP, CEA, CA 19-9 are also seen in liver cirrhosis, viral and chronic active hepatitis, infectious mononucleosis, pancreatitis, peptic ulcers [7].

Prostate-specific antigen (PSA) is used for monitoring prostate status. It is used for differential diagnosis between benign prostatic hyperplasia and prostate adenocarcinoma [11].

NSE (Neuron-specific enolase) can be used as an apudoma (e.g. insuloma, pheochromocytoma, etc.) [9] and small-cell lung carcinoma marker.

Chernobyl accident recovery workers (liquidators) tend to reveal complicated course of somatic (including gastrointestinal) disorders. They are also at high risk group for developing pre-cancer and neoplastic conditions.

TM were studied in liquidators as a part of tumours screening programme. High-risk group was formed based on the results of the study.

MATERIALS AND METHODS

84 male liquidators aged from 30 up to 55 y.o. were examined in the clinic of All-Russian Center of Emergency and Radiation Medicine in September 1994 - April 1995. External irradiation exposure amongst liquidators varied from 2 to 30 sGr. TM concentrations in serum and plasma were determined by conventional ELISA methods (CEA, AFP, CA 19-9, PSA and NSE test-kits were obtained from Hoffman-La-Roshe, Switzerland).

Upper limits of serum/plasma concentration of tumour markers in healthy persons were considered as "cut-off" values [1]. Those limits were set as 5 mg/ml for CEA, 10 IU/ml for AFP, 37 U/ml for CA 19-9, and 10 U/ml for PSA respectively.

All 84 liquidators were divided into three groups (n=28). After examination no pathology were seen in the first group of patients. Patients of the second group had demonstrated irradiation-iduced changes in peripheral lymphocytes (decentric or ringcentromere chromosomes), but no other pathology. Patients of the third group were diagnosed as having various gastrointestinal disorders (chronic gastritis, gastroduodenitis, peptic ulcers of stomach and duodenum).

RESULTS AND DISCUSSION

TM concentration values presented in Table I. Mean serum CEA, AFP, CA 19-9 concentrations did not exceed normal values. The third group patients demonstrated elevated levels of CEA, AFP, CA 19-9 comparing to the patients of the first and the second groups. The difference in CA 19-9 serum concentrations between the first group (4.7± 0.4 U/ml) and the third group (17.8± 1.16 U/ml) was statistically significant (P>95).

Table I

TM serum concentrations (X± m)

Group of patients	CA 19-9	CEA	AFP	PSA
Group # 1 (n=28)	4.70± 0.40	2.40± 0.77	2.10± 0.20	2.60± 0.50
Group # 2 (n=28)	14.50±1.50	2.26± 0.31	3.98± 0.61	2.50± 0.35
Group # 3 (n=28)	17.80± 1.16	3.55± 1.20	4.38± 0.85	2.45± 0.22

Mean PSA values were within reference range (up to 10 U/ml) in all groups. PSA concentration varied from 2.5 up 3.5 U/ml, e.g. at the moment of liquidators examination no signs of prostate pathology were revealed by chemistry tests.

The analysis of serum CA 19-9, CEA, AFP concentrations distribution showed raised CA 19-9 levels (45-63 U/ml) in 14.8% of cases in group # 3. One patient has CA 19-9 concentration - 708 U/ml. Patients with serum CEA and AFP elevated levels have not have figures of concentrations more than 10 mg/ml for CEA and 20 IU/ml for AFP correspondingly.

In the first and second groups only occasional elevations above "cut-off" value were observed. Those figures are presented at Table II.

Table II

Distribution of the elevated TM serum levels (%)

Tumour marker	Group # 1	Group # 2	Group # 3
CA 19-9	0	4.8	14.8
CEA	3.5	0	21.4
AFP	0	5	8
PSA	0	0	0

If pathologic changes of TM concentrations were seen on admission, TM levels were checked during staying in the clinic and after treatment course aimed to differentiate specific and non-specific CEA, AFP, CA 19-9 concentration changes. In most of the patients of the third group conventional treatment were beneficial for reducing CEA, AFP and CA 19-9 levels. No such changes in group # 2 and # 1 were observed (Table III).

Table III

Distribution of the elevated TM serum levels (%) after treatment

Tumour marker	Group # 1	Group # 2	Group # 3
CA 19-9	0	4.8	7.1
CEA	3.5	0	7.1
AFP	0	5	0

Simultaneous elevation of both CA 19-9 and CEA were seen in two patients of the third group (7.1%). One patient has demonstrated stable elevation of CA 19-9 - 708 U/ml and 690 U/ml before and after treatment respectively.

High risk group of six patients was formed in accordance with these results, for more thorough examination of digestive system organs and regular follow up TM control (Table IV).

Table IV

CA 19-9, CEA, AFP serum levels in high- risk group

Patient/group	CA 19-9 U/ml	CEA ng/ml	AFP IU/ml
Patient 1 (gr. 1)	15.7	5.5	2.0
Patient 2 (gr. 2)	95	0.4	3.0
Patient 3 (gr. 2)	21	1.5	24
Patient 4 (gr. 3)	690	1.6	4.4
Patient 5 (gr. 3)	63	6.0	1.8
Patient 6 (gr. 3)	41	31	5.0

NSE levels were also checked in plasma of liquidators. In the second group mean NSE level was 50.7± 13.7 ng/ml, in the first group - 25.7± 5.3 and in the third group - 29.9± 7.2 ng/ml respectively. NSE plasma concentration 22 ng/ml was chosen as a discriminatory value. Although NSE elevated may serve as a high- risk factor for lung carcinoma and neuro-endocrine system carcinoma, instability of lymphocytes, platelets and red blood cells membrane of liquidators may also cause this elevation. The investigation requires continuation.

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Cancer Morbidity Among the Emergency Workers of the Chernobyl Accident

Shantyr I. I., Makarova N.V., Saigina E.B.
Center for Extreme and Radiation Medicine, Ministry of Extreme Accidents
(St.-Petersburg, Russia)

ABSTRACT

The effects on human health of exposures to ionizing radiation have long been the subject of dispute. In this paper we focus on the primary cancer morbidity in the cohort of 8745 men who worked in the cleanup of the Chernobyl accident in 1986-1990 and were followed since exposure up to 1995. The official dosimetry data, mostly falling in the range of 0 - 25 cSv, are available for 75% of ameliorators.

Annual cancer morbidity rates turned out to increase rapidly. However, trend analysis in the age-specific subgroups provides evidence that the observed temporal gradients are to be attributed to the ageing (regression coefficients for the age groups of 40-44; 45-49; 50-54 are 0.201; 0.793 and 1.223, correspondingly). In the five-year age groups cancer morbidity of the emergency workers (Ews) makes no statistically significant differences with that of the male populations of Russia and St-Petersburg. No evidence of an association between radiation dose and cancer morbidity was observed. The highest primary cancer morbidity is registered among those EWs. who arrived to Chernobyl region within 360 days followed the accident and had been working there during less than 30 or more than 180 days. The follow-up of the cohort is to be continued.

As a matter of fact, malignant neoplasms are considered to be the most dangerous health effect of ionizing radiation. We studied the primary cancer morbidity in the cohort of 8745 men who took part in the cleanup of the Chernobyl accident in 1986-1990 and were followed since exposure up to 1995. At the time of exposure to ionizing radiation their mean age was of 35.3. As many as 75% of EWs have got official records concerning the radiation dose absorbed, 98% of them fall in the range of 0 - 25 cSv.

Annual cancer morbidity rates turned out to increase rapidly. In order to avoid age-dependence bias we estimated cancer morbidity in the stratified age groups (Figure 1).

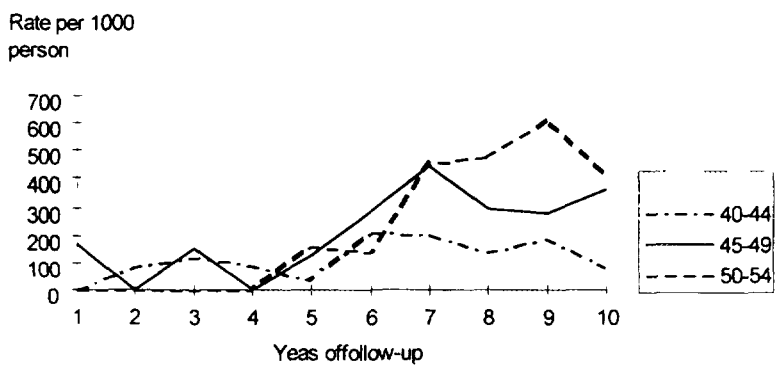

Figure 1. Cancer morbidity per 1,000 EWs in the age groups of 40-44. 45-49. 50-54 at baseline in the years of follow-up.

However, trend analysis in the age-specific subgroups provides evidence that the observed temporal gradients of the cancer morbidity are to be attributed mostly to the ageing effect (linear regression coefficients for the age groups of 40-44; 45-49; 50-54 are 0.201; 0.793 and 1.223, correspondingly).

In the five-year age groups cancer morbidity of the EWs makes no statistically significant differences from that of the male populations of Russia and St-Petersburg, former Leningrad (Table I).

Table I

Primary cancer morbidity rates among EWs of the Chernobyl accident and in the reference populations (per 1,000 persons)

Age groups	30-34	35-39	40-44	45-49	50-54	55-59
EWs, 1990-1994	0.557	0.788	1.601	3.007	3.696	4.494
Russian male population, 1994 [1]	0.33	0.61	1.49	2.97	5.33	8.29
St.-Petersburg male population, 1988 [2]	0.33	0.55	1.35	2.89	5.23	8.65

There is no evidence of an association between radiation dose and cancer morbidity. No statistically significant differences were revealed while comparing cancer morbidity rates among those who took part in the cleanup of the Chernobyl accident and got definite dose of the ionizing radiation (Table II).

Table II

Cancer morbidity rates among EWs of the Chernobyl accident with different radiation dose absorbed.

Radiation dose, cSv	Cancer morbidity rates (per 1,000 persons)
0-5	1.97
5.1-10	2.21
10.1-15	4.06
15.1-20	2.31
20.1-25	2.03
> 25	6.21

Additional results concerning cancer morbidity among the exposed cohort are based on non-linear regression and exponential functions. Taking into consideration the history of radiation exposure (duration of work in the cleanup and the number of days in between the accident and person's arrival to the contaminated region), we obtained expected morbidity rates. The regression equation is as follows:

$$Y = 1.043 + 3.706\, e^{(-0.002 * a - 0.048 * b)}$$

where Y - cancer morbidity;

a - number of days in between the accident and person's arrival to the contaminated region;

b - duration of work in the cleanup, days.

Estimates, based on 38 known cancer morbidity rates associated with definite history of radiation exposure, are displayed in the Figure 2. Results have been calculated with the use of the approximation procedure in CSS statistical package. The same magnitudes of the varibles are connected, corresponding cancer morbidity rates are given in the legend.

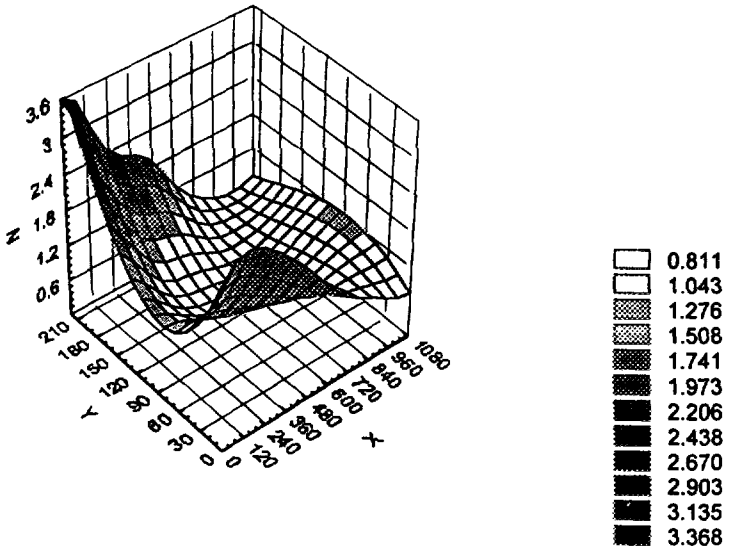

Figure 2. Cancer morbidity in relation to the history of radiation exposure.

X- number of days in between the accident and person's arrival to the contaminated region;

Y - duration of work in the cleanup, days;

Z - cancer morbidity rates per 1,000 persons.

The highest primary cancer morbidity is registered among those EWs, who arrived to Chernobyl region within 360 days followed the accident and had been working there during less than 30 or more than 180 days. The follow-up of the cohort is to be continued.

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MULTIPLE ENDOCRINE NEOPLASIA (MEN) - LIKE SYNDROME AND OTHER HORMONAL FACTORS OF PROMOTION AND PROGRESSION OF THYROID GLAND CANCER IN MALES-LIQUIDATORS OF CHERNOBYL ACCIDENT CONSEQUENCES

Strukov E.L., Dryguina L.B., Nikiforova I.D.
All Russia Centre for Emergency and Radiation Medicine
Ministry of Emergency Situations, Russia
St.Petersburg

XA9745639

ABSTRACT

The clinical and laboratory endocrinological screening performed in 1,000 males - liquidators of Cernobyl accident consequences revealed hormonal factors leading to node formation and having unfavourable influence on progression and promotion of thyroid gland cancer.

The factors include syndrome of low thriiodothyronine, hyperprolactinemia, latent hypothyrosis and increased production of thyroglobulin.

Peculiarities of hormonal status in liquidators allow us to suggest the presence of MEN-like syndrome among the liquidators population. Possible mechanisms of expression of RET oncogene in adults that may result in MEN- like syndrome have been discussed.

The experiments on animals demonstrated multistage character of thyroid carcinogenesis.

The recent studies made in 1,000 males-liquidators in 5-10 years after the accident show the most important factors contributing to promotion and progression of radiation-induced damage of thyroid gland to be the following:

- hyperprolactinemia
- the syndrome of low level of triiodothyronine (low T_3)
- latent hypothyrosis
- increase in thyroglobulin level

The interaction of these factors leading to the formation of both small (diameter less than 1 cm) and large (diameter more than 1 cm) sonographic nodes in thyroid gland which represent the stages of thyroid carcinogenesis, is shown in fig.1.

Prolactin is known to be tumor promotor and mitogen in mammalian [1]. It has been shown that hyperprolactenemia serves as a marker of the progression and severe course in a number of tumor disorders such as breast carcinoma, cervical carcinoma, colorectal carcinoma, leukemia.

The decrease in the triiodothyronine (T_3) level is characteristic of some severe nonthyroid general somatic diseases and some nonthyroid cancers.

At present the study of oncogene RET is considered to be essential in pathogenesis of thyroid gland cancer [2,3].

This oncogene is expressed in both papillary as well as radiation-induced thyroid gland cancers, and medullary cancers arising from C-cells which generally have genetic origin.

MEN syndrome is characterized by the presence of hyperplasia or carcinoma of two or more endocrine glands [4].

The evidence of medullary cancer of thyroid gland is one of the masnifestations of multiple endocrine neoplasia (MEN) syndrome of the 2nd type.

The study by V.A. Mishagin [5] demonstrated that exposure of thyroid gland in the dose range 200-500cSv as a result of Cernobyl accident resulted in the stimulation of thyroid gland C cells

The characteristic feature of MEN syndrome of the 1st type is the combination of hyperplasia of parathyroid gland, pituitary adenomas and hyperproduction of gastrointestinal tract hormones.

Our studies showed high incidence of hyperprolactinemia in males-liquidators that amounted up to 22%.

26% of liquidators had colonic polyps and elevated histamine - induced stomach secretion.

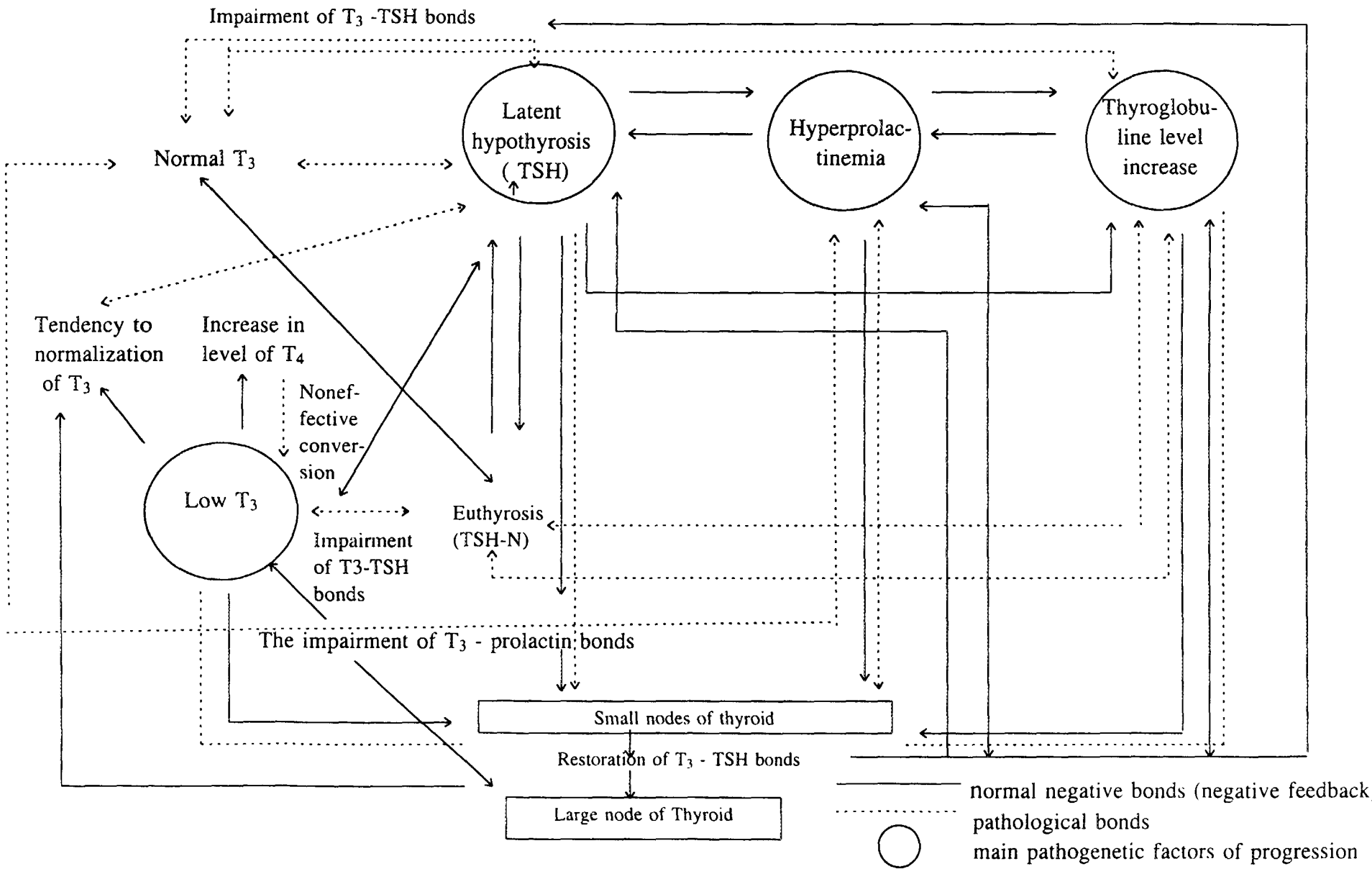

Fig. 1 Progression of nodular formation in thyroid gland in male-liquidators

The tendency to the decrease in mineralization (decrease in BMD) in bones of lower extremities and the increase in bone density in upper extremities under normal values of BMD in liquidators of 1986, found with the help of densitometry by the method of "total body", as well as the presence of osteoporosis of the whole body in some liquidators makes us to suspect the presence of hyperparathyroidism in a group of the individuals studied.

The MEN II syndrome is usually associated with medullary thyroid gland cancer and pheochromocytoma.

We followed up some liquidators with adrenal hyperplasia and the evidence of vanillylmandelic acid excretion. Thus there occurred hormonal shift in the spectrum similar to multiple endocine neoplasia syndrome.

The prognosis of the course of MEN is known to be quite favourable for life and decades may pass between the manifestations of hyperplasia of the second glands. Among 10 thousand of males liquidators of the North-Westen region of Russia followed up for eight years six histologically verified cases of thyroid gland cancer have been reported, with follicular cancers being predominant.

The presence of unstable genome in males liquidators of the Gernobyl accident consequences has been proved.

MEN like syndrome observed in liquidators is likely to be the reflection of genome instability at hormonal level.

Thus one can make a conclusion that RET oncogene expression in infancy leads to the development of papillary cancers, whereas in adults C-cells of the thyroid gland are activated and MEN like syndrome develops.

7 of 500 males liquidators studied were supposed to have the syndrome of multiple endocrine neoplasia, but no hyperplasia or cancer of the second endocrine organ has been found.

It must be pointed out that in the process of oncogene expression RET chromosome reorganization involves the 10^{th} chromosome 10 (q 11.2 q 21) [6] and structural abnormalities in the neighbouring 11^{th} cromosome lead to MEN I development [7].

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"TAILED" NUCLEI ARE A POSSIBLE CELL MARKER OF RADIATIONAL EFFECTS

Kravtsov V.Yu.*, Starkova E.V.*, Loginova Yu.A.*, Yakovlev A.F.*,
Nikiforov A.M.*, Fedortseva R.F.*
*All-Russian Center of Emergency and Radiation Medicine,
*All-Russian Institute of Animals Genetics
St. Petersburg, RUSSIA

ABSTRACT

Study of peripheral blood smears from irradiated patients (liquidators of consequences of the Chernobyl Atomic Electric Plant accident) has shown nuclei of some lymphocytes to have a protrusion into the cytoplasm. Such abnormal nuclei are called "tailed" nuclei (TN). The mean frequency of appearance of lymphocytes with TN in the group of irradiated patients (n=136) amounted to 0.59%, whereas in the group of healthy donors (n=50), 0.15% (the difference between the groups is statistically significant). The correlation coefficient between the indicators "frequency of lymphocytes with NT" and "frequency of lymphocytes with dicentric chromosomes" was 0.73 (n=47, $p<0.001$). By the method of bicolour FISH there was revealed localization of the near-centromere (not more than two signals) and telomere (not more than one signal) regions in the nuclear "tails". Abnormalities of the TN type in lymphocytes are likely to result from breakdowns of chromosomal bridges formed by dicentric chromosomes.

INTRODUCTION

Appearance of dicentric chromosomes leads, as a rule, to formation of chromosomal bridges. One of the possible results of completion of cell divisions can be breakdown of these bridges, with the subsequent formation of semi-bridges or, in other words, "tailed" nuclei (TN) [1]. As polycentric chromosomes are markers of radiational effects, anomalies of the cell nuclei of the "tail" type are rightly considered radiospecific.

The present work deals with the TN in lymphocytes of irradiated patients, liquidators of the Chernobyl Atomic Electric Plant accident. Incidence frequencies of lymphocytes with TN in the peripheral blood of the liquidators and of healthy donors were determined as well as a correlation between indicators "frequency of lymphocytes with TN" and "frequency of dicentrics". To study origin of the NT, we used method of the bicolour FISH to locate the near-centromere and telomere heterochromatin in the nuclear "tails".

MATERIAL AND METHODS

The group of patients was composed of 135 men, liquidators of the Chernobyl Atomic Electric Plant accident, who were irradiated 6-11 years ago, the control group, of 50 healthy men. Giemsa-stained hematologic preparations were obtained by the routine procedure. In each man, 500 lymphocytes were analyzed. Preparations of lymphocyte metaphase chromosomes were obtained by a micromethod after the 48-hr long cultivation [2].

The bicolour hybridization in situ was performed on the peripheral blood smears by the method [3]. As DNA probes for the FISH, there were used the plasmide Bluescript KS

that is biotinized using the nick-translation and contains the telomere-specific sequence (TTAGGG)n of the 181 n.b. length, as well as the alphoid DNA probe specific for the centromere regions of all human chromosomes (Cambio). To detect hybridizational signals, the standard system was used. FITC and TRITC served as detectors of the biotinized probe and of the probe labeled with digoxigenine, respectively.

RESUTS AND DISCUSSION

The "tails" of lymphocyte nuclei in our observations represented morphological anomalies, with the nuclei showing a protrusion into the cytoplasm. All types of the revealed TN (more than 1000 observations) are presented in Fig. 1.

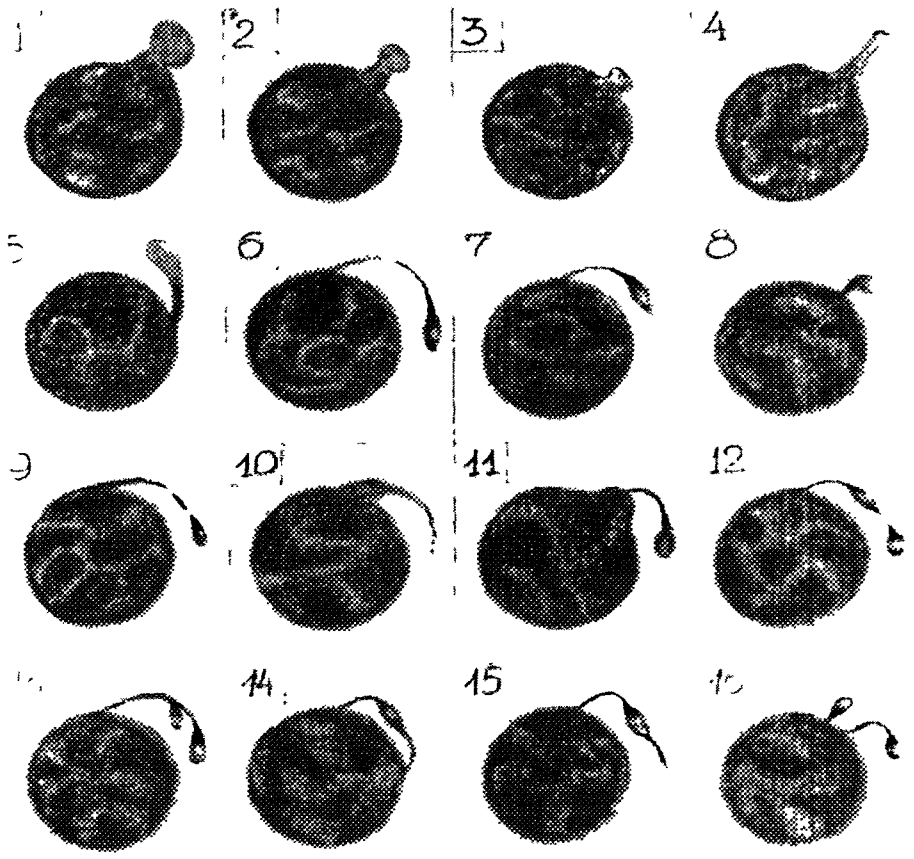

Fig 1 The observed types of "tailed" nuclei in lymphocytes of the human peripheral blood.

The TN in lymphocytes were seen in most liquidators (more than in 85%), whereas in the control group, more than 50% of the people had no lymphocytes with TN This difference between the liquidator and control groups was statistically significant ($p<0.0\,001$, the Mann-Whittney's test) The mean frequency of the incidence of lymphocytes with TN in the group of liquidators amounted to 0.59%, whereas in the control gtoup, to 0 15%

In 47 patients of the liquidators' group with different frequencies of incidence of lymphocytes with TN, frequency of metaphases with dicentric chromosomes was determined

There was revealed a positive correlation between the indicators "frequency of lymphocytes with TN in the peripheral blood in vivo" and "frequency of PHA-stimulated lymphocytes with dicentrics in culture in vitro"; this correlation turned out to be statistically significant ($p<0.001$), and the correlation coefficient computed according to Spearman amounted to 0.73.

It is important to note that the binuclear lymphocytes also were observed in the peripheral blood smears. Frequency of the incidence of such lymphocytes was 0.06% in the liquidators' group, whereas no bridges were found in the control group.

The bicolour fluorescent hybridization in situ revealed that centromeres were located predominantly in the base and/or in the region of the chromatin enlargement at the end of the "tails", while telomeres, only in the latter region (Fig. 2).

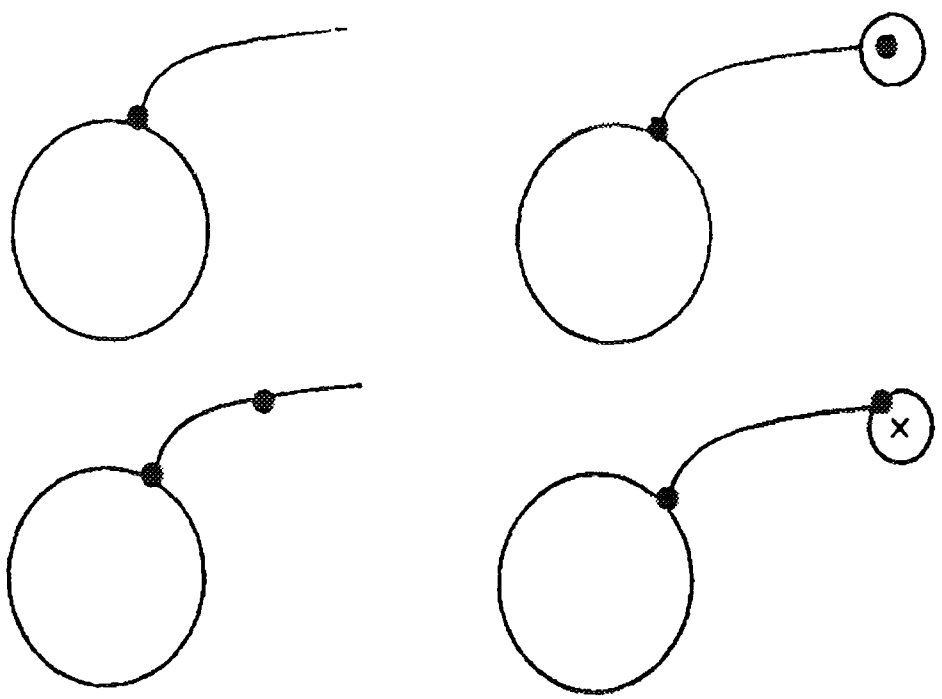

Fig. 2. Scheme of localization of the centromere signals revealed by TRITC (•) and telomere signals revealed by FITC (x) in the "tails" of lymphocytic nuclei.

Among 46 TN examined there were no "tails" with more than two centromere signals and one telomere signal. This indicates the nuclear "tails" to be probably formed by one and/or two chromosomes. It is also to be noted that sometimes in the lymphocyte culture in vitro there were revealed the "tailed" cells at the stage of prophase. In such cells, the "tails" always represented two parallel chromatin bands.

The data obtained seem to allow the following conclusions to be made. In the liquidators irradiated with small doses 6-11 years ago, the frequency of the incidence of lymphocytes with TN is increased. Most likely, this is due to the chromosomal cycles "breakdown ---> fusion ---> bridge" occuring in the lymphocytic population. The formation of the anomaly of interphase nuclei of the "tail" type seems to be due to appearance of dicentric chromosomes, chromosomal bridges with their subsequent breakdown. The proposed scheme of the formation of cells with the TN is presented in Fig. 3.

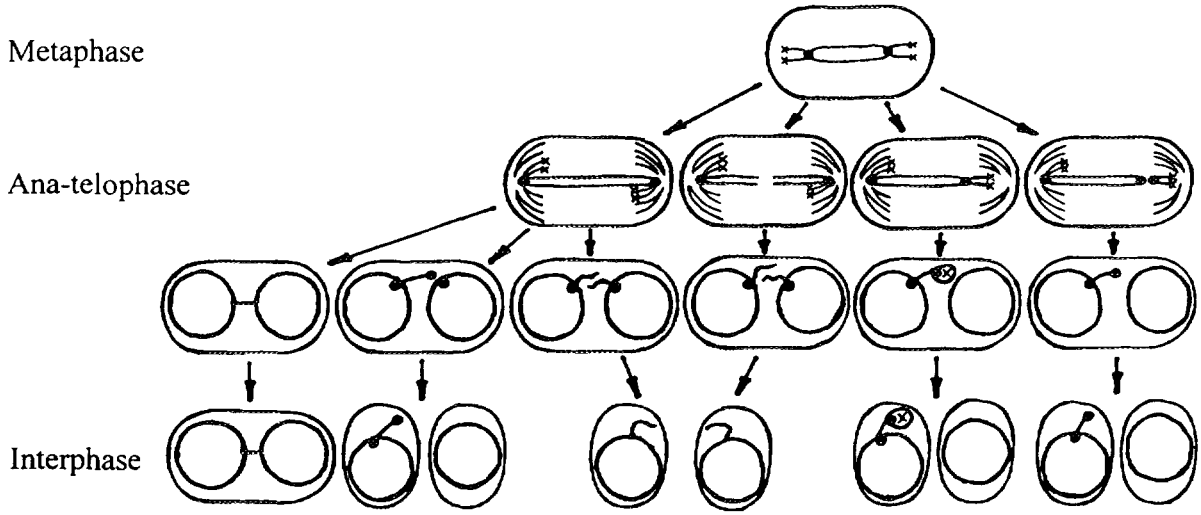

Fig. 3. The proposed schemes of formation of "tailed" nuclei.
•- centromere, x - telomere

It cannot be ruled out that the nuclear "tails" can include chromatin of the entire dicentric chromosome rather than a half of the broken dicentric only; this is confirmed by the data of study on the near-centromere and telomere regions of the chromosomes in the "tails". For this reason, to designate the nuclear anomalies considered in the current work, the term "tailed nuclei" rather than "semi-bridge" was chosen. We believe that the TN might become a convenient marker of radiational effects in radiobiologic investigations.

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CHANGING OF EXPRESSION LEVEL OF FAS-ANTIGEN (CD95), CYTOKINES SYNTHESIS AND PRODUCTION AFTER IRRADIATION IN LOW DOSES

N. M. Kalinina, O. S. Solntceva, N. V. Bytchkova, A.M. Nikiforov

All-Russian Center of Emergency and Radiation Medicine Emercom of Russia (ARCERM), Saint-Petersburg, Russia

Abstract

It is known that bone marrow progenitor (CD34+), tymocytes and peripheral blood lymphocytes (PBL) are most radiosensitive than other cell types. Even low doses of radiation induce apoptosis. The investigators suggest that it is possible relationship between synthesis and production of cytokines and apoptotic process. With the purpose to determine correlation between expression of Fas-antigen and synthesis of cytokines after low doses irradiation the experiments by irradiation PBL of healthy persons in vitro were held. Cells were X-irradiated by 12,5, 25 and 50 cGy. In consequence of the experiments increasing of Fas-antigen was revealed. This increasing correlated with changing in synthesis and production of cytokines. Also the Chernobyl's accident liquidators (CAL) were investigated. After comparison data in the group CAL (I) with data in the control group (II) increasing of Fas-antigen expression was revealed. Also in I group was discovered increasing of the cell number sinthesied interleukine-4 (IL-4) and interleukine-6 (IL-6). Interleukine-1β (IL-1 β) producting cell were decreased. These changes have been correlated with degree of immunodeficiency at CAL. These data allow to consider the apoptosis as cell mechanism included in pathogenesis of diseases, wich can be showed later long time after irradiation.

1. Introduction

All multicellular organisms have mechanisms for killing there own cell and use phisiological cell death for defence, development, homeostasis and aging. Studies on dying cells reveal two differential types of cell death: necrotic death and apoptotic or programmed cell death. Apoptosis as a kind of the cell death was orriginally recognised by Kerr, Wyllis & Currie [1] who coined the term "apoptosis" to specifically distinguish programmed cell death from necrotic death. A trenendous variety of both chemical and phisical stimuli can induce apoptosis. The normal healthy immune system utilizes apoptosis to regulate the numbers of effector lymphocytes in the body both prior and following exposure to foreign antigens [2]. Apoptosis is included in the pathogenesis of variety of diseases : cancer [3], acute inflammatory diseases [4] and autoimmunity [5]. It has been demonstrated that apoptosis induced by low doses of ionising irradiation [6,7]. The exposure by X- irradiation resulted in apoptotic changes in all lymphocyte subpopulations. Natural killer (NK) cells were the most radiosensitive, whereas CD8+ and CD4+ cells were relatively radioresistant [8]. Investigators [9] suggested that radiation- induced diseases of immune sistem resulted in immunodeficiency depended on dose of irradiation and time after irradiation. There is considerable interest is weather cytokines could protect or promote PBL apoptosis induced by radiation. It is known that IL-1β is a most effective protective after irradiation [10]. In the contrast TNF-α promote apoptosis in PBL [11]. Apart from IL-1β other cytokines demonstrated protective actions: IL-2, IL-4, IL-7 inhibited differentially radiation-induced apoptosis in PBL subpopulations [8], IL-10 - in B cells of lymph node germinal centers [12].

2. Materials and methods

Peripheral blood from healthy adult volonteers (n=15) and CAL (n=18) was collected. For experiment blood samples from volonteers was irradiated by 12,5; 25 and 50 cGy.

To reveal the apoptotic cells 100 μl of heparinised peripheral blood was incubated with RD-conjugated anti-CD95 monoclonal antibody (mAb) for 45 min at room temperature and washed once in PBS. RD-conjugated anti- mouse IgM was used as the control. After two washes these cells were lysied and fixed by whole blood lysing reagent (Coulter, USA) for 1 min at room temperature.

To analyse of cytokine synthesis and production in single cell level the peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Hystopaque density gradient centrifugation. After three washes PBMC were incubated with non-conjugated anti-IL -1β mAb, anti-IL-4 mAb, anti-IL-6 mAb, anti-TNF-α mAb and anti-IFN-α mAb for 30 min at 4°C. Than PBMC were stained with FITC for 30 min at 4°C. FITC-staining PBMC without mAb was used as the control. To analyse the PBMC cytokine synthesis saponin was used as detergent.

To analyse cells by flow cytometry all kinds of cell: non-irradiated, liquidator's PBMC and irradiated cells from healthy persons were washed once in PBS and evaluated by EPICS XL (Coulter Corporation, USA).

Number of lymphocytes subpopulations was estimated by using anti-CD4, CD8, CD16, CD20 mAb.

We are applied the methods of variation statistic and statistical significance was assesed using U-test Mann-Whitney.

3. Results

Data have been recieved in our experiments demonstrated increasing of Fas-antigen expression after exposure by radiation(4,2±1,2% cells in the control group; 31,4±6,8% after exposure by dose 12,5 cGy, $p<0,001$; 18,0±3,2% after exposure by dose 25 cGy, $p<0,01$; 22,0± 4,4 % after exposure by dose 50 cGy, $p<0,01$) (fig.1). Obtained data correlated with decreasing of CD16 cells after irradiation wich appears most radiosensitive then other lymphocyte subpopulations (tabl.I).

In the experiment we was shown decreasing of IL-1β producing cell level after irradiation at dose 12,5 cGy and significant increasing TNF- α producing cells in the same dose and 50 cGy (as compared with control) (tabl.I). At doses 25 and 50 cGy were obtained increasing of IL-4 synthesing cells (tabl. I). The number IFN-α producing cells was higher ($p<0,05$) after 50 cGy x-irradiation (tabl. I).

Together with experimental study CAL were investigated. We obtained increased number of apoptotic cells (13,4±2,2% as compared with 4,17±1,2% in a control group, $p<0,001$) (fig. 1). CAL also had decrease number of cell producting IL-1β which is appear the most of significant protector from radiation and decreased number of cell with IL-6 synthesis. Changes in Fas-antigen expression, cytokines synthesis and production at CAL correlated with degree of immunodeficiency.

4. Discussion

It is known that low doses of ionising radiation in experiments results in initiation of apoptosis in immune system [6,7]. The main role in immune cells apoptosis play thedisturbances of cytokine synthesis and production(IL-1β, IL-4, IL-6, TNF-α) [8,10]. Our data confurmed these positions. Disturbances in cytokines synthesis and production in I group (CAL) in many respects coincide with experimental data. Monitoring of blood sera cytokine levels in I group testify permanent increasing of TNF-α, promoting apoptosis. In contrast data about decreasing the number of cells

producting IL-1β permit to propose the existance of prolonged mechanism supporting the disturbances in cytokine synthesis and production, inducing apoptosis, which play certain role in pathogenesis of diseases in this group.

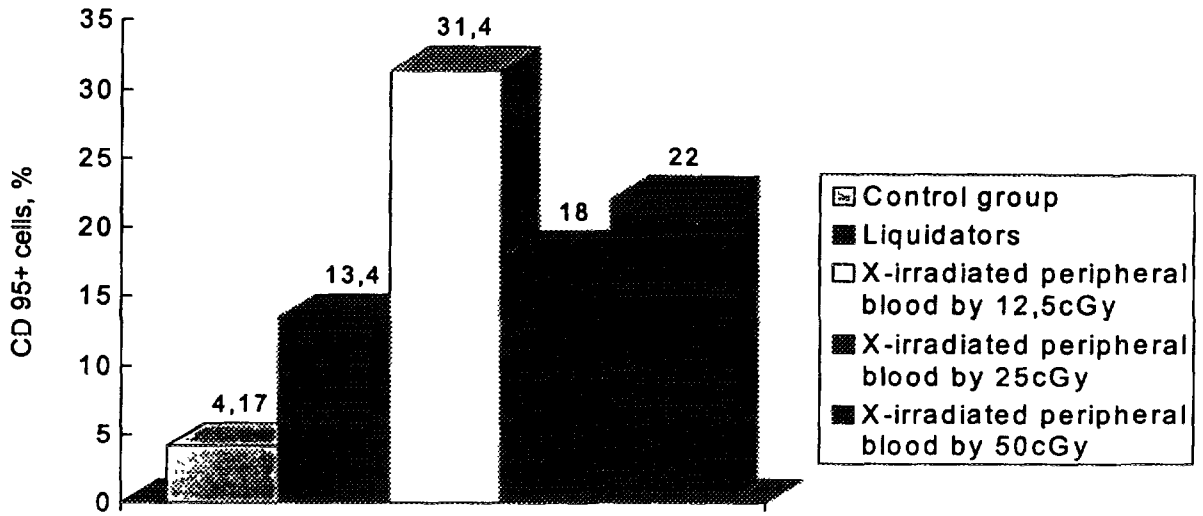

Figure 1. Fas-antigen expression in PBL of control group, liquidators and after irradiation in vitro.

Table I. CD16+ cells and lymphocytes with surface and intracellular forms of cytokines in control group, liquidators and after irradiation in vitro.

Parameters	Content of lymphocytes (%)				
	Control group	Experimental group			CAL
		12,5 cGy	25 cGy	50 cGy	
CD16	22,0±1,9	17,0±0,4*	18,6±1,6	20,6±1,3	20,9±0,5
Interleukine-1β (surface)	7,7±1,2	5,0±2,3*	8,8±1,9	8,2±2,1	4,0±0,7**
Tumor necrosis factor α (surface)	3,7±1,0	7,8±1,5*	7,0±2,0	6,8±1,3*	3,8±0,8
Interferone-α (surface)	3,1±0,9	4,9±1,2	4,6±1,2	6,8±1,8*	3,3±0,7
Interleukine-4 (intracellular)	5,6±1,1	8,2±1,3	10,5±1,6*	7,8±1,1*	7,8±1,7
Interleukine-6 (intracellular)	12,1±1,5	12,8±2,4	10,8±2,2	12,5±1,8	5,6±0,9**

* - $p<0,05$, ** - $p<0,01$ in comparison with control group

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PECULIAR CELLULAR MECHANISMS OF EFFECTS OF THE LOW-DOSE IONIZING RADIATION

Fedortseva R.F., Stepanov R.P., Antonov P.V., Nikiforov A.M., Bychkovskaya I.B.
All-Russian Center of Emergency and Radiation Medicine, Institute of Experimental Medicine RAMS
St. Petersburg, Russia

ABSTRACT

In biological objects of different organization, peculiar, non-mutational cell changes have been revealed, which, unlike the known changes, might be responsible for development of the tissue, organ, and organism disturbances after low-dose loads. Myocardium capillary endothelium have been examined ultrastructurally in 236 rats irradiated in a dose 0.5 Gy as well as (to characterize the effect) in doses of 2.25 and 4.5 Gy. Similarly 28 intact control animals were studied. Already of the lowest dose, 0.5 Gy, has been established to produce an increasing appearance of damaged cells with signs of oedema, partial cytolysis of cytoplasmic structures amd isolated damage of mitochondria. All these kinds of changes were also observed in control, but much less frequency. These changes fully develop already after the relatively small doses of ionizing radiation, are of a massive character and are practically irreversible. This effect is manifested as a steady rise in the probability of the cell injury and death as compared with the spontaneous level and can be considered a new setup of the cell homeostasis.

INTRODUCTION

From the viewpoint of classic radiobiology, it is difficult to agree with data that are obtained, in particular, when evaluating consequences of the Chernobyl Atomic Electric Plant accident, about various non-stochastic impairments resulted from small doses of ionizing radiation. Indeed, the traditionally studied radiation-induced cellular (predominantly cytogenetic) effects under these conditions appear in a slight amount, are prone to reparation and thereby cannot lead to this pathology. However, there are unusual cellular effects which, due to their massive and actual irreversibility, might participate in pathogenesis of the non-stochastic impairments after the low-dose irradiation.

Such effects were earlier discovered in model experiments in various unicellular organisms [1, 2]. In the currrent work, we have shown that similar responses are also peculiar to cells of multicellular organisms.

MATERIAL AND METHODS

The electron microscopy study was performed on the myocardium capillary endothelium of 236 randomly bred male rats weighing 120-150 g. They were submitted to the total X-ray irradiation in a dose of 0.5 Gy as well as (to characterize the effect) in doses of 2.25 and 4.5 Gy using a RUM-17 X-ray apparatus with the voltage 200 kV, current 15 mA, filters 0.5 mm + 1.0 mm A, focus distance 50 cm, power of the dose absorbed 0.92 Gy/min. The animals were sacrificed by decapitation after a preliminary narcosis. The standard procedure of preparation of the material for electron microscopy was used. The study was performed for 12-18 months which corresponds to the most part of the rat life span. At each time period after the effect the material was taken from 3-4 rats (after the dose of 4.5 Gy, from 6-15 animals), 4-8 pieces from different myocardium areas in each animal. Similarly with the

irradiated rats, 28 intact control animals of the same age were studied. In each rat, 150-900 endothelial cells were analyzed, and the percentage of changed or damaged cells among them was measured. Taken into account were the changes which were due to oedema (at the early stages of cell hyperhyd=0C ration and in the severe oedema), to a partial cytolysis, and to an isolated damage of mitochondria.

All these kinds of changes were also present in control, however, much less frequently. No significant age deviations were found.

These changes occured without any association with mitosis. since its morphological picture was revealed neither in control nor in irradiated animals, and experiments with 3H-thymidine label showed only one cells out of 1000-10000 to enter the mitotic cycle for 24 hr, the duration of the cycle amounting to about 200 days [3].

RESULTS

The experiments performed have shown that in all doses used and according to all indicators of the state of endotheliocytes there are evident deviations from control. These consist in an increase in the frequency of appearance of the changed or damaged cells throughout the study (Table).

Table

Dependence of frequency of appearance of endotheliocytes with different changes on the radiation dose at different time periods after total irradiation (mean values and confidence intervals at P=0.05)

Dose (Gy)	Time interval (hours, days, imonths)	Type of the alterations			
		Hyper hydrationi	Severe oedema	Defects of mito-chondria	Partial cytolysis
0	18 months	3.3±0.66	0.67±0.18	0.6±0.1	0
0.5	1-24 hours	10.0±2.8	3.2±1.4	11.8±1.5	1.8±1.4
	2-30 days	13.5±4.2	2.1±0.8	14.7±5.2	5.3±3.0
	3-18 months	8.6*	2.8*	6.3*	4.3*
2.25	1-24 hours	9.5±1.8	1.3±0.9	9.5±2.0	2.2±0.6
	2-30 days	15.7±5.9	2.6±0.8	17.2±3.9	4.8±3.9
	3-18 months	7.1*	1.9*	6.5*	2.5*
4.5	1-24 hours	6.3±2.6	0.8±0.7	10.6±7.8	2.8±1.9
	2-30 days	8.1±4.3	1.6±1.0	7.9±3.7	12.0±6.9
	3-18 months	10.0±2.4	1.5±0.6	8.5±3.3	1.4±1.1

* - confidence intervals are not presented, as the material is obtained at two time intervals only (3 and 12 months)

A particular attention should be paid to the efficiency in this aspect already of the lowest dose, 0.5 Gy, which is thought to have no effect on relatively radioresistant tissues with a slow turnover. Essential is a peculiar change dynamics not characteristic of the traditionally studied cellular effects. The differences from control appear as soon as for the first hours after the irradiation and then are retained for many months. The same was observed at higher doses, 2.25 and 4.5 Gy, with no increment of the effect with increase of the dose. =0C Such evident dose-independence was possible to be established due to the studied effect being not masked by cytogenetic changes (because of an extremely low mitotic activity). The stable effect for

such a long time indicates a steady preservation by the cells of some hidden potential changes and involvement of the vast majority (or all) cells in the population.

DISCUSSSION

We have demonstrated postradiational changes characterized by such unusual features as dose-independence, irreversivility for the most part of the life span of the animals, massive involvement of cells, early development of the maximal effect already after the low dose irradiation. The same features were revealed in previous experiments on unicellular organisms. Therefore, we believe such changes to be of a rather wide biological significance; they may be interpreted as triggering in different eukaryotic cells of a program providing for the change of cellular homeostasis.

Manifestations of this effect, first of all, its dose-independent and massive character, do not allow it to be explained by mutations. Most likely, we deal here with epigenetic changes [4]. In the medico-ecological aspect, it is essential that pronounced changes in the vascular endothelium were revealed already after a dose 0.5 Gy, i.e. the dose compatible with the average dose obtained by liquidators of consequences of the Chernobyl Atomic Electric Plant accident. This correlates with epidemiologic findings, such as frequent disturbances of the cardio-vascular system in the liquidators. .=0C

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ESTIMATE OF RADIATION DETRIMENT LONG PERIOD AFTER EXPOSURE TO LOW DOSES OF IONIZING RADIATION· CHROMOSOMAL ABERRATIONS IN LIQUIDATORS 6-10 YEARS AFTER THE CHERNOBYL ACCIDENT

A M Nikiforov, N M Slozina, E G Neronova, T V Kharchenko, L B Drygina, E L Strukov

All-Russian Center of Emergency and Radiation Medicine (ARCERM),
St Petersburg, Russia

Abstract

The group of 297 liquidators was cytogenetically investigated 6 - 10 years after the Chernobyl accident The significantly increased level of chromosomal and chromatid types exchange aberrations was shown

For all subjects questionnaires that provide consideration of known and suspected confounding variables were filled in The participation in recovery works at the Chernobyl nuclear power station was the only reason for dicentrics and rings rise in liquidators

An investigation of the tumor-specific markers (CEA, AFP, CA19-9, PSA, NSE) was carried out in 56 liquidators simultaneously with chromosomal analysis The increased level of NSE was found in liquidators bearing the chromosomal aberrations of exchange type

The results of this work let us to consider the liquidators who underwent to low doses of ionizing radiation 6-10 years ago as a detrimental group that needs special scientific and medical attention

1. Introduction

Many thousand inhabitants of former Soviet Union suffered from radiation after the Chernobyl accident More than 400 thousand of them took part in the cleaning works in the Chernobyl region The liquidators were exposed to different types of ionizing radiation As a rule the official dose of irradiation did not exceed 25 cGy but for the most of liquidators the individual doses were unknown The cytogenetical methods of biological dosimetry make it possible to estimate the total rate of radiation from different kinds of sources [1-3] The dose of irradiation in some groups of liquidators was established by the cytogenetical methods in a short period after leaving the zone of the accident [4, 5] Later with longer time after irradiation it became impossible to estimate the connection between the dose and the cytogenetical parameters Nevertheless first years after the accident the exceeded level of cytogenetical radiation markers was found in liquidators [6-8] Follow-up studies on individuals exposed to genotoxic agents have clearly demonstrated the predictive value of high chromosomal damage for subsequent cancer risk [9, 10] So the goal of the this study was to investigate whether any signs of biological detrimental effects exist 6-10 years after exposure to low dozes of radiation

2. Materials and methods

The cytogenetic study was carried out on 297 liquidators 6-10 years after irradiation (between 1992 and 1996), aged 25 to 68 years For the most of the liquidators the individual doses were unknown but liquidators were allowed to have received up to 25 cGy The control group consisted of 43 individuals with no history of radiation exposure aged 20 to 57 years

Lymphocytes cultures (48h) were set up according to the standard method For analysis of large numbers of metaphases Leica Miamed metaphase finder with a karyotyping capability was used Single and double fragments, chromatid exchanges, dicentrics, rings and chromosomes with unusual morphology (atypical chromosomes) were registered

For all subjects questionnaires that provide consideration of known and suspected confounding variables were filled in

An investigation of the tumor markers concentration in blood serum and plasma was determined by conventional ELISA methods An investigation of the tumor-specific markers (CEA, AFP, CA 19-9, PSA, NSE) was carried out in 2 groups of liquidators I- 28 persons with chromosomal aberrations of exchange type and II - 28 persons without this type of aberrations

Various statistical methods (Mann-Whitney U-test, Chi-square test, stepwise multiple regression analysis, Spearman Rank correlation test) were used according to the nature of data and type of analysis needed Calculations were performed using BMDP and Statistics for Windows v 4 3 statistical packages

3. Results

3.1 The frequency and types of chromosomal aberrations in liquidators.

The results of the cytogenetical investigation carried out in the group of liquidators and in the control persons show that there were essential differences in aberration rate The liquidators had a significantly higher frequency of chromosome breaks, chromatid exchanges, chromosome exchanges (dicentrics+rings) and atypical chromosomes (Table I)

Table I Frequencies of chromosomal aberrations in peripheral blood lymphocytes in liquidators and control subjects

	Liquidators	Control
No of individuals	297	43
Total no of cell scored	39879	6790
Aberrant cells	2 66±0 14[b]	1 67±0 24
Chromatid breaks	1 29±0 10	1 23±0 21
Chromatid exchanges	0 15±0 03[b]	0 00±0 02
Chromosome breaks	0 87±0 07[b]	0 37±0 09
Dicentrics, rings	0 21±0 03[b]	0 04±0 02
Atypical chromosomes	0.13±0 03[a]	0 04±0 03

a-Significantly greater frequency than in control at the 0 05 level of significance, b-at the 0 001 level of significance

The differences not only in frequency of chromosomal aberrations but in spectrum of chromosome disorders were found The ratio of chromatid chromosome types of aberration in control group was 3 1, whereas in exposed group 1 1,2 (Fig 1)

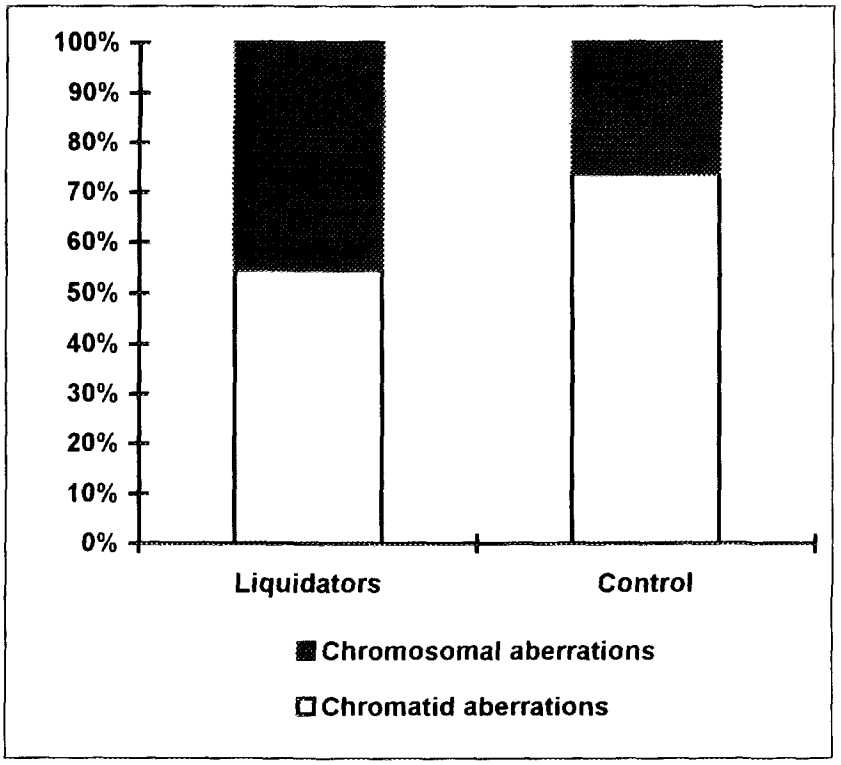

Fig. 1. The spectrum of chromosomal aberrations in liquidators and in control group.

The obtained cytogenetical results and data of questionnaires were entered into database. Long period after the accident we did not find any connection between the official dose of irradiation, year and duration of clean-up work, place and character of work in zone and the aberration level. The participation in recovery works at the Chernobyl nuclear power station was the only reason for dicentrics and rings rise in liquidators.

3.2. Tumor-specific markers at liquidators.

The investigation of the tumor-specific markers (CEA, AFP, CA19-9, PSA, NSE) was carried out in 56 liquidators simultaneously with chromosomal analysis. The increased level of NSE was found in liquidators bearing the chromosomal aberrations of exchange type: the significant differences ($p<0.01$) were determined in concentration of NSE in blood plasma group I - 50 7±6 3 ng/ml instead of group II- 25.7± 5.3 ng/ml).

4. Discussion

The cytogenetical investigations of liquidators suffered from low doses of ionizing radiation have shown that increased level of unstable chromosome aberrations has been discovered long period (6-10 years) after the Chernobyl accident. The people with chromosomal aberrations are considered to be a group of risk for health [7, 8]. That is why we investigated intercommunication between chromosomal aberrations and tumor-specific markers in group of liquidators. We have found the increased level of tumor-specific marker NSE in liguidators with chromosomal aberrations of exchange type. The increased level of NSE is considered to be a sign of risk of neuroendocrinological and respirators oncological diseases. Taking into consideration the results of cytogenetical observation the medical monitoring of liquidators have been started in ARCERM. Long-time observation of exposed people is one of the real methods of evaluation of induction of detrimental health effects at low doses of ionizing radiation.

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The distribution of chromosome aberrations among chromosomes of karyotipe in exposed human lymphocyte

Que Tran, Tien Hoang Hung
Nuclear Research Institute,
Dalat, Vietnam

Abstract

Induced chromosome aberrations (ch. ab.) in exposed Human peripheral blood lymphocyte have been used to assay radio.bio.doses, because of their characters such as: the maitaining Go phase in cell cycle in body,the distribution of cell in blood system and the distribution of ch. ab. in exposed cells of body and among chromosomes of karyotype.The frequency of ch. ab. reflected the quantity of radiation dose,dose rate and radiation energy. The dependence between radiation dose and frequency of ch. ab. was illustrated by the mathematic equations.The distribution of induced ch. ab. among the cells exposed to uniform radiation fields was Poisson's,but the distribution of ch. ab. among chromosomes in karyotype depended on radiation field and mononucleotid sequence of DNAmolecular of each chromosome. The minimum influence of mononucleotid sequence of DNA molecular in inform ch. ab. will be advantageous state for dose-assessments.

The location of induced ch. ab. in exposed Human lymphocyte had been determined by karyotype analyse . The data of statistic analyse had improved that the number of ch. ab. depended on the size of chromosomes in karyotype. The equal distribution of ch. ab.among chromosomes in karyotype provided the ojectiveness and the accuracy of using the chromosomal aberrant analysis technique on bio.dosimetry.

Introduction

Chromosome aberrations in peripheral bloob lymphocytes have been used as a measure of radiation dose in man for many years ,and evidence has meet certain criteria ,aberrations provide a usefull estimate of absobed dose (3).The studies on distribution of ch. ab. in karyotype will supplemented the role of this bio.evidence for radio. bio. dosimetric assessments.

Karyotype of a specices is particularized with the number and the figure of chromosomes. There are 46 chromosomes in human cell. Structure of chromosome is a DNA double helix ,histon moleculars and other proteins. The induced breaks in DNA molecular of the cell exposed to radiation are double strand break (DSB),single strand break (SSB) and base damage (BD). Ch. ab. are induced directly from DSB . DSB can be created directly by radiation action or undirectly by unrepaire or misrepaire mechanizm of SSB,BD. The distribution of DNA strand breaks depended on two principal regulations:

First: the probability of radiation actions. Second:the unprobability of bio.mechanizm such as " hot point mechanizm" ,'hot point'- the location of DNA strand ,which the DNA breaks were induced with the highest frequency.The " hot point " theory have been used to demonstrate the radio.sensitive character of DNA molecular .The difference in chromosomal aberrant ditribution among chromosomes is satisfactory for bio.dosimetric assessment, but the remaining of "hot point" is unsatisfactory for this purpose. If there is not "hot point", induced ch. ab. in lymphocyte have depended on the size of chromosome in cell,but it is not true if radiation induced DNA strand breaks in the cells depended directly on the 'hot point' mechanism.The "hot point" created the unlikeness of radiation effects on this or that chromosome ,therefore it will aspect on determined radiation doses. The study of distribution of induced ch. ab. in exposed human lymphocyte improved the possibility of using the ch. ab. and the role of them on radio.bio.dosimetric assessments

Subject and method :

The photographs of chromosomal sets consisted of induced ch. ab. of exposed Human lymphocytes was used to studies.The photographs were product of bio.dosimetric calibrations for gamma rays, thermal neutron and the mixture of other neutrons.

Protocol of cell culture in IAEA technical report no:260,1986 was used for lymphocyte culture. Karyotype was classified in the following steps: classification of firgure of chromosome paire in order, measuring of the size of chromosome and puting them in order of length. The origin of ch. ab. was determined by eliminable method of chromosome which had paire or length enough. The equal distributed theory was used to controle the investigated data. The verifiable formular of distribution theory $\chi^2 = \Sigma^k_i [(mi - npi)^2 / npi]$ (k=investigation units =23; mi= the numbei of detected ch. ab. in paire i; n= total of detected ch. ab.; pi= relative lengh of chromosome i).

Result and discussion

The statistic value of investigative parameters have related to the studies of karyotype of vietnamese ppulation and bio.dosimetric calibrations. Karyotype of Human lymphocytes of Dalat population(a city of Vietnam) was investigated and illustrated in table 1:

Table 1: The size of Human lymphocyte chromosome (%) (the rate of a chomosome per total of chromosome).

ch.	rate	ch.	rate	ch.	rate	ch.	rate	ch.	rate	ch.	rate
1	8.37	5	5.92	9	4.75	13	3.71	17	2.75	21	1.87
2	7.76	6	5.61	10	4.43	14	3.39	18	2.56	22	1.68
3	6.73	7	5.42	11	4.31	15	3.07	19	2.34	X	2.52
4	6.26	8	4.90	12	4.11	16	2.99	20	2.11	Y	0.94

(Ch.= Chromosome).

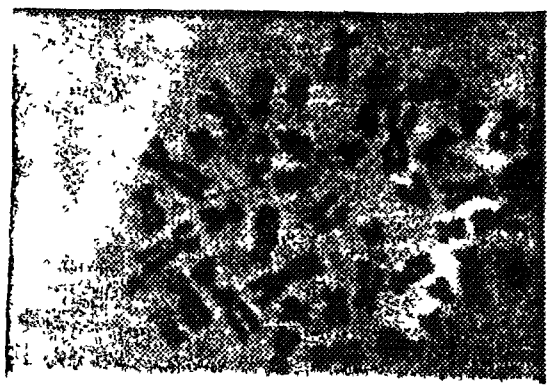
Standard error of the measuremental data were satisfactory. The investigation corresponded to Paris standard (1,2,3) .

The chromosomes were distinguished this paire from that paire with the size and fig , except some case such as : some time the third paire had the longer chromosome than other, the size of 12 th paire was shorter than the size of 13th... These evidences can be explained by helix processing of some chromosome happened ealier than other chromosome .

The blood samples were exposed to uniform radiation field such as: gamma rays, thermal neutron and mixture of other neutron. The evidence of uniform radiation field was also improved by the results of dosimetric calibrations such as : the distribution of ch. ab. per cell in a dose and the standard curves The distribution of induced ch. ab. in any dose was poisson (12,13,14). The results of radio.bio.dosimetric calibration were the response dose effect curves with popular equation form: $Y = \alpha D + \beta D^2 + C$ (12,13,14).

The ch.ab. were detected by microscope and photograph. The location of ch.ab. was determined by measure chromosomes, compare them together on size and figure and put them in corect paire . The ch.ab. were located in the chromosomes which were absent one in any paire or in the chromosomes which were absent all two in a paire.Example:the following photograph consisted of 46 chromosome units limited by 1 dicentric, 1 fragment and 44 normal chromosomes.

There were 21 whole paire and 2 absent paire .



Thewholepairewere:1;2;3;5;6;7;8;9;10;11;13;14 ;15;16;17;18;19;20;21;22;and xx.The absent paire were : 4 and 12. The size of dicentric was:1.24 cm ,fragment: 0.81 cm , di. + fra. = 2.05 cm ,the size of di. + fra. Was corresponding to the size of absent chromosome : ch.4: 1.29 cm and ch. 12: 0.77 cm, ch.4 + ch 12=2.06 cm. Now therefore di. and fra. aberrations induced from ch. 4 and ch. 12.

The data of located investigations of ch. ab.was showed in table 2.

Table 2 : The distributions of ch. ab. among chromosomes in karyotype of exposed human lymphocyte.

Σch.ab. (174)	Distribution of ch.ab. among chromosomes																						
Ch.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21+Y	22	X
Obs	18	17	13	8	10	6	14	8	6	8	9	10	7	6	7	8	4	7	3	1	7	3	2
Exp	15	14	12	11	10	10	9	9	8	8	8	7	6	6	6	5	5	5	4	4	5	3	4
Obs-exp	+3	+3	+1	-3	0	+4	+5	-1	-2	0	+1	+3	-1	0	+1	+3	-1	+3	-1	-3	+2	0	-2

ch. : chromosome; obs.: observed; exp.: expected.

The number of induced ch. ab. was direct proportion to the size of chromosome in karyotype,inverse proportion to the chromosomal order from first paire to 22th paire . There were difference in the rate of ch. ab. to the size of each chromosome between this and that chromosome in table 2 and between our result and Buckton's result . The classification 21th chromosome and Y chromosome in the size and firgue was uneasy ,therefore the data was added in 21th +Y group. The high ch. ab. in this group can be caused by the radiosensitive mechanism of 21th,the semilar result also detected by Buckton (3) . These results have given a question: What was distributive regulation of ch. ab. among chromosome in karyotype of exposed Human lymphocytes . The controlling of the result with equal distributive theory showed that the value of statistic parameters were determined χ^2 = 19,21 with k = 23 ; χ_{k-1}^2 (0,05) = 33.90 . The equal distributive theory of the number of ch.ab. per the length unit of the chromosome was verified.

The distribution of induced ch. ab. in any case was also aspected to the accuracy of dose-calibrations and dose-assessments. The distribution of induced ch. ab. among the cells (karyotype) exposed to uniform radiation fields was Poisson (3,5,8,9,10,11). The equal distribution of induced ch. ab. among chromosome in karyotipe will be satisfactory.The distrbution of radiation actions on materials was probability's , but the distribution of induced bio.effects depended on bio.responsive mechanism.The bio.responsive mechanism depended on bio.structure and bio.actions of cells and body. In this case ,it was the links of mononucleotids of DNA sequence and repaire mechanizms created miss repaire or unrepaire of DNA straind breaks (3,10) . The radiation sensivity of DNA double helix depended on the links of mononucleotids in DNA straind and DNA double helix. Some links were more sensitive than anothers,and the concentrated location of them will create more changes than anothers, and it was called the 'hot point'. The 'hot point' was detected in some chromosome of isect cells. The outnumber of ch. ab. detected in some chromosome in our and buckton's result showed that there were presentation of 'hot point' mechanism in inform ch. ab. ,but this evidence pressed in the chromosomes: 1,2,6,7,12,16,21 in our result instead of 7,10,13,16,17,18,19,21 in Buckton's result improved that the 'hot point' presented not so popular and the probability's distribution had better. The existance of the ' hot point' locations of DNA strand was presented clearly, but the distrbution of them among chromosomes was popular . The difference of ch. ab. friquencies happened only when the mononucleotid's order was high difference between this chromosome and that. The density of sensitive sites were different among them. The results of equal distribution of ch. ab. among the chromosomes in karyotype of exposed human lymphocytes showed that popular structure of mononucleotid's sequence of DNA sequence was so big that none of chromosome have a special structure which presented so' hot' or so' cold point'.

The presentation of 'hot point' aspected to naturily's distribution of radiation effects and accuracy of radio. bio. dosimetric calibration also bio. dosimetry. The result of equal distribution of ch. ab. pressed the important role of this effect on bio. dosimetry.

Conclusion

Chromosome aberrations were induced by DNA strand breaks , therefore the dependence between radiation effects in inform DNA strand breaks and presentable frequency

of ch. ab. was natural. The distribution of ch. ab. depended on two basic factors, there are the probability's of radiation actions and the difference of radiation responsive effects of bio.structures, which among them were sensitive sites of DNA molecular.The result showed that the distribution of ch. ab. among chromosomes of karyotype had dependence on the size of chromosomes, and confirmed in equal distribution regulation. This conclution pressed the important role of ch. ab. effect on bio.dosimetry.

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THE RISK OF CHILDHOOD CANCER FROM LOW DOSES OF IONISING RADIATION RECEIVED *IN UTERO*

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R. WAKEFORD
British Nuclear Fuels plc,
Risley, Warrington

R. DOLL
Imperial Cancer Research Fund Cancer Studies Unit,
Radcliffe Infirmary, Oxford

J. F. BITHELL
Department of Statistics,
University of Oxford, Oxford

United Kingdom

Abstract

Radiological protection is based upon the assumption that any additional exposure to ionising radiation leads to an increased risk of stochastic adverse health effects. The validity of this assumption is supported by the epidemiological association between childhood cancer and X-ray exposure of the fetus *in utero* for diagnostic purposes. Evidence for a direct causal interpretation of this association is compelling: the association has high statistical significance, it is consistent across many case-control studies carried out worldwide, and an appropriate dose-response relationship is indicated. Evidence against bias and confounding as alternative explanations is strong. Nonetheless, objections to causality have been raised. Four grounds for controversy are examined in detail, with the conclusion that they do not provide persuasive evidence against a cause and effect relationship. We conclude that acute doses of the order of 10 mGy received by the fetus *in utero* cause a subsequent increase in the risk of cancer in childhood, and that, in these circumstances, the excess absolute risk coefficient for childhood cancer incidence is 6-12% per Gy.

1. INTRODUCTION

The strongest direct epidemiological evidence that low doses of ionising radiation cause a subsequent increase in the risk of cancer is the association between childhood cancer and exposure of the fetus *in utero* to radiation for obstetric purposes. This association implies that acute doses of the order of 10 mGy of low linear energy transfer radiation produce a detectably raised risk of cancer. Although the excess absolute risk of cancer in childhood associated with such doses is small, at around 1 in 900, since the background risk of cancer developing before the age of 15 years is also small (about 1 in 600) this radiation-induced excess risk is relatively easy to discern in case-control studies. Clearly, this epidemiological evidence is consistent with a dose-response relationship for radiation-induced cancer in which the excess risk is small, but non-zero, for any additional dose of ionising radiation. The interpretation of this epidemiological association has, however, been controversial. A number of reasons have been advanced to question whether the association directly reflects an underlying causal relationship. It is important for the scientific understanding of radiation risks and for radiological protection that the evidence concerning this association is reviewed and, in particular, that the objections to causality are examined in detail so that their validity may be properly assessed. In this paper we review the evidence and the grounds for controversy concerning this epidemiological association.

2. BACKGROUND

In 1956, Stewart and her colleagues published the initial results of a case-control study of childhood cancer mortality in Britain during the years 1953-1955. The relative risk associated with an X-ray examination of the mother's abdomen during the relevant pregnancy was about 2 and the increase in risk was statistically significant. Two years later, Stewart and her colleagues published the results from an extended series which confirmed the initial findings. A major concern over the interpretation of this raised relative risk of childhood cancer was the real possibility of information bias: exposure information had been obtained entirely from questionnaire data and had not been corroborated by objective records. An explanation in terms of recall bias could not, however, be sustained when, in 1962, MacMahon confirmed the association in a study carried out in the northeastern United States in which X-ray exposure information was obtained from contemporary hospital records which were not susceptible to differential completeness or accuracy.

The association between childhood cancer and an obstetric X-ray examination has now been confirmed by many case-control studies conducted in a number of different countries. The study of Stewart and her colleagues, now known as the Oxford Survey of Childhood Cancers (OSCC), was continued until 1984, and contains nearly 75% of the available statistical information on this association. Similar and highly significant relative risks are, however, found irrespective of whether attention is confined to the OSCC (RR = 1.39; 95% CI: 1.30 to 1.49) or to all other studies combined (RR = 1.37; 95% CI: 1.22 to 1.53). The increased risk of around 40% associated with a radiographic examination of the mother's abdomen during pregnancy is not large, and explanations other than cause and effect must be seriously considered, particularly confounding.

It has been suggested that some factor related to the health of the pregnant mother which gives rise to the need for a radiographic examination, might also lead to an increased risk of cancer in the child. This proposed confounding was first addressed by Mole using the data for twins in the OSCC. Twins are usually exposed to diagnostic radiation for purely obstetric reasons rather than for any concerns over the general health of the mother. Twins are also exposed at a higher frequency than singletons: 55% of twins were X-rayed in the OSCC against 10% of singletons. Mole found a similar strength of association between childhood cancer and an obstetric X-ray examination for twins as for singletons, a finding which points away from an alternative explanation of the association based on confounding. The finding for twins has now been confirmed in case-control studies carried out in Connecticut and in Sweden.

For X-ray examinations during the third trimester, and for which information on the number of X-ray films exposed during the examination was available, a statistically significant linear trend of increasing relative risk with increasing number of films exposed has been found. This indicates an appropriate dose-response relationship. Evidence for such a relationship is also provided by the highly significant decline in the relative risk with year of birth over the period 1941-1965, when the fetal dose received during an obstetric X-ray examination was decreasing. Additional support for a causal interpretation of the association is to be found in the results of animal experiments, particularly those involving beagle dogs, although these experiments were conducted at higher doses than those received during obstetric radiography. Further, the influence of low dose irradiation *in utero* upon the risk of mortality beyond 3 months of age is specific to cancer, as would be expected of a radiation-induced effect, rather than being associated with a range of diverse health effects which might be indicative of bias or confounding.

Despite the evidence supporting a causal explanation of the association, controversy has continued on four grounds, which appear to challenge this interpretation. The four grounds for controversy are considered below.

3. GROUNDS FOR CONTROVERSY

The first of these is that twins, as a group, have not been found to experience a raised risk of childhood cancer, although they have collectively experienced a higher frequency of obstetric X-ray examinations. This objection is only valid, however, if cohort studies of twins have had sufficient power to be capable of detecting the predicted radiation-induced excess risk, and if twins have the

same background risk of childhood cancer as singletons. In fact, even the largest of the twin cohort studies, conducted in Sweden, has insufficient statistical power to be expected to discern the predicted excess risk, and it is unknown whether twins experience the same risk as singletons in the absence of exposure to radiation.

The second objection is that the relative risk associated with irradiation *in utero* is almost the same for childhood leukaemia as for childhood solid tumours, whereas the Japanese children exposed to radiation from the atomic bomb explosions while under 10 years of age, exhibit an excess of childhood leukaemia alone. This objection is legitimate, however, only if the carcinogenic effects of fetal irradiation and childhood irradiation are expected to be the same. The cells which are sensitive to the induction of the characteristic forms of childhood solid tumours are present only *in utero* and, perhaps, for a short time after birth, and so irradiation of the child would not be expected to produce an excess risk of these childhood cancers. Data for the short period of possible sensitivity after birth are insufficient to test whether childhood solid tumours might be induced by exposure to radiation in the immediate postnatal period. The cells that give rise to the typical cases of childhood leukaemia continue, in contrast, to be present for several years postnatally.

Over 90% of *in utero* exposures in the OSCC occurred during the last trimester of pregnancy; but the cells from which the typical cancers of childhood arise remain active throughout gestation. It is not surprising, therefore, that the common types of childhood solid tumours (with the possible exception of bone cancer, the one major type of childhood cancer largely composed of tumours similar in character to adult tumours) all exhibit an excess risk associated with third trimester exposure. Nor is it necessarily anomalous that these typical childhood cancers show similar levels of sensitivity to induction by radiation, in contrast to the cancers of adult life. Adult cancers are, for the most part, so distinct from the principal cancers of childhood, and the mechanisms that give rise to them so different, that a comparison of the carcinogenic response to radiation in these two age groups may very well be inappropriate.

The third ground for controversy concerns the estimated values of the risk coefficients for irradiation *in utero* relative to those for irradiation in childhood. Some early risk estimates derived from the OSCC were thought to be implausibly high, but they relied upon estimates of fetal doses which may not be accurate. The most reliable risk coefficient is that derived from a model of the variation of the relative risk with year of birth together with the fetal dose estimates inferred by the Adrian Committee for births in 1958. This method produces an estimate of the excess absolute risk coefficient for childhood cancer incidence in the range 6-12% per Gy, although this estimate does not take into account all sources of uncertainty (such as those associated with fetal doses). This leads to an excess absolute risk coefficient for childhood leukaemia of 2-4% per Gy which is not far removed from the risk coefficient of just under 2% per Gy for a dose of 10 mGy received immediately after birth that may be derived for childhood leukaemia from a model based upon the experience of the Japanese atomic bomb survivors. This agreement is reassuring for the causal hypothesis. As has been noted above, a similar comparison cannot be made for the risk coefficient for childhood solid tumours because, in general, these cancers cannot be induced by irradiation after birth.

Although the great majority of the OSCC data concern third trimester exposures, there has been a suggestion from an analysis of this dataset that the risk coefficient for exposure during the first trimester is significantly higher, especially during the embryo stage, than that for exposures later in pregnancy. This conclusion, however, does not take into account the greater frequency of radiographic examinations for non-obstetric reasons during the first trimester, including examinations involving contrast media, or that most of these examinations took place in the early years of the study. Doses from such examinations would be expected to be higher than those typical of third trimester exposures and, as a consequence, the risk coefficients are not comparable. Further, data for exposures during the embryo stage are limited and, because they relate mainly to births in the early years of the study, may not be as reliable as those for the third trimester. Consequently, although some risk of childhood cancer may arise from exposures in the first few weeks of pregnancy, the level of this risk cannot be derived with confidence from the available epidemiological data.

The fourth and final, and perhaps the most serious, objection to causality is the absence of a comparable excess risk of childhood cancer in cohorts of children known to have been irradiated *in utero*, most notably the Japanese children exposed to radiation from the atomic bomb explosions

while in the womb. The Japanese data are, however, few. Two of the 753 children who received a dose of 10 mGy or more *in utero* developed cancers (both solid tumours) while under 15 years of age, against 0.43 cancer cases expected from Japanese national rates. An excess absolute risk coefficient for childhood cancer of 0.7% per Gy (95% CI:-0.1% to 2.6% per Gy) may be derived from the Japanese data, which is considerably less than the equivalent coefficient derived from the OSCC data. The absence of leukaemia cases among the Japanese cohort is notable. It could be, however, that in the difficult conditions which existed in the first few years after the bombings, some cases of childhood cancer were unrecorded. This might be especially so for childhood leukaemia, since infections are particularly common in the early stages of the disease, and the leukaemic nature of some deaths from infectious disease may not have been recognised. It may be that the absence of a commensurate excess risk of childhood cancer among the Japanese children irradiated *in utero* could be accounted for by a few cases missing from the early period of follow-up, and an unusual play of chance.

Two substantial cohort studies of children who experienced radiographic examinations *in utero* in Baltimore and in London and Edinburgh, did not find relative risks which differed significantly from unity, and the British study (of childhood leukaemia) found a relative risk which was less than 1. One of us (RD), however, was an author of this latter study and long ago concluded that follow-up may have been incomplete and that, as a consequence, the findings are unreliable. Since childhood cancer is an uncommon disease, even large cohort studies, such as the Baltimore study, cannot be expected to have high statistical power. Hence, although the results of the Baltimore study, appropriately combined with those of other studies of smaller cohorts exposed *in utero* to diagnostic radiation, do not produce a significantly raised relative risk, they are compatible with the increase in risk of about 40% indicated by the case-control studies. Interestingly, a cohort of children who were exposed *in utero* to radioactive iron for a study of iron metabolism carried out in Nashville, did exhibit a significant excess of childhood cancer.

4. CONCLUSIONS

With the exception of the findings of the study of the Japanese cohort of children exposed *in utero* to radiation from the atomic bomb explosions, which may be due to a few missing cancer cases among young children and an unusual effect of chance, none of the grounds for controversy produces convincing evidence against a direct causal interpretation of the association between childhood cancer and exposure *in utero* to diagnostic radiation, an interpretation which is strongly supported by a range of scientific evidence. On the balance of evidence, therefore, we conclude that acute doses of the order of 10 mGy received by the fetus *in utero* increase the subsequent risk of cancer in childhood and that, in these circumstances, the excess absolute risk of cancer developing before the age of 15 years is 6-12% per Gy. This evidence supports the existence of a dose-response relationship for radiation-induced cancer which approaches zero dose with a positive slope; but these epidemiological data are insufficient to define the detailed nature of the relationship at low doses.

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EXTRAPOLATION OF EXPERIMENTAL DATA ON LATE EFFECTS OF LOW-DOSE RADIONUCLIDES IN MAN

V. S. Kalistratova, P. G. Nisimov
Institute of Biophysics, State Research Centre of Russia

Abstract

The situation of living of population on radionuclide contamination areas was simulated in the experimental study using white strainless rats of different ages. The significance of age for late stockhastic effects of internal radionuclide contamination with low doses of ^{131}I, ^{137}Cs, ^{144}Ce and ^{106}Ru was studied. Some common regularities and differences in late effects formation depending on age were found. Results of the study showed that the number of tumors developed increased in groups of animals exposed at the youngest age. The younger animal at the moment of internal radionuclide contamination, the higher percentage of malignant tumors appeared. It was especially so for tumors of endocrine glands (pituitary, suprarenal,- and thyroid). Differences in late effects formation related to different type of radionuclide distribution within the body were estimated. On the base of extrapolation the conclusion was made that human organism being exposed at early postnatal or pubertal period could be the most radiosensitive (1.5-2.0 or sometimes even 3-5 times higher than adults). Data confirmed the opinion that children are the most critical part of population even in case of low dose radiation exposure.

Among late effects radionuclide contamination the tumor effects are the most significant. Since the information on dose-effects for malignancy in human is limited, the experiment with animals become very important. It is scientifically proved that spontaneous tumors' frequency among experimental animals is very close to those in human [1].

The situation of living of population on radionuclide contaminated areas was simulated in the experimental study using white strainless rats of different ages. The significance of the age the moment of exposure for late stockhastic effects of internal radionuclide contamination with low doses of ^{131}I, ^{137}Cs, ^{144}Ce and ^{106}Ru was studied. Age heterogeneity of population was simulated using 1540 white strainless rats of three age groups: 7 days old, 30 days old and 120 days old. These subgroups corresponded to: early postnatal, pubertal and sex-mature (adult) periods of human. Animals received radionuclides "per os" in quantities providing the following cumulative doses to critical organs: ^{131}I - 5 Gy to thyroid gland; ^{137}Cs - 0.5 Gy to whole body; ^{144}Ce - 6 Gy to colon; ^{106}Ru - 1.0 Gy to whole body. Development of tumors was registered during the period of 24-26 months since exposure. Total number of tumors in each age group and percentage of malignant among then were estimated. Control group of animals was also studied with 70 animals in each age subgroup.

Results of pathomorphological and histological study showed:

(1) - the percentage and rate of tumors' growth were higher in experimental than in controls animals of all age groups; for example, among those received ^{137}Cs at age 30 days the percentage of animals developed tumors was about 94% with 62.5% in corresponding controls, and in adult animals 87.3% and 66.5% respectively were registered.

(2) - total number of tumors, in general, as well as malignant ones were highest in experimental animals of lower age. Table I demonstrates this fact, where frequency of malignant tumors in all experimental and control groups of rats is shown.

Table I. Percentage of malignant tumors in animals contaminated with radionuclides (E) at different periods of life , in comparison with non-contaminated animals (C).

Age (days) of animals at the time of contamination	^{131}I		^{137}Cs		^{106}Ru		^{144}Ce	
	E	C	E	C	E	C	E	C
7	52.2	7.2	-	-	41.0	0	45.6	19.3
30	37.3	17.9	36.4	12.5	34.1	16.6	29.2	25.5
120	0.8	0	29.7	16.7	27.2	17.2	30.9	29.5

The most significant differences were found in group of animals received ^{131}I at age 7 days. Part of malignant tumors was 52.2% in experimental and only 7.2% in controls group. The same radionuclide given at age 30 days produced some less malignancy effect (37.3%) with twice lower percentage in controls. In adult animals percent of malignant tumors was only 0.8 in experimental animals. The same effect, however, some slighter expressed was found in animals contaminated with ^{137}Cs and ^{106}Ru. In group of animals contaminated with ^{144}Ce the higher percent of malignant tumors was found only in animals of "7 days" subgroup.

It is very important to note that the youngest animals, in general, developed malignant tumors of endocrine glands more frequently than adult ones. This is, probably, related to some disturbances in hypophysis-adrenal system, which is very radiosensitive in young organism. So, after internal ^{137}Cs exposure 77.7% and 42.0% of malignant tumors of hypophysis were found in young groups (in respective controls groups only 14.2% and 12.5%). The same tendency were found for ^{131}I and ^{144}Ce. Adult experimental animals did not show differences in comparison with control on this criterion.

Malignant tumors of mammary gland, thyroid and adrenal glands were also found more frequently in youngest groups of rats. However, there are differences related to the type of the radionuclide distribution in the body. In case of ^{137}Cs incorporation the most frequent tumors, including malignant ones, were found in mammary glands, adrenal glands and, as well as, in blood marrow. Malignant tumors of thyroid glands were found mostly in animals incorporated with ^{131}I in lowest age; their percentage were 62.5% of general number of thyroid tumors (in adult group only 25%). ^{144}Ce - incorporation produced malignant tumors of thyroid gland in 41.7% of young animals and only in 16.7% of adults. Malignant tumors of adrenal gland were found only among "30 days old" group with ^{144}Ce - incorporation.

The data received in our experiment permit to suppose that internal radionuclide contamination of population with ^{131}I, ^{137}Cs, ^{144}Ce and ^{106}Ru in relatively small doses can produce twice (and more) in children higher number of malignant tumors, especially exposed in early postnatal and pubertal periods, than in adult. The number of tumors of pituitary could be two times higher in children than in adult. The frequency of malignant tumors of thyroid in children contaminated with ^{131}I and ^{144}Ce probably would be 2.5 times higher than among non-contaminated population.

The results presented here and those of others [2-3] show that, susceptibility for induction of late effects seemed to decrease gradually with increasing age during the adult period.

It is necessary to note that:

- in case of peroral contamination of human with low doses of cerium, caesium, ruthemiun and iodine in more youngest part of population: children would be the most radiosensitive group, especially if exposed in early postnatal and pubertal periods (in average, 1.5 ÷ 2.0 times higher radiosensitivily could be registered).
- the attention should be paid to prophylactical measures directed of malignant effect, especially in critical groups of population (children!), living on contaminated with radionuclides areas.

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MULTICOMPONENT RISK INHERENT TO NUCLEAR OR RADIATION ACCIDENTS

V.A.Poyarkov
European Center of Technogenic Safety
Kiev, Ukraine

Abstract

A nuclear or radiation emergency response planning is based on expected avertable doses for a short (4 hours, 2 days, 1 week) and a long (50 or 70 years) periods of time. On calculating the doses one should take into account not only the sources of ionizing radiation with their foreseen characteristics, e.g. a half-life, but also the possibility of their probabilistic transformations. It can be illustrated by the chronicle of Chernobyl accident, where for nine days it was impossible to envisage with reliability the quantities of released radionuclides due to many uncontrolled factors related to the scope and character of the zone wreckage. Any other developments of the accident, such as destruction of the under reactor support plate, sinking of the melted zone into a highly radioactive water down at the reactor cavity or changing of the wind could have resulted in a substantial contamination of 3 mln. Kiev and other densely populated area of Ukraine.

Another factor to be taken into account in the emergency response is a way of an actual risk perception by the population.

The article suggests an approach to take into account the time-dependent secondary sources of exposure and the disparity in accepting the hazard of real risk of an accident by the trained workers and population.

Time-dependent multicomponent accident sources of radiation

An expected avertable dose (EAD) is usually found by:

$$D_{av} = \int_{t_0}^{t_0+\tau} \dot{E}(t)dt \qquad (1)$$

where, $\dot{E}(t)$ is the effective dose rate due to accident sources of radiation.

EAD is to be estimated prior to exposure or at an early stage of the accident as it is a decisive factor in taking decisions about appropriate countermeasures: evacuation, sheltering, relocation, iodinic prophylactic, limitations on consumption of some food products, etc. [1, 2]

The likely EADs for population and personnel in case of nuclear or radiation accident are defined due to various eventual accident scenarios and the effectiveness of countermeasures to protect population and personnel Then EAD is found by

$$D_{av} = D_{exp} - D_{cm} \qquad (2)$$

where, D_{exp} is the expected effective equivalent dose (EED) from accident sources of radiation estimated without regard to countermeasures; D_{cm} is EED with due account of countermeasures and their efficiency D_{exp} is found by

$$D_{exp} = \int_{t_0}^{t_0+\tau} \sum_i \sum_j \xi_{ij} E_{ij}(t)dt \qquad (3)$$

where, ξ_{ij} is the probability of the i-th irradiation component for the j-th variant of the eventual accident scenario; E_{ij} is the corresponding effective dose rate (EDR), D_{cm} is determined by

$$D_{cm} = \int_{t_0}^{t_0+\tau} \sum_i \sum_j \xi_{ij} d_{ij} E_{ij}(t) dt \qquad (4)$$

where, d_{ij} is the efficiency of the undertaken countermeasures varying from 0 to 1.

By way of example, consider various components and corresponding probabilities of exposure for the population of Pripyat for different scenarios of the accident at the Fourth unit of Chernobyl Nuclear Power Plant (NPP).

Town Pripyat with its population of more than 40,000 people is located less than 3 km north-west of the Fourth unit of Chernobyl NPP. In case of a severe nuclear accident due to the destruction of reactor core, the population can be subjected to an exposure various components of which have different sources and probabilities, dose capacities and time-dependencies $E(t)$. The following components can be defined:

(a) External and internal exposure from the released radioactive cloud;
(b) External exposure from the radioactive fallout;
(c) Internal exposure from contaminated food products and water.

Consider ξ_{ij}, d_{ij} и $E_{ij}(t)$ for various eventual scenarios (including the occurred one) of the accident at Chernobyl NPP.

About 3% of total radioactivity or 11EBq was released at the accident (the occurred scenario). An average dose rate of external exposure was about 10 mSv/h on April 26-27, 1986 in Pripyat. However, nobody knew the scenario to occur on April 26, 1986. If it were not for the west but north wind at the moment of the first release, the capacity of the external exposure from radioactive cloud would have exceeded 100 mSv/h in Pripyat (the dose capacity was 1Sv/h in "Red Forest" 2 km from the source) and in this case all 40000 people of Pripyat could have exposed to fatal doses. Having estimated the accident as a serious one that involved destruction of the active zone, the decision to evacuate population of Pripyat immediately became indisputable.

Another episode from Chernobyl accident that deals with the population at the contaminated territory and exposure doses for thyroid gland from radioactive iodine illustrates the importance of taking into account various eventual scenarios.

The estimated doses of exposure for thyroid gland exceed 2 Gy for children of Narodichi region (70 km from Chernobyl) born between 1979 - 1986. The largest contribution (about 70%) into the dose is due to the milk consumption.

As it is impossible to estimate the density of radioactive iodine fallout by direct measurement in 1-2 days after an accident everywhere in 70 km zone, the counteraction seems to be effective in imposing a limitation on milk consumption for 2-3 days until the density of the fallout is measured. Iodinic prophylactic is also advisable in the zone.

The main contribution (≈90%) into the dose 10 years after the accident is due to internal irradiation by ^{137}Cs. Therefore the most effective countermeasures the committed effective dose of the delayed consequences of the accident is lowering of ^{137}Cs in food products. It is achieved either by diminishing consumption of agricultural products from contaminated territory, or by agricultural technique to reduce coefficients of ^{137}Cs intake into the products (application of organic fertilizers, ferrocen agents, etc.). For example, the committed effective dose due to ^{137}Cs internal irradiation at Dubrovitsky region of Rivne oblast is estimated as 2.5 man-Sv, while in fact it equals 0.21 man-Sv owing to the undertaken countermeasures [4].

On the whole countermeasures undertaken in Ukrainian farming allowed to exclude ingress of milk with the specific activity exceeding 370 Bq/l to diary plants.

Prior to complete monitoring set over the accident radioactive source, it is necessary to take into account various likely scenarios of its behavior. About 70% of the initial radioactivity

of the destroyed Fourth unit at the Chernobyl NPP is enclosed with the shielding construction "Sarcophagus". Due to various degrading processes a considerable amount of fuel has turned into dust [4]. In case of a possible complete or fractional collapse of the "Sarcophagus" the dust will be raised and dispersed as far as 30 km and a considerable territory will be contaminated with radionuclides ^{137}Cs, ^{90}Sr and isotopes of plutonium. The possibility should be taken into account to protect workers on mission in a particular zone.

Estimation of D_{exp} by the expressions 1-4 allowing for variants of the event development turns apparently into a complex and laborious procedure that is particularly difficult to follow at the time of an accident.

Therefore it seems to be reasonable for emergency planning to differentiate three following periods in evaluating the accident irradiation: the *acute* (at and 4-6 hours after a radioactive discharge), the *short-term* (duration of the acute period plus 48 hours) and the *long-term* (50-70 years).

The primary task in the acute period is to make a territorial forecast of radioactive contamination in order to prevent deterministic effects as the irradiation doses can exceed 1Sv at the moment of discharge and in the following 4-6 hours. Estimation of the averted dose D_{av} is made by the formulae (2-4) with the integration for the period $\tau = 6$ hours and due account of all possible scenarios of the accident. The principal protective measures are evacuation, sheltering, relocation, iodinic prophylactic, ban on consumption of food products and water contaminated at the accident.

The acute appraisal is generally made on the forecast of the state of the reactor core or another accident source including data furnished by the system of emergency monitoring around NPP.

The main purpose of the short-time period appraisal is to forecast territories, where doses will exceed 1 Sv in the following month. The forecast is made on the base of accident radiomonitoring with due account of protective measures undertaken.

The averted dose D_{av} is estimated by the corresponding formula with integration being made for period $\tau = 1$ month and $\xi_{ij}, d_{ij}, E_{ij}(t)$ allowing for undertaken and planned countermeasures.

The long-term appraisal is designed to forecast territories where doses for 50-70 years can exceed permissible levels, notwithstanding the countermeasures. The forecast is made on the base of comprehensive radiomonitoring, soil characteristics, expected "soil-plants" transfer coefficients, other harmful effects, the economic possibilities to carry out corresponding countermeasures, the analysis of socio-psychological situation.

Correction for socio-psychological risk

People involved into accident, are subjected not only to the risk of direct irradiation, but also to harmful effect of the socio-psychological stress triggered by the accident. The total risk to life and health can be expressed in the following form

$$R_t = R_0 + R_s$$

where, $R_{0\,0}$ is the objective additional risk related to the expected averted dose;

$$R_o = k_0 D_{av}$$

where, k_0 is the dose risk factor.

R_s is the subjective risk that is formed from many factors including the population intelligence in radiation safety, the coverage of events in mass-media, the sequence of decision-making and carrying out countermeasures, etc.

It is possible to assume that

$$R_s = K_s D_{exp}$$

where, K_s is the subjective risk factor.

Chernobyl tragedy demonstrated the subjective risk to have been formed mainly during the first months after the accident with the consistency of government actions and comprehensive coverage of the event in mass-media having been of utmost importance. The psychological effects of the Chernobyl accident resulted from the lack of public information, particularly immediately after the accident, the stress and trauma of relocation, the breaking of social ties, and the fear that any radiation exposure is damaging and could damage people's health and their children's health in the future. It is understandable that people who were not told the truth for several years after the accident continue to be skeptical of official statements and to believe that illnesses of all kinds that now seem more prevalent must be due to radiation. The distress caused by this misperception of radiation risks is extremely harmful to people.

The lack of consensus about the accident's consequences and the politicized way in which they have been dealt with have led to psychological effects that are extensive, serious and long lasting for the population. Severe effects include feelings of helplessness and despair, leading to social withdrawal and loss of hope for the future. The effects are being prolonged by the protracted debate over radiation risks, countermeasures and general social policy, and also by the occurrence of thyroid cancers attributed to the early exposures [5].

Conclusion

The contribution of NPPs into the world electric power generation is growing with all being done to reduce the risk of serious radiation accidents. However, the accidents in Three-Mile Island and Chernobyl have shown that due safety in operation should be complemented by the high readiness for accidents with the detailed description of dose assessment and criteria for decision-making and all eventual variants of accident scenarios taken into account.

ACKNOWLEDGEMENT

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State of Research and Perspective on Adaptive Response to Low Doses of Ionizing Radiation in Japan

SADAO HATTORI
Central Research Institute of Electric Power Industry (CRIEPI)
100, Otemachi, Chyodaku, Tokyo, Japan

Abstract

In a review article entitled "Physical Benefits from Low Levels of Ionizing Radiation," published in Health Physics in December of 1982, Professor T.D. Luckey of the University of Missouri, asserted the "radiation hormesis" with 200 references.

This resulted in the first International Symposium on Radiation Hormesis in Oakland, California (August 1985). CRIEPI consulted many specialists about Luckey's paper and studied many other papers such as Lorenz, 1954; Luckey, 1980, Liu et al., 1985.

Radiation hormesis research in Japan has been based on the rationale that if Luckey's claim were to be true, radiation management in Japan has been extremely erroneous.

CRIEPI organized a Hormesis Research Steering Committee composed of leading specialists in the field concerned, and began research in cooperation with a number of universities, as well as the National Cancer Research Institute, and the National Institute of Radiological Sciences. After obtaining interesting results in various experiments on the health effects of exposure to low doses of radiation, we have proceeded on an expanded program, which involves fourteen universities and two research institutes throughout Japan.

The interesting results we obtained can be categorized in five groups.

1. Enhancement of immune systems such as lymphocytes and suppression of cancer,
2. Radio-adaptive response relating to the activation of DNA repair and adoptosis,
3. Rejuvenation of cells such as increase of SOD and cell membrane permeability,
4. Radiation effect on neuro-transmitting system through increase of key enzymes,
5. Others, including the therapy of adult-disease such as diabetes and hypertension.

We are now carrying out experimental activities on the effects of low-dose radiation on mammals. After several years of research activities, we are recognizing Luckey's claim. Some basic surveys including Hiroshima Nagasaki and animal experiments in Japan have brought us valuable informations on the health effects of low-dose radiation. The followings are some topical research informations obtained across Japan.

Topics of Low Dose Radiation Research

(1) Survey of A-bomb Survivors

The follow up data of people who received radiation from the Atomic Bomb show us an interesting feature especially in the low dose range. A certain optimum dose

for the suppression of leukemia was shown through the survey of the people of Hiroshima and Nagasaki exposed to the radiation of the Atomic Bomb.

(2) The Beneficial Effect of Misasa Spa

Professor Emeritus of Osaka University Dr. Kondo and Dr. Tanooka, former Chairman of Japan Radiation Research Society, conducted statistical comparisons of cancer of the people of Misasa villages (i.e. high radon levels in drinking water), adjacent villages and Japan. The result was meaningful especially on the suppression of total cancer.

(3) Medical Application: Treatment of Cancer

Professor Sakamoto used low dose radiation to cure and to suppress the reappearance of cancer in the hospital of Tohoku University. For example, he applied 10 cGy three times weekly for several weeks successfully against liver cancer and lymphatic tumors. He applied whole body or half body low level dose combined with local high dose irradiation to treat non-hodgkin's lymphoma. The low survival rate of 36% in patients with non- hodgkin's lymphoma after five years of the therapy improved to a 90% survival rate with a low dose treatment schema. Some analytical results demonstrate an increase of the ratio of the helper T cells to suppressor T cells.

(4) Cell Rejuvenation

Yamaoka of CRIEPI found cell rejuvenation on the properties of cell membranes and superoxide dismutase activities by 25 cGy to 50 cGy of irradiation.

After low dose of X-ray whole body irradiation, increase of SOD enzyme and decrease of Lipid-peroxide had been kept more than six weeks.

(5) Adaptive Response

Ikushima of Kyoto Univ. examined the radio-adaptive response . Yonezawa of University of Osaka prefecture confirmed two phases of radio-adaptive responses by using a priming dose and survival after a sublethal dose administration. He found that a low enhanced resistance to sublethal x-radiation given two months after 5 to 10 cGy whole body dose, and two weeks after 30 to 50 cGy also.

(6) Response of p53

Professor Onishi of Nara Medical College discovered a marked increase of stress protein production by p53 genes. Dose of 10 to 25 cGy were effective.

(7) Importance of Low Dose Steady Irradiation

Prof. Nomura confirmed the importance of steady low dose irradiation for gene repairing activities, giving evidence that steady low dose administration is essential for obtaining beneficial health effects.

Research Program on the Adaptive Response to Low Dose Radiation in Japan

CRIEPI is running with fourteen Universities on twelve research subjects of adaptive responses, intending to examine the extensive range of biological functions related to low-dose radiation.

The subjects being interested in the research program are as follows:

(1) SOD response, Lipid-peroxide reduction, and membrane permeability

(2) Cell apoptosis and anti-cancer effects

(3) P53 response and its effects
(4) Response of the central nervous system
(5) Responses of the intercellular signal transduction
(6) Enhancement of immune system inhibitory effects on carcinogenesis
(7) Inhibitory effects of diseases of grown up people such as diabetes
(8) Effects on the energy metabolism regulation
(9) Radioadaptive response by DNA repair and apoptosis
(10) Enzyme response and stress relaxation
(11) Repair mechanism of DNA aberrations
(12) Epidemiological analysis of atomic bomb survivors

Closing Remarks

Formation of ions, free electrons and free radicals by ionizing radiation enhances and creates many comprehensive bio-chemical reactions, followed by significant biological responses.

Animal tests results give us a certain scientific synopsis on the adaptive response to low dose effect on carcinogenesis and malignant tumor. Suppression of cell aging. Activation of biological defense mechanisms.

We have such an impression that a certain low dose radiation raises some vitalizations of basic biological functions. The recent progress of analytical technique on the observation of DNA structural responses greatly contributes the unbelievable success of our research on the adaptive responses of low dose radiation.

Analysis of the history of the evolution of living materials through a billion of years shows us all kinds of environmental conditions were put in the extremity of positive utilization without exception in our physical processes, air, water, sun light, temperature, salt, and radiation. This pursuit of the extremity of the positive utilization of the all kinds of environmental factor through the process of evolution is the life itself, in a sense. It is obvious the natural radiation back ground on the earth was fairly higher than present situation in the past days.

On this sense, the adaptive response is the fundamental characteristics of lives. All kinds of damages caused by environmental influence, diseases, loss of power are to be overcome by enhancement of DNA repair and apoptosis activities. This is the way of adaptive response.

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THE INDUCTION OF A TUMOR SUPPRESSOR GENE (*p53*) EXPRESSION BY LOW-DOSE RADIATION AND ITS BIOLOGICAL MEANING

TAKEO OHNISHI

Department of Biology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634, Japan

ABSTRACT-- I report the induced accumulation of wild-type p53 protein of a tumor suppressor gene within 12 h in various organs of rats exposed to X-ray irradiation at low doses (10- 50 cGy) The levels of p53 in some organs of irradiated rats were increased about 2- to 3-fold in comparison with the basal p53 levels in non-irradiated rats Differences in the levels of p53 induction after low-dose X-ray irradiation were observed among the small intestine, bone marrow, brain, liver, adrenal gland, spleen, hypophysis and skin In contrast, there was no obvious accumulation of p53 protein in the testis and ovary Thus, the induction of cellular p53 accumulation by low-dose X-ray irradiation in rats seems to be organ-specific I consider that cell type, and interactions with other signal transduction pathways of the hormone system, immune system and nervous system may contribute to the variable induction of p53 by low-dose X-ray irradiation I discussed the induction of p53 by radiation and its biological meaning from a aspect of the defense system for radiation induced cancer

Extrapolation is generally employed to estimate the risks of low-dose radiation, as no direct data on such risks in the form of health indicators or cytogenetic indices are available [1] Studies on tumor incidences in mice [2] and epidemiological data on cancer incidence in populations exposed to low radiation doses in areas with high back-ground radiation [3,4] have provided good support for the threshold model of such risks However, the use of health indicators as well as cytogenetic indices appears to be unhelpful for gaining an understanding of the mechanisms underlying the threshold for cancer incidence[5] Therefore, it is deemed necessary to search for evidence of cellular responses to low-dose radiation at the molecular level We have focused on the response of a tumor suppressor gene product, p53 protein, since recent studies have revealed that this may play an important role in carcinogenesis [6] and radiosensitivity [7] Data obtained using cultured cell systems have demonstrated that marked accumulation of p53 protein, found to associate to various kinds of proteins and bind to a specific DNA sequences located at upstream of p53 targeted genes (Fig 1) In addition, the depression of several genes is dependent on p53 through binding to TATA box binding proteins p53 is also a consequence of a post-transcriptional event [8] The accumulation of cellular content of p53 is induced by various types of stress, such as heat [9] and DNA-damaging agents, including ionizing radiation, UV light [10] through the activation of protein kinase C Therefore, these chain-chemical reactions after stress is called as p53-dependent signal transduction pathways Elevated levels of p53 protein induce G1 arrest [11,12] or apoptotic cell death in some cell types [13] (Fig 1) p53 is also directly and indirectly involved in both DNA repair machinery and DNA replication through association with transcription factors such as ERCC3 [14], and replication protein A [15], or by inducing GADD45 [16] (Fig 1)

Although these are many reports on cultured cells irradiated with X-rays at high doses, there are no data on the *in vivo* p53 response in various organs of animals after whole-body exposure to low dose radiation.

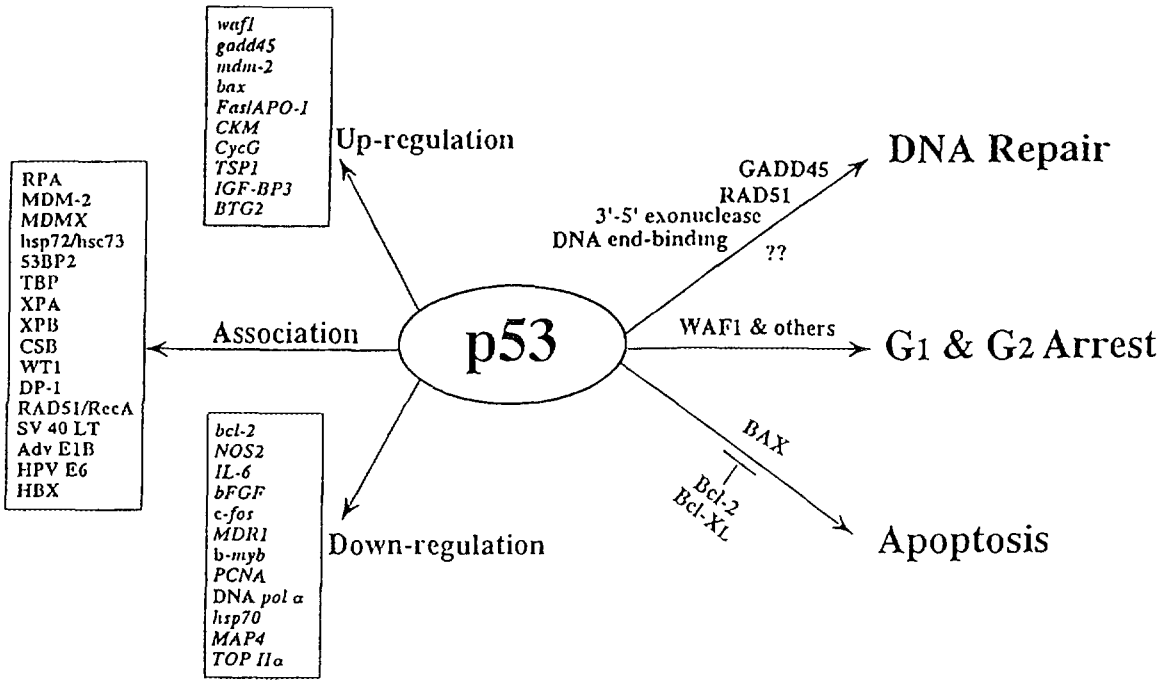

Fig. 1 Functions of p53.

MATERIALS AND METHODS

Animals and X-ray irradiation Six-week-old F344 rats were used, and divided randomly into irradiation or non-irradiation (control) groups Three rats per time-point were used They were irradiated with X-ray at a dose rate of 50 cGy/min (Radiation Biology Center of Kyoto University) After receiving a total dose of 10-50 cGy, they were kept at 25°C with a 12-h light/dark cycle and allowed free access to food and tap water

Preparation of protein samples from rat organs The rats were killed by cervical dislocation at various times (-36 h) after irradiation, and their organs were removed, frozen immediately and stored at -80°C until analysis The tissues were then pulverized by freeze-fracturing and suspended in RIPA buffer containing SDS The bone marrow was washed out from the femurs with RIPA buffer and also subjected to freeze-thawing The insoluble cell debris was removed, the supernatants were collected and the protein concentration was quantified using protein assay reagent and a spectrophotometer

Western blotting analysis with anti-p53 monodonal antibody and quantitation of p53 protein The total protein samples (20 μg) were subjected to SDS-polyacrylamide gel electrophoresis, then transferred electrophoretically to Immobilon™ PVDF membrane The membranes were incubated with an anti-p53 monoclonal antibody, PAb 421, then treated with a horseradish peroxidase-conjugated anti-mouse IgG antibody The sensitivity of the visualization of the p53 bands was enhanced using the BLAST blotting amplification system The densities of the p53 bands were measured using a personal image analyzer The amount of p53 protein was derived by taking the average value of the three rats in each group

RESULTS AND DISCUSSION

A group of kinetic diagrams of p53 accumulation in all the organs of the exposed rats examined are shown in Fig 2. The time course of p53 accumulation can be classified into four kinetic patterns We defined the pattern for the small intestine as pattern 1, the response of which to low-dose X-ray irradiation was rapid with p53 accumulation evident 3 h after

exposure to all three doses. The elevated p53 level was maintained for 24 h, then increased further after 36 h. The characteristics of pattern 2 were an increase in the level of p53 protein 6 h after irradiation with all three doses, maintenance of this elevated level by 24 h, then the start of a drop or maintenance of the same level for up to 36 h. The bone marrow, liver, adrenal gland and brain fell into this category Three organs, the spleen, hypophysis and skin, were classified into the category of pattern 3, in which a significant p53 response was observed only after one specific dose, rather than all three doses The doses which resulted in significant p53 accumulation in the rat skin, hypophysis and spleen were 10, 25 and 50 cGy, respectively. No p53 accumulation in the organs showing pattern 3 was observed after the other two doses. Pattern 4 was defined as no p53 response after any of these three doses as shown in the testis and ovary. In this study there were striking differences in the p53 responses among the organs. This organ-specificity may be attributable to differences in cell differentiation, differences in the mechanisms of response in cells of various organs to X-rays or differing interactions with other signal transduction pathways of the hormonal and immune system. Involvement of the nervous system in the interaction with the p53 signal transduction pathway cannot be excluded, as apparent fluctuations in the in-creased level of p53 were observed in the rat brain, which is one of the most sensitive organs to low-dose X-rays as demonstrated by stress-induced changes. With regard to organs that respond to only one specific dose, the mechanism underlying this phenomenon is still unclear. The apparent randomness of the effect may be due to complex interactions among the nervous, immune and/or hormonal systems of the body.

Exposure of mammalian cells to ionizing radiation induces transcription of a variety of proteins involved in DNA repair, cell cycle arrest and cell death[17-20]. Marked increases in the levels of p53 protein have been observed in mammalian cultured cells exposed to γ-rays, UV[10,21]. Here we have obtained firm evidence of increases in cellular p53 level in rat organs in response to low-dose X-rays irradiation We assume that even the low doses of X-rays caused DNA damage Since an activation of p53 dependent apoptosis was induced in certain cultured cells by high-dose ionizing irradiation[10] Also low-dose X-ray-induced apoptosis in the rat cerebellum has been demonstrated in several studies. This induction of apoptosis by low-dose X-ray irradiation may be due to p53 accumulation as shown in Fig 2

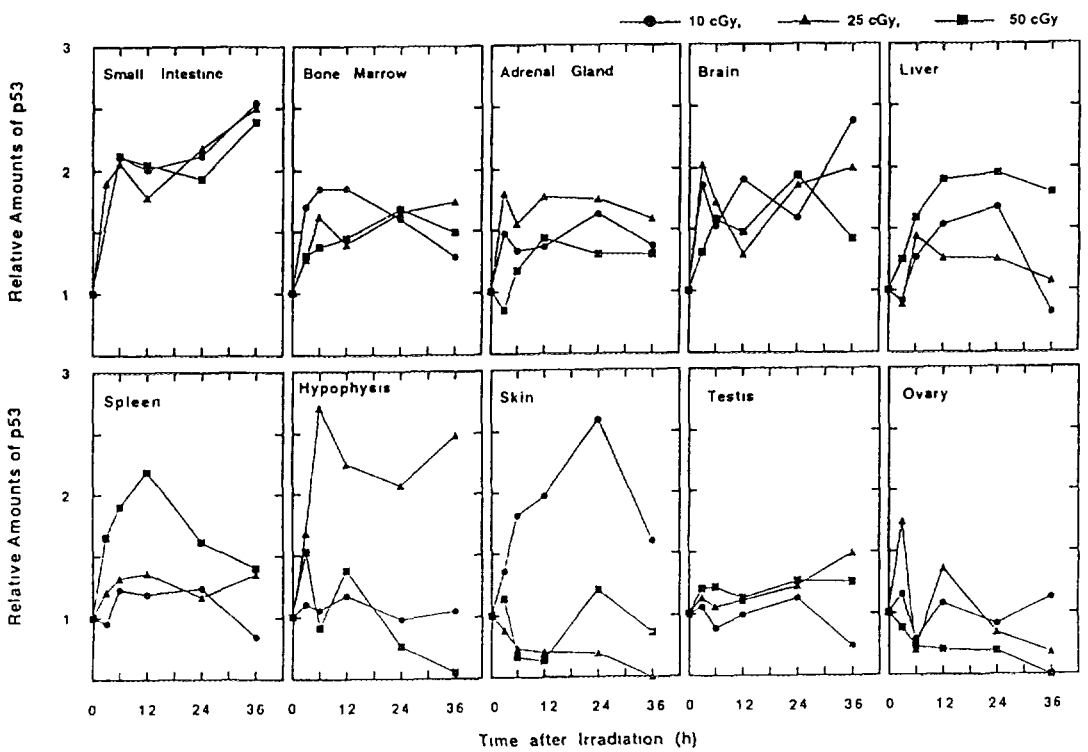

Fig. 2 Kinetics of p53 accumulation in the organs of rats exposed to low-dose X-rays The p53 protein levels are expressed as ratios to that in non-irradiated rats The amount of p53 at each time point was derived by taking the average of the values in three rats

Further *in vivo* studies of DNA repair in animals exposed to low-dose irradiation are also needed to obtain a full understanding of the biological significance of the p53 accumulation, as p53 appears to have multifunctional role in cell cycle control, DNA repair and DNA replication through association with transcription factors such as ERCC3 and replication protein A, or by inducing the expression of GADD45. Therefore the induction of p53 by low dose radiation may contribute to the prevention of cancer event, because there are threshold in several kinds of radiation-induced cancer.

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Participation of Intercellular Communication and Intracellular Signal Transduction in the Radio-adaptive Response of Human Fibroblastic Cells

Keiichiro Ishii *, Yuko Hoshi*, Toshiyasu Iwasaki* and Masami Watanabe**
*Bio-Science Department, Komae Branch, Central Research Institute of Electric Power Industry, 2-11-1 Iwatokita, Komae-shi, Tokyo 201, Japan.
**Laboratory of Radiation and Life Science, School of Pharmaceutical Sciences, Nagasaki Univ., 1-14 Bunkyo-machi, Nagasaki-shi, Nagasaki 852, Japan.

Abstract

To investigate the radio-adaptive response of normal cells to low-dose radiation, we irradiated human embryonic cells with low-dose X-rays and examined the changes in sensitivity to subsequent high-dose X-irradiation. When the cells were irradiated by 200 cGy, the growth ratio of the viable cells five days after the irradiation decreased to 37 % of that of the cells which received no X-irradiation. When the cells received a conditioning irradiation of 10 to 20 cGy four hours before the irradiation of 200 cGy, the growth ratio increased significantly to 45-53 %, and a peak was reached at a conditioning dose of 13 cGy. Cells blocked off intercellular communication either in Ca^{2+} ion-free medium or in TPA added medium during the conditioning irradiation of 13 cGy did not show the improvement of growth ratio. Addition of H-7, as an inhibitor of PKC, to the medium during the conditioning irradiation inhibited the induction of the radio-adaptive response. However, addition of either inhibitor of A kinase, H-89, or inhibitor of G kinase, H-8, failed to inhibit the induction of the radio-adaptive response.

These results suggest that: (1) normal cells show an adaptive response to low-dose radiation, (2) intercellular communication may play a role in radio-adaptive responses, (3) the transduction of the signal induced in cells by low-dose X-irradiation via protein kinase C was involved in radio-adaptive responses, not via A kinase nor G kinase.

Introduction

In the past, radiation was considered to cause damages to DNA and do harm to cells in proportion to the dose, however low it might be. In 1984, Wolff et al. discovered that human lymphocytes which received ^{3}H-TdR treatment showed an adaptive response to radiation [1]. Radio-adaptive responses are also induced by X-rays and gamma rays in human lymphocytes [2], Chinese hamster V79 cells [3] and normal human embryo-derived fibroblastic (HE) cells [4]. However, the mechanisms of adaptive responses to radiation and the conditions for induction of it have not been clarified. Therefore, we examined how the intercellular communication and intracellular signal transduction are involved in radio-adaptive responses.

We irradiated HE cells in culture with low-dose X-rays and examined their radio-adaptive responses by measuring the changes in sensitivity to subsequent high-dose X-ray irradiation. To examine the effects of Ca^{2+} ions and TPA which are supposed to be involved in intercellular communication, we also conducted experiments in which Ca^{2+} ions were eliminated from the culture medium or TPA was added to the medium during the low-dose conditioning irradiation. We also inhibited proteins that play major roles in various pathways of intracellular signal transduction when radio-adaptive responses of HE cells were induced by conditioning irradiation. We evaluated the survival rates to investigate the pathway of intracellular signal transduction thought to be involved in the induction of radio-adaptive response.

Materials and Methods

(1) Dose-dependency of Conditioning Irradiation Effect

Four hours after the start of culture of HE cells, the cells were irradiated for conditioning with X-ray ranging from 0 to 20 cGy. The cells were cultured for another 4 hours, then subjected to challenging irradiation of 200 cGy. After challenging irradiation, the cells were cultured for 5 days before the number of viable cells was counted by the trypan blue dye-exclusion test method. The control groups received mock treatments for both the conditioning and challenging irradiation. The growth ratios of the respective groups to controls were determined.

(2) Effects of Calcium Ions and TPA

Four hours after the start of culture of HE cells, the regular medium was discarded and replaced by Ca^{2+}-containing Hank's Balanced Salt Solution (HBSS) or Ca^{2+}-free HBSS. Then each group received conditioning dose of 13 cGy or mock treatment. Ten minutes after the conditioning or the mock treatment, the HBSS were replaced by the regular medium again. Then the cells were cultured for 4 hours before receiving the challenging dose of 200 cGy. TPA was added to the medium at a concentration of 100 ng/ml at 3 hours and 40 minutes after the start of culture, and the cells were then irradiated with conditioning dose of 13 cGy 20 minutes after the addition of TPA. The medium was discarded 20 minutes after conditioning irradiation, the cell sheet was rinsed 3 times with PBS, and the fresh regular medium was poured to the culture flask. The cells were cultured for 4 additional hours, and then irradiated with challenging dose of 200 cGy. After that, the cells were cultured for 5 days, and the numbers of viable cells were counted to determine the growth ratios of the cultures. The control groups were treated in the same manner as the irradiated groups except that both the conditioning irradiation and the challenging irradiation were mock treatments.

(3) Effects of Inhibitors on Intracellular Signal Transduction

Various inhibitors of intracellular signal transduction were added to the culture medium at 3 h and 50 min after the start of culture of HE cells. At 10 min after addition of an inhibitor, the cells were irradiated with conditioning dose of 13 cGy, and the medium containing the inhibitor was then discarded 10 min later. After that, the cell surface was rinsed twice with PBS, and fresh

regular medium was poured into the flask. At 4 hours after conditioning irradiation, the cells were irradiated again with challenging dose of 200 cGy and cultured for another 6 days. Then, viable cells were counted. The intracellular signal transduction inhibitors used were H-89 as an inhibitor of cAMP-dependent protein kinase (A kinase), H-7 as an inhibitor of protein kinase C (PKC), and H-8 as an inhibitor of cGMP-dependent protein kinase (G kinase). In the control group, only DMSO, in which these inhibitors were dissolved, was added.

Results

(1) Dose-dependency of Conditioning Irradiation Effect

The results are shown in Fig. 1. The growth ratio of the viable cells after challenging irradiation of 200 cGy decreased to 37 % of that of the controls. While growth ratio of the cells exposed to 10 to 20 cGy four hours before the challenging irradiation significantly increased to 45-53 %; and a peak was reached at a conditioning irradiation dose of 13 cGy.

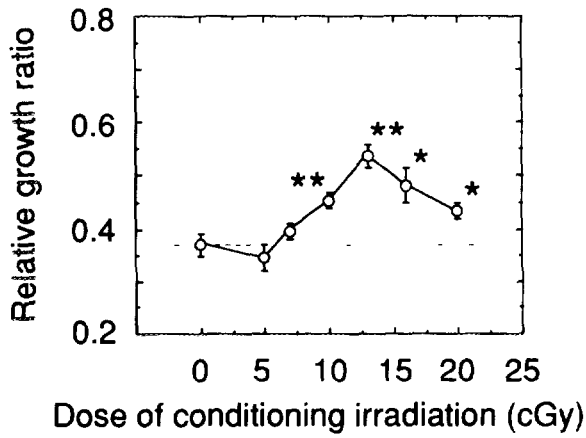

Fig. 1 Changes in growth ratio of the cells after receiving the challenging irradiation of 200 cGy, as a function of pre-irradiated conditioning dose. Each point is the mean ± SD of six independent determinations. **p<0.01, *p<0.05 by paired t-test.

(2) Effects of Calcium Ions and TPA

When HE cells were exposed to a challenging irradiation of 200 cGy with mock conditioning irradiation in HBSS with or without Ca^{2+}, the growth ratio of the viable cells decreased to 31-37 % of the control groups. When a conditioning irradiation of 13 cGy was given to HE cells in the Ca^{2+}-containing HBSS four hours before the challenging irradiation, the growth ratio of the viable cells increased significantly to 53 %. However, when HE cells were given a conndtioning irradiation in the Ca^{2+}-free HBSS, the growth ratio of the viable cells was about 32 %. When TPA was added to the culture medium at 100 ng/ml during the conditioning irradiation, the growth ratio of the viable cells significantly decreased to 42%.

(3) Effects of Inhibitors on Intracellular Signal Transduction

When H-89 or H-8 was added to the medium for only 20 min from 10 min before to 10 min after conditioning irradiation, no significant difference in number of the viable cells was observed. Viable cells significantly decreased in number by adding H-7, as compared with the control group.

Discussion

To examine the role of intercellular communication in the adaptive responses of cells to radiation, we irradiated normal HE cells with low-dose X-ray and examined changes in their

sensitivity to subsequent high-dose X-ray irradiation. As a result, the conditioning irradiation of low-dose X-ray moderated the decrease in the growth ratio of the cells due to the subsequent 200 cGy irradiation, and increased the radioresistance. This adaptive response was observed when the conditioning irradiation dose was in a range from 10 to 20 cGy. When conditioning irradiation was given to the cells in a Ca^{2+}-free medium, no radio-adaptive response was observed. Ca^{2+} ions are considered to be involved in intercellular communication. From the results of the experiment, in which HE cells in the culture medium containing TPA as an inhibitor on intercellular communication were irradiated at 13 cGy, it was confirmed that intercellular communication is involved in the radio-adaptive response. Therefore, it is possible to assume that intercellular communication is involved in the response of irradiated cells [5].

When H-7 was added to the medium before conditioning irradiation, the number of viable cells at 6 days after challenging irradiation significantly decreased, as compared with that of the cells given a conditioning irradiation in the medium without H-7. The finding indicates that the induction of radio-adaptive response is reduced if the activity of PKC is inhibited by adding 5 mM of H-7. The concentration of the inhibition constant (ki) of H-7 against PKC is 6.0 mM [6]. This supports the previous report demonstrating that intracellular signal transduction related to the radio-adaptive response induced by low-dose irradiation is mediated by PKC [7]. Although the Ki concentration of H-89 against A kinase is 0.048 mM [8] and H-8 against G kinase is 0.48 mM [6], addition of these inhibitors at a concentration corresponding to the Ki concentration, 0.05 mM and 0.5 mM respectively, failed to inhibit the induction of radio-adaptive response. These findings indicate that the intracellular signal transduction for the induction of radio-adaptive response is not mediated by A kinase or G kinase.

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Effects of low doses of A-bomb radiation on human lifespan

Y. Okumura and M. Mine

Atomic Bomb Disease Institute, Nagasaki University School of Medicine, Nagasaki, Japan

Abstract

Among about 100,000 A-bomb survivors registered at Nagasaki University School of Medicine, male subjects exposed to 31 - 40 cGy showed significantly lower mortality from non-cancerous diseases than age-matched unexposed males. And the death rate for exposed male and female was smaller than that for un-exposed. It was presented that the low doses of A-bomb radiation increased lifespan of A-bomb survivors.

1. Introduction

The hypothesis that radiation is hazardous even at small doses without threshold has been widely accepted. Bases on this hypothesis, radiation protection practices have presumed low-dose risk estimates by linear extrapolation from observed high-dose effects. However, the validity of the no-threshold model has seldom been critically assessed with actual data with actual data on humans exposed to low doses. Simizu *et al.* continued studies on mortality of a large cohort of A-bomb survivors in Hiroshima and Nagasaki, which is called RERF (Radiation Effects Research Foundation) population, and concluded that there was no threshold of the increase in the relative risk of mortality with radiation doses, even though there were their findings that death rate frequently showed seemingly lower values in persons exposed to low doses than unexposed persons [1]. The importance of U-shaped dose-response relationship was first pointed out by Stewart and Kneale, using the RERF population [2-3]. We examined the effects of low doses in a cohort of Nagasaki A-bomb survivors which are considerably different from the Nagasaki survivors included in the RERF population.

2. Materials and Methods

Since 1970, a database of about 100,000 A-bomb survivors in Nagasaki has been maintained at the Atomic Bomb Disease Institute at Nagasaki University School of Medicine [4-5]. The data include personal histories, cumulative records of health checks and death certificates. The data for all persons recognized as A-bomb survivors and given an A-bomb

Health Book from Nagasaki City have been collected. From the data, we selected those for a total of 3456 persons exposed more than 1 cGy and a total of three times 3456 persons age-matched controls who were alive in 1970. The control group (zero-exposure) consisted of persons with the A-bomb Health Hand Book who were more than 3 km from the hypocenter at the time of the A-bombing. Persons who moved out of Nagasaki City before were not included in this follow-up study, therefore death certificates were obtained with 100% efficiency. The relative risk of deaths (total deaths, deaths from cancer, and deaths from non-cancerous deaths) in 1970-1988 was analyzed.

3. Results and Discussion

The relative risk of death from all causes, cancer and non-cancer was analysed. For deaths from all causes, the relative risk did not show significant increase with dose. The relative risk of deaths from cancer increased with a dose threshold at about 50 cGy. However, for non-cancer deaths, the relative risk at 31 - 40 cGy range was below unit for male statistically significant ($p<0.05$) as shown in Figure 1.

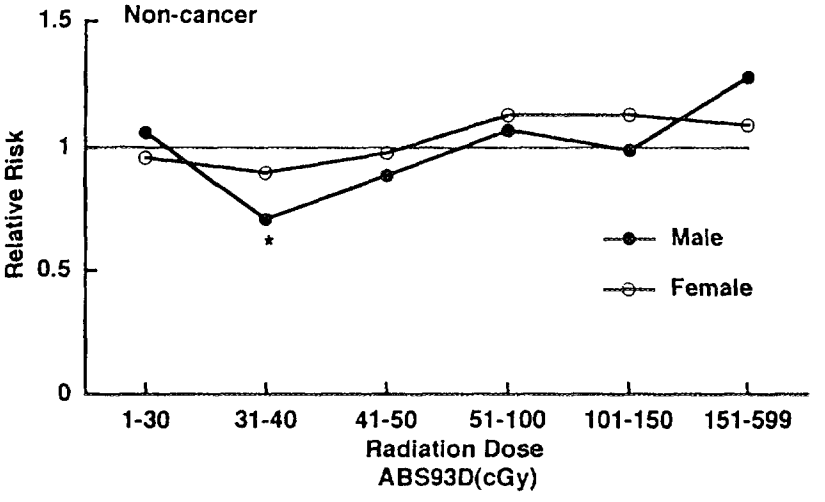

Figure 1. The relative risk of death from non-cancer.

Figure 2 shows the death rate for male and female. Closed symbols are of A-bomb survivors whose exposed radiation dose was less than 0.5 cGy and was assumed as non-exposed. Open symbols are of A-bomb survivors whose exposed radiation dose was more than 1 cGy and was assumed as exposed. The average of dose of exposed population was 125 cGy. The death rate was lower for exposed A-bomb survivors than for non-exposed survivors.

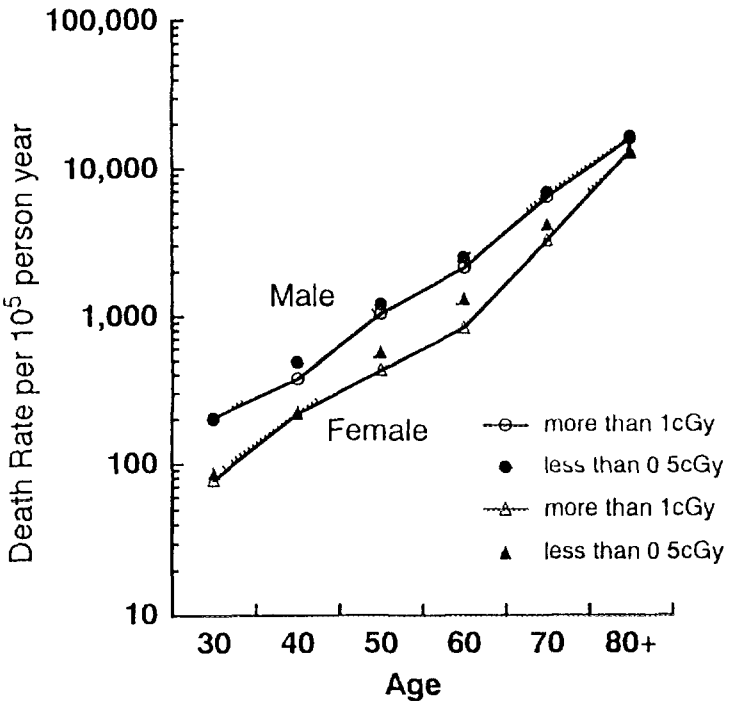

Figure 2. Death rate of A-bomb survivors in comparison with exposed doses.

It is clear that A-bomb radiation causes cancer in survivors dependent on radiation dose. The above data suggest that small doses of A-bomb radiation decreased death rate and relative risk and that increased lifespan of A-bomb survivors [6].

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Effect of Small Doses of γ-Ray on the Glutathione Synthesis in Mouse

SHUJI KOJIMA,* OSAMU MATSUKI,* TAKAHARU NOMURA,* MAREYUKI TAKAHASHI** and KIYONORI YAMAOKA***
*Research Institute for Biological Sciences, Science University of Tokyo, Yamazaki, Chiba, Japan and **Research Center for Advanced Science and Technology, The University of Tokyo, Komaba, Tokyo, Japan and ***Central Research Institute of Electric Power, Komae, Tokyo, Japan

XA9745652

ABSTRACT

The induction of biological adaptive response against small doses of γ-ray irradiation was investigated in C57BL/6 mice, in connection with the reduced form of glutathione (GSH). A significant increase in GSH content was recognized in several organs, including liver and brain, from 3 to 6 hr after irradiation with 50 cGy of γ-ray. These changes were consistent with those of the total radical scavenging activity of these organs against 1,1-diphenyl-2-picrylhydrazyl (DPPH), a chemically stable radical. These increases persisted for around 24 hr. γ-Rays at doses of 25-50 cGy elevated GSH content, but this was never seen more than 100 cGy. The elevation of GSH content was accompanied by elevated glutathione reductase, glutathione peroxidase, and γ-glutamylcysteine synthetase. Furthermore, the mRNA inductions for these enzymes were observed at an earlier time post-irradiation.

INTRODUCTION

It has generally been considered that any dose of ionizing radiation is detrimental to living cells, even in the case of small-dose radiation. This has been inferred by theoretically scaling down from the known deleterious high-dose effects of high doses. Interestingly, it has recently been shown that low level ionizing radiation (LLIR) induces various stimulating effects on living cells, for example, a radio-adaptive response,[1-5] the prevention of brain disorders,[6] an increase in the lifespan of insects,[7] enhancement of resistance to oxygen stress,[8] and so on.[9, 10] With respect to the efficacy of LLIR on its *in vivo* antioxidant potential, an increased activity of superoxide dismutase (SOD), which converts $O_2^{\cdot-}$ to H_2O_2, has already been reported.[11, 12] This phenomenon is understandable, since radiation toxicity to living cells is, in essence, due to active oxygen species generated by the interaction between water molecules and ionizing radiation,[13-15] and antioxidant enzymes such as SOD[16] are induced under certain conditions of oxygen stress. Furthermore, it is now well established that living organisms increase their synthesis of some well-characterized proteins, e.g., metallothionein[17] and heat shock proteins, which may serve adaptative functions in response to oxidative stress.[18, 19] There is, however, the need for additional, carefully documented investigation in selected biological systems exposed to low-level radiation.

We examined the effect of small doses radiation on the induction *in vivo* of antioxidant potential in various tissues of C57BL/6 mice in order to elucidate additional stimulating effects of low-level radiation in connection with glutathione, and/or to provide scientific evidence for radiation hormesis.

MATERIALS AND METHODS

Ascorbic acid (Asc), the reduced form of glutathione (GSH), the oxidized form of glutathione (GSSG), vitamin E (Vit E), 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) were purchased from Wako Pure Chemicals (Osaka, Japan). NADHand NADPH were from Oriental Yeast Co. Ltd (Tokyo, Japan). GSH reductase (GR, 120 U/ml) was obtained from Sigma (St. Louis, MO, USA).

Female C57BL/6 mice, 8 weeks old, were purchased from Tokyo Experimental Animals (Tokyo, Japan). They were housed in standard polycarbonate cages with sterilized wood chip bedding and were acclimated to the animal facility environment for 1 week. Mice were allowed free access to water and sterilized normal diet (CE-2, CLEA Co., Ltd., Tokyo, Japan).

Mice were irradiated with γ-rays from a ^{137}Cs source (GAMMACELL 40, Nordin International, Inc., Canada) at a dose of 50 cGy (1.19 Gy/min). Mice were also exposed to different doses of γ-rays and sacrificed 12 hr after irradiation. The dose-dependent effect of radiation was examined by analysis of various organs after sacrificing the mice at each time

Reduced glutathione or total soluble SH content in various tissues was measured by a modification of the spectrophotometric technique. The rate of change in absorbance was measured at 412 nm. GSH standards (0-20 mg/ml) were analyzed in the same manner. GSH concentrations of the sample were calculated as nmol/mg protein. The protein content was measured according to method of Lowry and colleagues.

The activity of GR (EC 1.6.4.2), glutathione peroxidase (GPX) and γ-glutamylcysteine synthetase (γ-GCS) were measured spectrophotometrically at 340 nm in terms of the rate of NADH/NADPH oxidation at 37 °C.

Expressions of GR-, GPX- and γ-GCS-mRNA were analyzed by Northern blotting. Total RNA was isolated from mouse liver, and the concentrations of all RNA samples were determined spectrophotometrically at 260 nm. RNA samples were resolved by electrophoresis in 1% agarose gels containing 0.6 M formaldehyde, transferred to nylon membranes, then hybridized with α-^{32}P-labeled nick-translated probes for mouse GR, GPX and γ-GCS. Membranes were autographed and analyzed using a Fuji Bio-Analyzer BAS-2000.

The data were analyzed by Student's *t* test. The criterion of significance was taken as $P<0.05$.

RESULTS

GSH is one of the major antioxidants which can act as an endogenous scavenger against active oxygen radicals. As shown in Figure 1, the GSH content in the liver was increased, from 3 hr post-irradiation, with 50 cGy γ-ray, and this level was maintained until around 24 hr. Next, the possible dose-dependent effect of γ-rays on the GSH level of the liver was investigated at 12 hr post-irradiation. Both 25 and 50 cGy of radiation increased the GSH level, but there were no significant alterations at doses of more than 100 cGy.

Since the reduced form of glutathione is generated from GSSG in a reaction mediated by NADPH and catalysed by GR, possible alterations of GR activity in the liver of mice after irradiation were examined as a function of time. As shown in Figure 2, the activity of GR was also elevated from 3 hr post-irradiation at a dose of 50 cGy, and significant increases ($p<0.01$ or $p<0.001$) persisted at 24 hr. In studies of the dose-dependency of the effect of radiation on the activity of this enzyme, an increase was also observed in the liver irradiated with γ-ray doses of 25 and 50 cGy. However, no effects were observed at the higher doses of 100 and 200 cGy. The elevation of GSH content was also accompanied by elevated GPX, and γ-GCS. Furthermore, mRNA for GR were induced at an earlier time post-irradiation (Fig. 3).

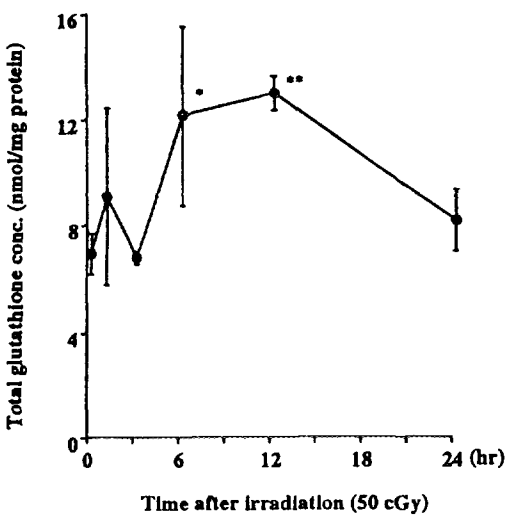

Fig. 1. Gluthatione concentration of mouse liver after γ-ray irradiation at a dose of 50 cGy
Each point indicates the mean ± SD for 4 mice. *, ** Significantly different from the value at 0 hr, at $p<0.05$ and $p<0.01$, respectively.

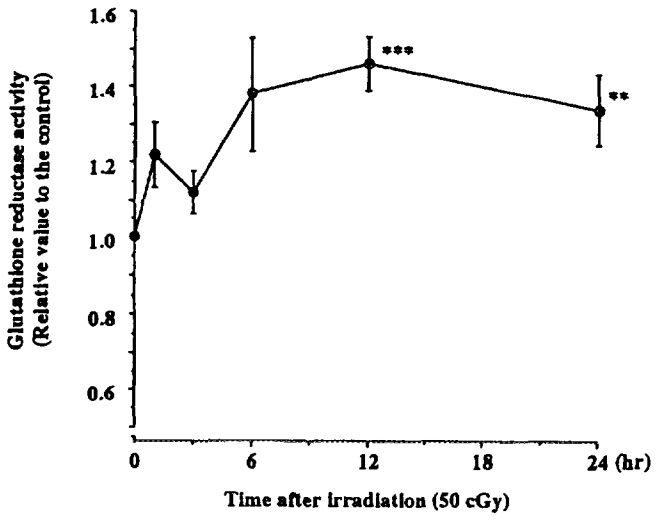

Fig. 2. Glutathione reducatse activity of mouse liver after γ-ray irradiation at a dose of 50 cGy
Each point indicates the mean ± SD for 4 mice. **, *** Significantly different from the value at 0 hr, at $p<0.01$ and $p<0.001$, respectively.

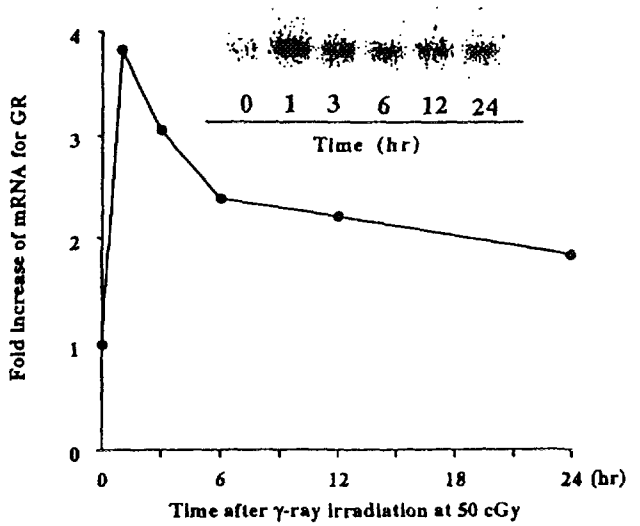

Fig. 3. Northern analysis of glutathione reductase (GR) of mouse liver after irradiation with γ-ray at a dose of 50 cGy

DISCUSSION

Active oxygen species such as hydrogen peroxide, hydroxyl radical, and superoxide anion radical, are readily generated in many cells by metabolic processes such as respiration, ischemia/reperfusion, and oxidation of fatty acids, and they are highly toxic to cells by damaging such components as DNA, lipids and enzymes. Cells can be injured, and even killed under the most serious conditions, when the content of active oxygen species exceeds the cellular antioxidant capacity. It is understandable, then, that cells have evolved effective defense systems against active oxygen radicals, not only through enzymatic mechanisms, such as catalase, superoxide dismutase and GSH peroxidase, but also non-enzymatically via GSH, thioredoxin and vitamins C and E. The best characterized endogenous antioxidant of these non-enzymatic molecules is GSH. GSH is considered to act as a radical scavenger, with the redox-active sulphydryl group reacting with oxidants to produce oxidized glutathione, then to be regenerated in a reaction mediated by NADPH and catalysed by GR. Lowered concentrations of GSH have generally been considered an index of increased oxidative stress, resulting from the increased formation of active oxygen radicals and the depletion of GSH from mammalian cells, ultimately causing cell damage due to oxidative stress.

In addition, the induction of antioxidant-related proteins, such as SOD and heat shock protein (Hsp 70), has already been shown to be effective in various organisms after treatment with sub-lethal pressures of oxygen. This protein induction is thought to act as an adaptive stress response, though the complex mechanisms involved are still being elucidated.

Ionizing radiation can also be considered to be a source of active oxygen radicals. Therefore, some of the adaptive responses described above can be anticipated after treatment with small-dose radiation. In this study, we first confirmed the induction of the increased antioxidant potential of various tissues after treatment with small-dose γ-ray irradiation. Small doses (25-50 cGy) of γ-ray irradiation significantly increased the scavenging potential of tissue cytosol fractions against DPPH. This phenomenon was seen soon after post-irradiation and persisted, suggesting an adaptive response to the active oxygen species generated by the radiation. It was suprising to find that this effect is only seen over a very narrow dose range of radiation and only in certain organs including the liver, pancreas and brain. Also, this response varied slightly among the liver, pancreas and brain, suggesting different sensitivities of these organs to the radiation.

The involvement of enzymatic and non-enzymatic defense systems can be anticipated to contribute to the mechanism of the elevated antioxidant potential of each organ. In this study, we focused our attention on GSH.Temporal changes in the GSH level in the liver were examined after 50 cGy γ-ray irradiation. As shown in Figure 1, the GSH content was increased from 3 hr post-irradiation, and this pattern was consistent with that of the change in the total scavenging potential of liver cytosol fraction against DPPH. Further, significant elevations of GSH content were recognized at 25 and 50 cGy, but not at doses of more than 100 cGy in the dose-response studies, similar to the changes in the total scavenging potential. The increase in GSH was complemented by the fact that the radiation also increased the GR activity, which regulates the regeneration of GSH. We have also conducted examinations of the efficacy of small-dose radiation on other GSH-related enzymes, such as GPX and γ-GCS. The activity of GPX, which plays a major role in scavenging active oxygen radicals, was

significantly increased, in a similar fashion to GR. γ-GCS, a rate enzyme for GSH synthesis from glutamate and cysteine, was significantly increased as well. These adaptive responses of enzymes were confirmed by the induction of their mRNAs. In conclusion, it could be suggested that small dose of radiation triggers an adaptive response against active oxygen species.

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Thioredoxin : Inducible radioprotective protein by low-dose radiation

Yuko Hoshi*, Keiichiro Ishii*, Hiroshi Tanooka*,†, Kunihisa Miyazaki† and Hiro Wakasugi†,
*Central Research of Electric Power Industry, Iwado-kita, Komae, Tokyo 201 † National Cancer Center Research Institute, Tsukiji, Chuo-ku, Tokyo 104, JAPAN

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Abstract

Thioredoxin (TRX), that has many biological activities, is radioprotector and a key protein in regulating cellular functions through redox reaction. We observed time course and dose dependent alteration of TRX gene expression in human peripheral lymphocytes after low-dose irradiation. TRX mRNA level increased to a peak, 5.7-fold higher than the control at maximum, 6 h after irradiation, and then decreased. The optimum radiation dose for enhancement of induction of the TRX mRNA was 0.25 Gy. The TRX protein, also increased to a peak, a 3-fold increase at maximum, with the same timing as that for TRX mRNA. Induction of the expression of TRX gene was followed after ionizing irradiation of lymphocytes from human donors. The similarity of time course between TRX gene expression and induction of radioadaptive response by low-dose radiation suggests that TRX may be involved in adaptive response.

Biological effects of low-level ionizing radiation are becoming important from the viewpoint of human health in the environment [1]. At the molecular level, ionizing radiation modulates expression of a number of mammalian genes controlling cell growth, such as *p53* and cyclin B, and apoptosis. The presence of the responsive element to ionizing radiation and the alteration of transcription factor binding after radiation indicate that ionizing radiation modulates gene expression at the transcription level. The molecular mechanism of these ionizing radiation-inducible events is thought to be related to such radiation-inducible biological phenomena as adaptive response [2] and induced radioresistance [3].

Moreover, the redox status of a number of gene products also regulates various cellular functions. Recently, the redox/DNA repair protein, Ref-1, was shown to be essential for early embryonic development in mice [4].

Thioredoxin (TRX) is a key protein which controls cellular redox status. TRX was originally purified from *Escherichia coli* [5] and shown to be an oxidoreductase consisting of 104 amino acids [6,7]. Human TRX gene [8] is a homologue of adult T cell leukemia-derived factor [9,10], having cytokine activity. Interestingly, human TRX is a radio-protector [11] and has many biological activities, such as growth promotion and a catalase-like radical scavenging activity [12,13]. Therefore, TRX gene expression potentially can play an important role in cellular functions responding to radiation.

Fresh human venous blood from donor A was used immediately for experiments after sampling. Other blood samples were obtained from healthy male donors (B-E) supplied by the Japan Red Cross Blood Center, Tokyo. Lymphocytes were isolated by centrifugation at 1000 rpm for 30 min in a layer of Lymphocepal. Lymphocytes suspended in the culture medium at 10^6 cells per ml were exposed at room temperature to various single doses of γ rays generated by a ^{60}Co source at a dose-rate of 0.72 Gy/min or to X-rays generated by a 150 Kvp generator with filters of 0.2 mm Cu and 1.0 mm Al at a dose rate of 0.25 Gy/min. Irradiated cells were incubated at 37°C in humidified 5% CO_2/95% air for various periods of time. Aliquots, containing 10^7 cells each, were used for extraction of RNA and protein. TRX mRNA was measured by the Northern blots method with a probe of TRX cDNA. Amounts of TRX proteins were measured by the ELISA method, using anti-TRX antibody.

TRX mRNA levels in various preparations of human lymphocytes from fresh venous blood (donor A) showed the lowest TRX mRNA level. Lymphocytes stimulated for growth with IL-2 and CD3 exhibited a 3.6-fold higher TRX mRNA level than untreated lymphocytes. The highest

TRX mRNA expression so far measured was exhibited in the immortalized cell line 1G8, which showed a level 11-fold higher. Expression of TRX mRNA in human lymphocytes was induced with a peak at 6-8 h after irradiation. The TRX mRNA reached 5.7-fold higher level at 6 h after irradiation in sample from donor A, whose lymphocytes were freshly prepared from venous blood. However the increased levels was lower in the samples from other donors. As a positive control, lymphocytes treated by a tumor promoter TPA also showed the elevated TRX mRNA level with a peak at 2 h. TRX mRNA level in non-irradiated lymphocytes remained unchanged during incubation. TRX protein level was also tracked after irradiation of the lymphocytes with 0.25 Gy. The peak expression was found 6-8 h after irradiation, just as for mRNA, although its increased level was not so high as the mRNA increase. The TRX protein level in non-irradiated sample from donor A lymphocytes was 85 pg/cell or 20.3 ng/mg of total cellular protein. To see the dose response of the TRX mRNA and protein induction, lymphocytes were irradiated with various radiation doses and incubated in the culture medium for 6 h. The optimum dose for TRX mRNA and protein appeared to be 0.2-0.5 Gy.

The present study showed that the TRX gene expression in human lymphocytes increased after low-dose irradiation. The expression level and timing varied among different donors. Therefore, this increase is thought to occur commonly in human lymphocytes. The optimum radiation dose for TRX induction was 0.25 Gy, which is much lower than doses used for molecular studies reviewed in the Introduction. Interestingly, the elevated level of p53 protein is observed in tissue specimens of various organs of mice, with the same optimum dose of 0.25 Gy as that in the present study [14]. Although the biological consequence of TRX induction by ionizing radiation is unknown, TRX appears to be a ubiquitous source of reducing potential in mammalian cells and it is now becoming clear from various evidences as stated in the introduction that the cellular redox status may play an important regulatory role in transcription factor activity and cell cycle control. In this consequence, the TRX induction by ionizing radiation must have some biological effects. In addition, time course of TRX gene expression is similar to induction of radio-adaptive response by low-dose radiation [15,16]. This result suggests that TRX may be involved in adaptive response.

The main body of the present observation will be published elsewhere [17]

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SUPPRESSION OF SPONTANEOUS AND ARTIFICIAL METASTASIS BY LOW DOSE TOTAL BODY IRRADIATION IN MICE

Yoshio Hosoi[a]*, Kiyohiko Sakamoto[b]

Departments of [a]Rdiation Research and [b]Radiology
Tohoku University School of Medicine
2-1 Seiryomachi, Aobaku, Sendai 980-77, Japan.
Correspondence address*

ABSTRACT. We investigated whether low dose total body irradiation (TBI) suppresses metastasis using both artificial and spontaneous lung metastasis in WHT/Ht mice. When mice were irradiated with 15-60 cGy immediately before tumor cell injection into a tail vein in artificial lung metastasis, lung colony formation was suppressed significantly by the TBI, and 20 cGy was the most effective dose. The suppressive effect of 20 cGy TBI lasted for 6 hours. TBI with 15-20 cGy suppressed spontaneous lung metastasis significantly, and 15 cGy was the most effective dose.

1. INTRODUCTION

Irradiation with low doses (0-25 cGy) has little effect on the survival rate of solid tumor cells. However, it has been reported that total body irradiation (TBI) with the low doses has carcinostatic effects. In 1915, Murphy and Morton have shown that total body exposure to a "stimulating dose of X-ray" immediately before tumor transplantation suppressed growth of the grafted tumor in mice [1]. Long after the report, similar carcinostatic effects of low dose TBI have been reported. Tumor growth delay and increased TD50 value (the number of cells required to produce a tumor in half of a group of injected sites) following the low dose TBI have been reported in other mouse-tumor systems [2, 3]. Sakamoto *et al.* have reported that 10 cGy TBI sensitizes the mouse tumor cells to local irradiation which was carried out 9 hours after the TBI [3]. Fractionated 5-15 cGy TBI decreased the incidence of spontaneous thymic lymphoma in AKR mice [4]. Fractionated 10-15 cGy TBI has been successfully applied to the clinical treatment of non-Hodgkin's lymphoma [5]. In the present report, we show the effects of the low dose TBI on artificial and spontaneous metastasis in mice [6, 7].

2. MATERIALS AND METHODS

2.1. Irradiation

TBI was conducted with X-rays at 230 KV and 20 mA with filters of 1.0 mm Cu and 1.0 mm Al (Shimadzu SHT 250 M-3). The dose rate was 0.64 Gy/min at the mid-line depth of the abdomen of mice. For the preparation of heavily irradiated cells (HR cells), tumor cells were irradiated *in vitro* with X-rays of 100 Gy from SOFTEX M-100SW (100 KV; 5 mA; 0.1 mm Al filter) at a dose rate of 4.10 Gy/min.

2.2. Mice

Mice used in the experiments were the inbred albino strain, WHT/Ht [8], bread in our specific pathogen-free (SPF) facility. Female mice were used at the age of 8-10 weeks. The experiments were conducted according to the 'Guidelines for Animal Welfare and Experimentation' issued by Tohoku University on January 11, 1989.

2.3. Tumor

The highly metastatic tumor cell line used in this experiment was selected from the low immunogenic spontaneous squamous cell carcinoma [8] maintained in our laboratory by the method by Fidler [9]. For selection of a highly metastatic cell line, mice were given a subcutaneous injection of 1000 viable tumor cells and were killed by cervical dislocation 2

weeks later. Their lungs, which contained tumor nodules, were removed. Several pulmonary metastases were dissected, thoroughly minced, suspended with phosphate-buffered saline (PBS) and subcutaneously injected into new hosts. This procedure was repeated 35 times, and a highly metastatic tumor cell line was established. Because the TD50 value of the tumor used was found to be 9-12, the tumor used in this experiment was thought to be low immunogenic [6].

2.4. Preparation of single-cell suspension from tumors

Mice were given a transplantation of one thousand of tumor cells in axilla. The mice were sacrificed and their tumors were removed 2 weeks later. Then tumors were well minced and disaggregated with 0.1% collagenase and 0.1% hyaluronidase at 37℃ for 15 minutes. Tumors were further treated with 0.25% trypsin and 0.1% EDTA at 37℃ for 15 minutes. The resulting suspension was filtered through a No. 200 stainless steel wire mesh to obtain a single cell suspension. The concentration of viable tumor cells was determined using a hemocytometer [8].

2.5. Artificial metastasis

Viable tumor cells of $3X10^3$ added with $1X10^6$ HR cells in 0.2 ml of medium (Dulbecco's Modified Eagle Medium) were injected into a tail vein. Fourteen days after the injection, the mice were killed, and their lungs were removed and fixed in Bouin's fluid for 24 hours. The lobes of the lungs were separated and the total number of superficial visible colonies per lung was scored.

2.6. Spontaneous metastasis

One thousand viable tumor cells in 0.01 ml of the medium were injected subcutaneously into a hind leg. Thirty two days after the injection, mice were killed and total number of superficial visible colonies per lung was scored [6].

3. RESULTS

Injection of $3X10^3$ viable tumor cells with $1X10^6$ HR cells into the tail vein resulted in 55.2±15.4 (mean±SD, n=267) of colonies on the lung surface 14 days later. TBI with 5-60 cGy was carried out immediately before tumor cell injection, and its effect on lung colony formation was investigated. TBI with 15-60 cGy suppressed lung colony formation significantly (Fig. 1). Twenty cGy was most effective in the dose range of 15-60 cGy. In order to investigate how long the suppressive effect of 20 cGy TBI lasts, interval time between the TBI and the tumor cell injection was changed. TBI with 20 cGy suppressed lung colony formation significantly when the TBI was carried out between 3 hours before and 3 hours after the tumor cell injection (Fig. 2). The TBI tended to suppress lung colony formation when it was carried out between 9 hours before and 21 hours after the tumor cell injection. Similar suppressive effects were observed when HR cells were omitted and only the viable tumor cells ($1X10^5$) were injected (data not shown). Injection of tumor cells irradiated with 10-50 cGy in vitro showed no difference from the control value, which indicated that the suppressive effect of the low dose TBI was based on the radiation effect on mice but not on tumor cells.

Next, we examined whether the TBI with 20 cGy is actually effective on spontaneous tumor metastasis. The injection of $1X10^3$ viable tumor cells into a hind limb resulted in 11.6±1.8 (mean±SE, n=37) of lung colonies 32 days later. Mice were irradiated with 20 cGy on 4, 8, 12, 16 or 20 days after the tumor injection. When the TBI was carried out on the 12th day, lung colony number was significantly suppressed to 56.3±13.4% of the control (Fig. 3). The dose dependency of TBI was further checked to evaluate optimal dose in spontaneous metastasis. Mice were irradiated with 10-100 cGy on the 12th day after the tumor cell injection. As shown in Fig. 4, significant suppression was observed at 15-20 cGy.

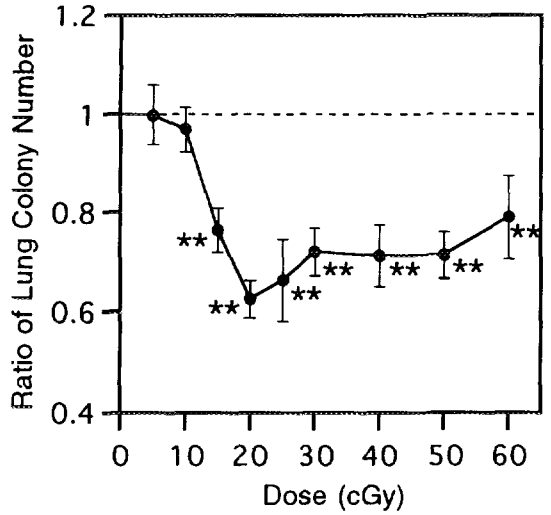

Fig. 1. Effect of low dose TBI on artificial lung metastasis. Mice were irradiated with 5-60 cGy immediately before the tumor cell injection. Data were expressed as the ratio of the number of lung colonies observed in irradiated mice to that in sham-treated mice. Bars indicate SE of 20-40 mice for each point. *; $p<0.05$, **; $p<0.01$.

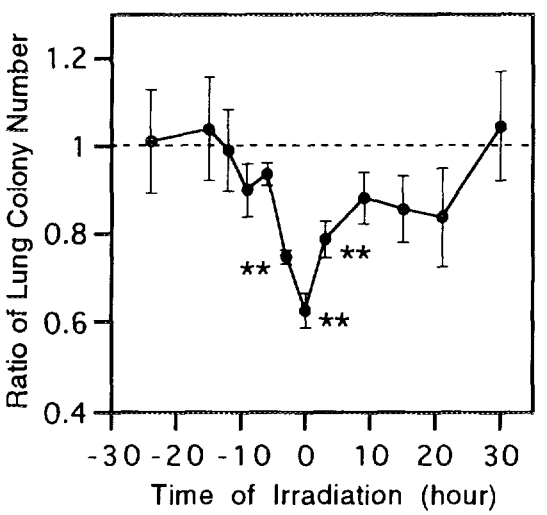

Fig. 2. Effect of 20 cGy TBI on artificial lung metastasis. Mice were irradiated with 20 cGy between 24 h before and 30 h after the tumor injection. Symbols as in Fig. 1.

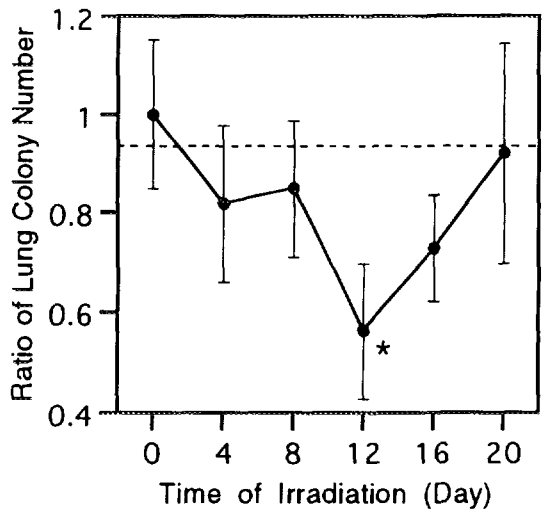

Fig. 3. Effect of 20 cGy TBI on spontaneous lung metastasis. Mice were irradiated with 20 cGy on 4-20 days after the tumor injection into a hind limb. Bars indicate SE of 26 mice for each point. Symbols as in Fig. 1.

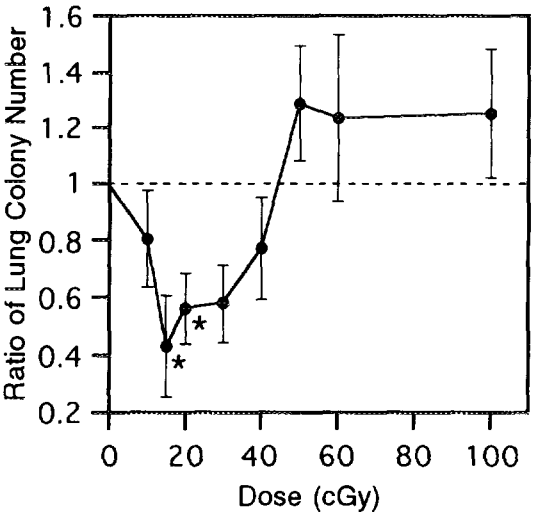

Fig. 4. Effect of 5-100 cGy TBI on spontaneous lung metastasis. Mice were irradiated with 10-100 cGy 12 days after tumor injection into a hind limb. Symbols as in Fig. 3.

4. DISCUSSION

Decreased incidence of lung metastasis and decreased TD50 value have been observed in our system [3, 6, 7]. Anderson *et al.* have reported the tumor growth delay when the low dose TBI carried out immediately before the tumor injection [2]. In the present study on spontaneous metastasis, the low dose TBI on the 12th day after the tumor injection did not affect the tumor sizes of the injected sites. These data suggest that the low dose TBI affects the survival of

newly transplanted or metastasized tumor cells, but that it little affects the cell survival of the established solid tumor. However, lymphoma is thought to be a exception of this hypothesis. It has been reported that the incidence of spontaneous thymic lymphoma in male AKR mice was decreased from 80.5% in sham-irradiated mice to 67.5% in mice which received 5 cGy TBI three times a week and 48.6% in mice which received 15 cGy twice a week for 40 weeks [4]. For clinical treatment of non-Hodgkin's lymphoma, fractionated 10-15 cGy TBI up to 150 cGy of total dose has been applied [5]. Because (1) total irradiation dose is high in these cases and (2) lymphoma cells are sensitive to ionizing radiation compared with other solid tumor cells, direct cell killing effect might make some contribution to the carcinostatic effect of the low dose TBI in lymphoma.

It is unknown how the low dose TBI suppresses metastasis. Augmentation of immune system is one of the possible mechanisms. There have been many reports on augmentation of the immune system by the low dose irradiation [2, 3]. On the other hand, it has been reported that the low dose irradiation affects the prostacyclin production in endothelial cells which relates to the tumor metastasis [10]. Mechanisms of the suppression of metastasis by the low dose TBI would be complicated.

The low dose TBI has been reported to act synergistically with a immuno-modulator, OK-432 in suppressing metastasis and augmentation of immune responses [7]. Because side effects of single 10-20 cGy TBI could be negligible for cancer patients, low dose TBI alone or combination treatment with other agents could be a practical clinical treatment for suppression of metastasis.

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Analgesia Induced by Repeated Exposure to Low Dose X-Rays in Mice, and Involvement of the Accessory Olfactory System in Modulation of the Radiation Effects

YUKIHISA MIYACHI* and TAKESHI YAMADA**
**Department of Physiology, and **Biology, Toho University School of Medicine, Ohmori-nishi, 5-21-16 Ohta-ku, Tokyo 143, JAPAN.*

ABSTRACT: The effects of low-dose X-rays on mouse nociceptive behavior were examined using a formalin injected test which rated the amount of time the animals spent licking the injected hind-paw. Male ICR White Swiss mice showed a marked suppression of licking behavior after repeated low-dose X-irradiation (5 cGy/day, 6 consecutive days). The most profound effect was observed on the day 30 after irradiation. The decline of licking behavior, however, was not observed at all following olfactory bulbectomy or vomeronasal tract cut. The analgesic effects could be observed in writhing animals administered acetic-acid intraperitoneally. Moreover, analgesia was totally blocked by the administration of *N*-nitro-L-arginine, a nitric oxide synthase inhibitor, to accessory olfactory bulbs prior to the exposure. The present results indicate that the olfactory system plays an important role in modulation of radiation-induced analgesia, and a possible involvement of nitric oxide in the formation of recognition memory subjected to repeated X-rays. Relatively higher doses (5 cGy × 9 days, 5 cGy × 12 days), however, did not induce such effects, namely, the decline of nociceptive response was limited to the animals irradiated with the smaller dose.

INTRODUCTION

It is well known that many noxious, non-noxious and environmental stimuli can induce changes in pain reactivity. Most commonly, a rise in the nociceptive threshold, antinociception, has been described in rodents following the administration of electric foot shock, immobilization or warm and cold water swims. This phenomenon is termed stress-induced analgesia. Although several neurotransmitters in the brain and spinal cord have been implicated, the full details of the neuronal pathways involved have not yet been elucidated.

X-rays also can be classed as physical stressors. But X-ray stimulus is particular, as X-rays cannot be perceived by the sensory organs of mammals. It is of interest to determine whether or not X-ray stress produces analgesia similar to that caused by perceivable stimuli such as electric foot shock.

Stress-induced analgesia is thought to be mediated by endogenous pain inhibitory systems, involving both opiate and non-opiate mechanisms. Enkephalin, an endogenous opiate-like peptide, is a neurotransmitter known to have various effects on the brain, including decrease of pain, alteration of response to stress, and modification of the neuroendocrine activity. We reported that brain Met-enkephalin in rodents rapidly decreased after 10 to 20 cGy X-irradiation [1, 2]. The most profound effect of radiation was observed in the hypothalamus. The secretion presumably provide the organism with means of adaptating to stressful environments such as X-irradiation. But no report has yet dealt with changes in nociceptive behavior induced by low-dose radiation of less than 50 cGy. We have therefore examined the effect of low-dose X-rays on the behavioral changes induced by pain, using an inflammatory agents such as formalin or acetic acid.

We recently reported that a brief exposure to X-rays served as an arousal stimulus in mice [3]. Exposure to X-rays (4 cGy) induced an immediate change in EEG patterns from low-frequency and high-amplitude (sleep) to high-frequency and low-amplitude (arousal). In anosmia mice by olfactory bulbectomy, no arousal response could be

observed. These results indicate that the olfactory bulbs play an important role in the immediate detection of X-rays.

To confirm the involvement of the olfactory system in the radiation effects on the nociceptive behavior, the anosmia mice following bulbectomy or vomeronasal tract cut were also examined.

RESULTS

Changes in licking behavior after repeated low-dose X-irradiation are shown in Table 1. After 5 cGy × 3 days irradiation, the time intervals which animals spent licking the injected paw tended to be slightly lower than in the sham-control. The depressive effect became remarkable when the radiation dose was elevated to 5 cGy × 6 days. The significant decrease was already noticed on the day 10, and the most profound effect was observed on the day 30. It reached a value of about one-fourth of the control.

Increasing the radiation dose further 5 cGy × 9 days or × 12 days, however, resulted in the complete disappearance of the effects, namely, the mice irradiated with the higher doses showed no differences from the sham control. These results suggest that the decrease in nociceptive effects is limited to animals irradiated with the smaller dose.

As shown in Table 2, the number of writhing response decreased significantly on the day 30 after 5 cGy × 6 days exposure, reaching a value that was 25 % of the control. Furthermore, increasing the radiation dose caused the complete disappearance of the effects. The suppression of writhings corresponded to that of licking behavior after 5 cGy × 6 days.

As shown Table 3, the time intervals of paw-licking in sham-control of all groups decreased markedly, namely, analgesia was clearly induced by 5 cGy for 6 days exposure. The licking behavior, however, increased significantly and reached to the level of non-irradiated group following OB or VNZ treatment that caused a dysfunction in the main and accessory olfactory system. Interestingly, the licking response of the animals receiving VN transaction also increased significantly. There was no difference, however, between the control and Z treatment, which could be disruption of only the main olfactory system. The present results suggest that the integrity of the accessory system is far more important than the main olfactory system for the expression of radiation-induced analgesia.

Table 4 showed that the licking behavior in mice injected with the NO synthase inhibitor intraperitoneally increased significantly compared to saline-treatment groups, and reached the level of the non-irradiated mice. The effect upon writhing response was the same. The licking response increased markedly in mice given a local infusion of nitro-arginine, compared with those given saline. The results indicate the complete disappearance of the radiation-induced analgesia.

Table 1. Depressive effects of mouse's licking behavior induced by low-dose X-irradiation.

	Day 10	Day 20	Day 30
Sham-control groups	196.5 ± 21.8 (15)	191.5 ± 20.6 (15)	188.2 ± 18.4 (15)
Split exposed groups			
5 cGy × 3 days	155.6 ± 25.3 (15)	159.6 ± 18.3 (15)	196.6 ± 16.3 (15)
5 cGy × 6 days	95.2 ± 14.6 (15) **	92.6 ± 15.0 (15) **	47.1 ± 17.3 (15) ***
5 cGy × 9 days	163.9 ± 19.5 (15)	174.3 ± 20.1 (15)	190.4 ± 20.5 (15)
5 cGy × 12 days	162.4 ± 18.5 (10)	172.3 ± 24.1 (10)	200.3 ± 17.1 (10)
Single exposed groups			
30 cGy	196.4 ± 25.8 (10)	175.9 ± 18.7 (10)	220.3 ± 22.1 (10)

Licking behavior was measured on days 5, 10, 20 and 30 after low-dose X-irradiation.
Data represent as an accumulated interval of licking after injection of formalin (sec/0-30 min).
Significant (*** $p<0.01$, ** $p<0.02$) when compared to sham-control. Values are mean ± S. E.
Figures in parentheses are numbers of mice used.

Table 2. Depressive effects of mouse's writhing response induced by low-dose X-irradiation.

	Day15	Day 30
Sham-control groups	45.0 ± 1.3 (15)	44.2 ± 1.8 (15)
Split exposed groups		
5 cGy × 3 days	46.1 ± 2.0 (15)	26.4 ± 2.4 (15) **
5 cGy × 6 days	40.3 ± 2.9 (15)	10.3 ± 1.9 (15) ***
5 cGy × 9 days	48.4 ± 2.4 (15)	38.4 ± 2.8 (15)
5 cGy × 12 days	39.9 ± 2.5 (10)	41.9 ± 2.5 (10)

Wrthing response was measured on days 15 and 30 after low-dose X-irradiation.
Significant (*** $p<0.01$, ** $p<0.02$) when compared to sham-control.
Values are mean ± S. E. Figures in parentheses are numbers of mice used.

Table 3. Disappearance of radiation-induced analgesia by olfactory bulbectomy or vomeronasal tract cut

Experimental condition	Licking response	Writhing response
Non-irradiated group	172.3 ± 14.9 (10)	48.5 ± 1.8 (10)
Irradiated groups		
OB sham	53.2 ± 14.6 (10)	11.2 ± 0.8 (10)
OB	184.4 ± 19.6 (10) ***	42.6 ± 2.3 (10) ***
VN sham	48.4 ± 13.8 (10)	9.8 ± 0.9 (10)
VN	159.3 ± 22.8 (10) ***	43.7 ± 2.0 (10) ***
Z sham	63.4 ± 18.1 (10)	13.5 ± 1.1 (10)
Z	84.9 ± 24.6 (10)	22.6 ± 2.7 (10)
VNZ sham	57.6 ± 17.5 (10)	13.5 ± 2.2 (10)
VNZ	162.9 ± 20.5 (10) ***	41.6 ± 2.4 (10) ***

The test was performed on day 30 which was observed the profound depressive effects of nociceptive response after 5 cGy for 6 days exposure. Significant (*** $p<0.01$) when compared to sham-control. Values are mean ± S. E. Figures in parentheses are numbers of mice used.
OB=Olfactory bulbectomy, VN=Vomeronasal tract cut, Z=$ZnSO_4$ nasal perfusion, VNZ=$ZnSO_4$ + Vomeronasal tract cut.

Table 4. Disappearance of radiation-induced analgesia by *N*-nitro-L-arginine given prior to the exposure

Experimental condition	Licking response	Writhing response
Non-irradiated group	174.6 ± 18.9 (10)	47.3 ± 2.4 (10)
Irradiated groups		
i. p. saline (sham-control)	53.4 ± 18.1 (10)	11.3 ± 0.7 (10)
i. p. nitro-arginine	144.8 ± 17.6 (10) ***	44.5 ± 1.8 (10) ***
l. i. saline (sham-control)	58.7 ± 17.9 (10)	14.6 ± 0.9 (10)
l. i. nitro-arginine	163.7 ± 20.5 (10) ***	48.9 ± 2.7 (10) ***
l. i. bicuculline	97.8 ± 19.4 (10)	28.6 ± 3.4 (10)

The test was performed on day 30 which was observed the profound depressive effects of licking behavior after 5 cGy for 6 days exposure. Significant (*** $p<0.01$) when compared to sham-control. Values are mean ± S. E. Figures in parentheses are numbers of mice used.
i.p=intraperitoneal injection, l.i=local infusion.

DISCUSSION

It is well known that exposure to stressful stimuli perceivable by sensory organs of mammals such as electric foot shock can produce analgesia. X-rays, a unperceivable agent, also can induce apparent analgesia. When the mice were deprived of their olfactory sense by OB VN or VNZ, the decline of licking response after the exposure was not observed at all. There was no difference, however, between the control and Z groups in which only the main olfactory system was disrupted. The present results suggest that the integrity of the accessory system is far more important than the main olfactory system for the expression of radiation-induced analgesia.

The other interesting finding reported here is that the effect was only observed in the lower dose range (5 cGy × 6 days), and not in cases of relatively higher doses (5 cGy × 9 days or × 12 days).

Stress-induced analgesia typically lasts only a few hours. The analgesia shown here, however, continued for up to 4 weeks after the exposure. We think that though little is known about the mechanisms, a long time-interval after irradiation might be essential to induce the low-dose radiation effects, in contrast to common stressors such as electric foot shock.

NO is a simple gas which possesses a radical structure under atmospheric conditions. Accumulating evidence suggests that NO simultaneously serves as a messenger for neurons, much like a neurotransmitter, in brain. A central focus in neurobiology is the growing interest in the search for the mechanisms underlying the changes in synaptic plasticity characteristic of learning and memory, as well as other neural phenomena. The results presented here showed that the radiation-induced analgesia was totally blocked by administering NO synthase inhibitor to the AOB, prior to the exposure. We think that the recognition memory subjected to repeated X-rays might be formed by NO in the accessory olfactory system.

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CHROMOSOME ABERRATIONS IN LYMPHOCYTES OF WORKERS OCCUPATIONALLY EXPOSED TO IONISING RADIATION

E.J. TAWN, K. BINKS, J.D. TUCKER*, R.E. TARONE**

Westlakes Research Institute, Moor Row, Cumbria, CA24 3JZ, UK
* Lawrence Livermore National Laboratory, USA, ** National Cancer Institute, USA

Abstract

Cytogenetic studies on workers employed at the Sellafield nuclear installation are reviewed and their relevance discussed in relation to biological dosimetry and risk assessment.

Introduction

Dose response relationships for radiation-induced cancer are derived from epidemiological studies of populations exposed to high doses. However, the classical epidemiological analysis of workforce data lacks the power to establish whether the low levels of exposure encountered occupationally carry any discernible risk to health and current risk estimates for low doses and low dose rates rely on extrapolation from high dose studies and the application of a dose and dose rate effectiveness factor (DDREF) of 2 [1].

Considerable *in vitro* cellular research suggests that the critical target for the deleterious action of radiation is DNA and chromosome aberrations are one of the most thoroughly studied outcomes of the conversion of the initial DNA damage to a mutational endpoint. Most work has concentrated on unstable aberrations, e.g. dicentrics, rings, acentrics, since these can be easily observed, and the dose response kinetics for acute doses over 50 mSv are well established. Indeed, following the finding that for acute exposures the *in vitro* and *in vivo* responses were similar, biological dosimetry based on dicentric frequency in peripheral blood lymphocytes has become a well established technique for assessing the extent of recent acute exposures [2].

Cancer arises as a result of mutation in critical target genes which are involved in the regulation of cell division, cell differentiation, apoptosis and genomic stability. Two types of gene have been identified, proto-oncogenes and tumour suppressor genes. Dominant mutations that convert proto-oncogenes into oncogenes resulting in gain of function are frequently achieved through chromosome translocations. Such chromosome rearrangements are well documented and many exhibit tumour specificity [3]. Mutations in tumour suppressor genes are generally recessive in action and result in loss of function. They can occur by gene mutation or gene deletion, with some deletions encompassing the gene being detectable cytogenetically [3]. Therefore, the types of radiation-induced genetic changes which are consistent with cell viability, e.g. translocations, inversions and small deletions, will be the important endpoints of relevance for malignant transformation. These stable aberrations are more difficult to identify, although classic genetic theory suggests that they should be induced with equal frequency and with the same dose kinetics as their unstable counterparts [4]. Studies of A bomb survivors and radiotherapy patients have shown that cells with stable chromosome aberrations persist for many years following exposure [5,6] and repeated cytogenetic examinations indicate that the frequencies remain unchanged [6], implying constant replenishment by cells derived from aberrant stem cells. The important target cells for carcinogenesis will be the stem cells in the haemopoietic system and other organs but, to date, the relationship between the induction of non-specific chromosome rearrangements and the specific oncogenic mutations necessary for cell transformation is not known.

Cytogenetic Studies on Occupational Radiation Workers

The Sellafield nuclear installation in West Cumbria, UK began activities in 1950 and since 1971 has been operated by British Nuclear Fuels plc. There has been relatively little turnover of the male workforce and there has, therefore, been opportunity for men to be employed as classified radiation workers for long periods of time and thus accumulate relatively high doses of ionising radiation. Cytogenetic studies have been ongoing for many years, initially concentrating on asymmetrical (unstable) aberrations. However cells containing such aberrations will not continue to

undergo repeated successful divisions and therefore more recently G-banding and fluorescence *in situ* hybridisation (FISH) techniques have been employed to identify symmetrical (stable) aberrations. In all the studies chromosome analysis was performed on peripheral blood lymphocytes at their first *in vitro* division. Radiation exposures were measured by external film badge dosimetry [7].

Asymmetrical Aberrations

In 1989 Tawn and Binks [8] reported a study of 71 radiation workers with cumulative radiation exposures >500 mSv and 66 controls with no known previous occupational or medical exposure to clastogenic agents. Cytogenetic analysis using conventional block staining was confined to asymmetrical aberrations (Table I). The mean dicentric frequency for the 71 radiation workers was significantly higher than the control value (p=0.001). However, when the radiation workers were divided into 4 dose groups no significant difference was found between them despite the fact that the men in group 4 had received approximately 2.5 times the mean dose received by group 1. Current smoking data were available. No significant difference was found for dicentric frequency between smokers and non-smokers but when a heavy smoker group, comprising men who admitted to smoking >20 cigarettes per day, was compared to the remainder a significant increase was seen for both controls and the pooled exposed workers. Dicentric frequency rose from $0.34\pm0.24\times10^{-3}$/cell to $2.80\pm2.00\times10^{-3}$/cell in the controls (p=0.05) and from $2.42\pm0.29\times10^{-3}$/cell to $4.71\pm0.82\times10^{-3}$/cell in the radiation workers (p=0.01). There is some evidence to suggest that dicentrics are lost from the peripheral blood with a half-life of approximately 3 years [9]. The dose accumulation pattern for each worker was examined and the annual doses weighted for a 3 year half life and summed to give an equivalent acute dose at time of blood sampling. This was used to establish a dose response for dicentrics. A slope of $1.57\pm0.20\times10^{-2}$/Sv was found when the effect of heavy smoking was considered and $1.44\pm0.20\times10^{-2}$/Sv when heavy smoking was not taken into account.

Table I **Asymmetrical Aberration Frequencies**

Group	Control	1	2	3	4	Total Radiation Workers
No. of individuals	66	15	23	16	17	71
Mean age (y)	40.2	49.5	55.5	56.4	57.0	54.7
Mean total dose (mSv)	-	560	750	950	1230	870
(range)		(510-580)	(630-840)	(900-1000)	(1020-1610)	(510-1610)
Mean radiation work (y)	-	24	29	27	28	27
(range)		(13-33)	(21-33)	(21-31)	(23-30)	(13-33)
Smokers (%)	33	60	61	44	65	58
Dicentrics/cell$\pm$S.E.$\times10^{-3}$	0.61±0.30	2.80±0.61	2.52±0.47	3.25±0.64	3.06±0.60	2.87±0.28
Acentrics/cell$\pm$S.E.$\times10^{-3}$	2.12±0.57	5.47±0.85	3.39±0.54	2.25±0.53	2.71±0.56	3.41±0.31

G-Banding Analysis

The accurate detection of symmetrical aberrations using a G-banding technique is technically demanding and time consuming. Nevertheless interest in establishing a genetic marker for the cumulative effect of chronic low dose radiation led to the study of the 38 radiation workers who comprised the 2 lower dose categories of the previous dicentric study. However, when evaluating frequencies of stable aberrations in relation to radiation exposure the identification of any lifestyle factors involving clastogenic exposure is important since the frequency is likely to reflect a lifetime's exposure to genotoxins. Smoking and age are both significant factors affecting stable aberration frequencies [10,11] and therefore the G-banding data from the 2 radiation worker groups was compared to a subset with the same age profile from a larger study on background frequencies and the data for smokers and non-smokers analysed separately (Table II). The small control smoker group and the inability to quantify lifetime smoking habits made it difficult to deduce anything from the smoking data. The non-smokers demonstrated an increase in dicentrics with increasing dose which did not reach significance but a significant increase with dose was found for translocations (p=0.05)

and for total symmetrical aberrations (p=0.01). Indeed a dose response for translocations of 1.54±0.02x10^{-2}/Sv can be derived from the means of the 3 groups but this simplistic approach hides the variability in the data.

Table II **G-banding Aberration Frequencies**

	Non-smokers			Smokers		
Group	Control	1	2	Control	1	2
No. of individuals	20	6	9	8	9	14
Mean age (y)	51.0	49.5	55.4	52.3	49.2	55.1
Mean total dose (mSv)	-	550	750	-	560	750
(range)		(510-580)	(690-800)		(530-580)	(630-840)
Mean radiation work (y)	-	26.3	30.6	-	23.0	27.9
(range)		(19-33)	(26-33)		(13-31)	(21-32)
Dicentrics/cell±S.E. x 10^{-3}	2.00±1.41	3.33±2.36	4.44±2.21	0	7.78±2.94	2.86±1.43
Translocations/cell±S.E.x10^{-3}	5.00±2.24	13.33±4.71	16.67±4.30	20.00±7.07	13.33±3.85	18.57±3.64
Terminal deletions/cell±x10^{-3}	1.00±1.00	1.67±1.67	4.44±2.21	5.00±3.54	2.22±1.47	2.14±1.24
Asym exchanges/cell±S.E.x10^{-3}	2.00±1.41	5.00±2.89	4.44±2.21	0	10.00±3.33	4.29±1.75
Sym exchanges/cell±S.E.x10^{-3}	8.00±2.83	13.33±4.71	25.56±5.33	25.00±7.91	16.67±4.30	22.86±4.04

Chromosome Painting by FISH

The work described above led to a further collaborative study of a larger group using G-banding and FISH chromosome painting. Tucker *et al* have recently reported the chromosome painting data [12]. Samples from 81 radiation workers, 23 with minimal exposure (<50 mSv) and 58 with exposures ranging from 173 to 1108 mSv, all but 3 being >500 mSv, were examined. Since the painting technique only allows a fraction of all chromosome exchanges to be identified, the results were converted to frequencies for the whole genome. For data analysis the men were evaluated in 5 dose categories (Table III). The mean stable aberration frequencies showed a significant increase with dose category (p=0.032) and with cumulative dose when dose was treated as a continuous variable (p=0.015). When dose and smoking status were considered, a dose response for stable aberrations of 0.79±0.22x10^{-2}/Sv was derived. No significant increase was found for dicentrics. Thus fewer stable aberrations per Sv were observed in these men exposed within permitted limits over several decades than were observed in people receiving acute exposure from the Japanese A-bombs.

Table III **Chromosome Analysis by FISH Chromosome Painting**

Group	1	2	3	4	5
No. of individuals	23	12	15	16	15
No. of smokers	10	6	6	5	5
Mean age±S.E.	54.4±1.6	51.1±1.9	56.3±1.3	53.4±1.4	57.6±0.7
Mean total dose±S.E. (mSv)	9.4±2.1	456.3±41.0	603.9±8.4	708.2±8.3	857.8±27.1
(range)	(1-46)	(173-558)	(565-653)	(660-759)	(768-1108)
Mean radiation work (y)	14.3±2.2	29.9±2.2	32.9±1.1	31.8±1.1	35.5±0.6
Stable aberrations/cell±S.E.x10^{-3}	7.4±1.3	8.6±2.4	10.5±1.9	12.4±2.1	13.9±2.5
Dicentrics/cell±S.E.x10^{-3}	1.6±0.4	1.0±0.6	1.1±0.3	1.7±0.6	1.3±0.5

The most comprehensive A-bomb data comes from a study using conventional staining and DS86 kerma doses, with statistical analysis based on the percentage of cells carrying at least one stable aberration [13]. The analysis applied to the Sellafield data gives virtually equivalent results because few cells had more than one stable aberration. The slopes of the dose response curves are 5.6±0.3x 10^{-2}/Sv and 4.0±0.4x10^{-2}/Sv for Hiroshima and Nagasaki respectively. Dividing these by the observation of 0.79±0.22x10^{-2}/Sv obtained from the Sellafield study results in DDREF estimates of

7.0±2.6 and 5.0±1.5 respectively. These data provide direct human *in vivo* information, on a permanent and stable endpoint, confirming that the effects of radiation delivered at low dose rates are smaller than comparable doses given in a short period of time.

Conclusions

Our studies on occupationally exposed radiation workers confirm that chromosome aberration analysis is a valid method of monitoring radiation exposure. Dicentric frequency provides a good method of dose assessment for acute exposures of recent occurrence whereas translocations, which persist and accumulate, can indicate exposures over many years. For risk assessment, however, the challenge is to define the relationship between the dose response for the non-specific chromosome aberrations reported in these studies and the dose response for the induction and persistence of cancer initiating rearrangements.

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DO WE NEED A NEW COST/BENEFIT ASSESSMENT FOR LOW RADIATION DOSES?

K. BECKER*
DIN German Standards Institute, Berlin
and
International Standards Organization, Geneva

Abstract

Current cost/benefit estimates related to radiation protection, e.g. regarding the consequences of population exposures after accidents, decommissioning and waste management programs, etc., are based on the linear-no-threshold hypothesis and the related collective dose concept, as recommended in ICRP 60, the Basic Safety Standards (BSS), and EU directives. However, the extrapolation from very high to very low doses is increasingly questioned by radiation scientists for fundamental radiobiological reasons, as well as by epidemiological studies with exposed populations. Moreover, if also applied to natural radiation (e.g. in mining or high natural radiation areas, or radon in buildings), the resulting high costs justify, for ethical as well as socio-economical reasons, a careful analysis of the actual benefits of such measures, to be compared with demonstrable health detriments and the cost/benefit ratio in other public health and risk reduction programs in modern industrial societies. Some aspects of these problems will be discussed briefly, and summarized in questions addressed to the advisory bodies on whose recommendations current regulations are based. As a first step, abolishment of the use of the collective dose concept below about 100 mSv total of "artificial" radiation per person of the public, and below 50 mSv p.a. for radiation workers, appears advisable.

In risk analysis, there have always been the key problems of correct determination of the probability of detrimental effects to persons, environment, etc., and the estimation of the monetary equivalent of such effects. Radiation protection regulations are part of risk analysis. On the basis of a linear-no-threshold (LNT) hypothesis and the closely related collective dose concept, this resulted in discussions which individual or collective dose would correspond to one additional cancer death, or one year less life expectancy, and which amount of money should be equated to such a risk. Figures between approx. 10^5 and 10^7 "$ per life" have been suggested. However, the "$ per man-Sv" remained a largely academic question, and its economic impact remained relatively small. In Germany, for example, only very few persons each year received (mostly without a real scientific justification) "radiation damage" benefits in the professional insurance system. Some expert groups eventualla agreed on a "price" of 100.000 U.S. $ per man-Sv. Assuming such a price, the mass-killing of reindeer in Norway after the Chernobyl accident could be considered "successful", with a population dose of one man-Sv being avoided for 57.000 $, while the killing of sheep at 170.000 $ per man-Sv was less successful (1).

In recent years, however, the situation has been changing dramatically, with "big money" being involved. To give only a few examples from Germany:

1. After the Chernobyl accident, the costs of destruction of slightly contaminated produce, milk (in one of the federal states down to a level of 20 Bq/l of J-131, corresponding to 20% of the natural k-40 activity in milk), etc., have been about 300 mill. $ in the western part of the country (2).
2. The radiological component in the remediation of former uranium mining areas in eastern Germany amounts to about 2.000 mill. $ (3).

*) c/o DIN, D-10772 Berlin, Tel.: (04930) 2601 2701, Fax: (04930) 2601 1148, e-mail: Millitzer@NKE.DIN.DE; after retirement: Boothstr. 27, D-12207 Berlin, Tel.: (04930) 772 1284

3. The decommissioning of the pilote reprocessing plant WAK in Karlsruhe is estimated to cost approx. 25 times its original construction costs, including a 250 mill. $ facility for the vitrification of only 80 m^3 of liquid wastes.
4. With the current exemption level for low-level wastes corresponding to exposures of the public of no more than 10 μSv p.a. (which is 0.4% of the average natural exposure, and 0.04% or less of some high background areas) thousands of millions of $ are being spent for the "radiological component" in the decommissioning of nuclear power plants - costs which could be substantially reduced by using a higher limit.
5. Earlier this year, the cost of police protection for a simple radwaste transport to one of the temporary storage facilities (Gorleben) was 60 mill. $, not counting hundreds of acts of sabotage against railways and roads, based on Greenpeace claims of a QF of 600 for fast neutrons, etc.

Many more examples could be listed, with the situation in countries with large nuclear military facilities, ships, etc., such as the former Soviet Union and USA, being particularly difficult and expensive. This was, for example, recently pointed out in a study for the U.S. Army (4). There are, however, also other aspects of the present regulatory system in radiation protection which raise serious questions. To mention only a few examples:

1. *Increased natural radiation levels.* With the average background in Europe fluctuating substantially, and being exceeded by a factor of 10 to 100 in areas of Brazil, India and Iran without any detectable health effects over many generations, it would make little sense to consider the evacuation of whole towns or regions in Saxony, Finland or Cornwall, or to close down mining operations in Southern Africa which would be required if current radiation policy were to be applied uniformly.
2. *Non-medical use of X-rays.* In order to prevent the theft of diamonds, X-ray screening of mine workers by Namibia's largest employer and tax payer, amounting to an additional exposure of the workers of about 1 mSv p.a., has helped to keep this industry profitable. However, the Basic Safety Standards do not permit application of X-rays for crime detection and prevention (also regarding drug smuggling, etc.).
3. *Radon.* Current regulations of the U.S. Environmental Protection Agency (EPA) apparently require the radon level in buildings not to exceed the outdoors level (which is practically impossible), and radon levels in tab water not to exceed 10 Bq/l, while the normal Rn content of drinking water exceeds 1000 Bq/l in many parts of the world, and water with 100.000 Bq/l used for the treatment of various diseases in radon spas. In Europe, the maximum recommended in-door radon levels currently vary between 200-600 Bq/m^3, but no detectable increases in lung cancers have been found at levels which are at least ten times higher (with the possible exception of very heavy smokers). In fact, levels up to 700.000 Bq/m^3 in air have been observed in some public water facilities in Bavaria (3), and 20-50% of all homes in S.W. England are above the current U.K "action level".
4. *Unnecessary medical radiation exposures.* It is well established that a substantial fraction of mankind's collective "artificial" radiation exposure, in particular in radiodiagnostics, could be avoided by simple measures such as
   - computer tomography (which is known to cause relatively high doses, and to be used frequently not without economical motivation) only for strictly medical reasons;
   - reduction in the number of radiographs which are unnecessarily duplicated without medical justification within short time intervals; and
   - improvements in the techniques and the equipment, in particular in poorer countries.

   Thus, hundreds of times the collective dose related to nuclear energy could easily, and relatively inexpensively, be avoided.

Considering that in the long-term trend ICRP-recommended dose limits became smaller, the obvious question arises about the validity of the underlying linear no-threshold (LNT) hypothesis and the closely associated collective dose concept. Does it, for example, really make sense (or is it radiobiologically plausible) to officially publish estimates on "additional Chernobyl - caused cancer deaths" of about 300 in Sweden, 450 in Finland, and exactly 363 in Bulgaria (5)? The direct and

indirect socio-economical and political implications of ICRP-based "predictions" of casualties not only in the directly affected areas around Chernobyl, but in the whole Northern Hemisphere, have been tremendous, and resulted not only in tens of thousands additional abortions by scared women in Western Europe, but also to economic losses in the 15.000 mill. $ range in Germany alone due to the cancellation of nuclear programs, etc. (2).

It is, therefore, more than justified to ask how stable the foundations of the current "House of Radiation Protection" actually are - and, in case they are not, whether this house can be repaired by evolutionary processes or will require a total re-construction. Instead of attempting a definitive answer to this probably most important question in our field not only in this decade, some questions urgently require an answer from the best in the radiation science community - for the benefit not only of mankind in general, but more specifically for that of regulators and administrators acting on behalf of the tax-payers and utility costumers:

1. How much of our rapidly decreasing funds can we afford to devote to the further reduction of potential risks which, if they exist at all, are so small that they could not be detected in decades of painstaking and expensive research efforts? Tens of billions of dollars are spent every year worldwide in decommissioning, redemption, or nuclear waste programs, which could obviously be used much more beneficially in other areas of public and individual health, in rich and even more so in poor countries.
2. In claiming frightening numbers of additional cancer fatalities due to the Chernobyl accident, of radon in houses, medical radiography, etc. - based essentially on the multiplication of zero with infinity - how much psychological and economical damage in the public acceptance of many beneficial radiation uses including energy production without climatic side effects, radiation medicine, and research, has been done?
3. How do we explain to the critical observer the multitude of well-documented observations of adaptive response (some of them documented in UNSCEAR 1994 with 400 references (6)) and hormesis (Luckey cites 2000 references in his wellknown 1991 book on this subject - see also (7)) as well as the many epidemiological and experimental studies clearly showing either thresholds (between about 0.2 and 2 Gy, ranging from leukaemia among the bomb survivors in Japan to bone and lung cancer in humans and animals), or biopositive effects in Cohen's (8) and many other radon studies, the absence of observable genetic disorders in Hiroshima/Nagasaki and the Chernobyl region, etc.? Many of the very good arguments for no negative, and in many cases positive effects of slightly increased radiation levels have been summarized in recent compilations (9-14). Very reasonable explanations for such bioneutral or biopositive effects, based on the dominating influence of stimulated repair of non-dominant radiation doses, have been abundantly presented (9, 10, 14). Obviously, for each indication which could be interpreted as a "bionegative" effect of low radiation doses, there is at least one for no, or biopositive effects.
4. How about the cost/benefit ratio in the current radiation protection programs relative to our treatment of other civilizatory and natural risks, e.g. in the chemical industry? Could it be that elements of self-interest are involved in "keeping the radiation hazards alive" (after all, it is an industry involving more than 10^{10} U.S. $)? And how about scientific integrity and credibility in suppressing results which to not confirm "official" dogmas, such as the U.S. Naval shipyard workers study (14), or the opinion of the French Academy of Sciences (15)?
5. How could it happen that over-conservative administrative concepts such as LNT and collective dose, originally created to simplify bookkeeping under certain limited circumstances, could degenerate to such an extent in the hands of regulators and ill-informed public opinion makers? And how could we correct this situation soon against the ideological objections of ill-informed journalists and politicians, and other doomsday "Zeitgeist" prophets?

There is certainly a long list of such questions which will require answers soon. As a compromise between those wanting to repair, and those wanting to build a new House of Radiation Protection Regulations, one could at least agree on some simple measures such as abolishing the collective dose concept for individual dose levels below a certain limit (the Health Physics Society proposed in its

March 1996 Position Statement 50 mSv/p.a.), and agree on the fact that "below 100 mSv risks of health effects are either too small to be observed, or are non-existent".

Other distinguished institutions (e.g. (15)), as well as prominent scientists in this field have come to similar conclusions, including the former Chairman of ICRP and NCRP, Lauriston Taylor, former UNSCEAR Chairman Zbiegniew Jaworowski, the retired director of the French National Radiation Protection Organization Pierre Pellerin, and Nobel Laureate Rosalyn Yalow (for a compilation, ref. 11-13). There is hope that the newly formed international expert organization "Radiation, Science & Health Inc." (16) will also contribute to solving the present inconsistencies in dealing with low radiation doses.

Obviously, it would be highly unfair to blame the cautious experts in ICRP, NCRP, BEIR, NRPB, SSK, and many other committees and commissions for what happened to well-considered recommendations during their long way into national regulations and practical implementation. It seems that "reasonably" in ALARA easily is forgotten along this way and becomes de facto "as low as possible, at any cost", and many people equate the extremely conservative ICRP 60 limits with a magical threshold of immediate danger. Clear words from our wise friends in those commissions, as well as a more transparent and democratic handling of what to many occasionally looks like a "good old boy's network" of insiders, would be highly welcome.

Acknowledgments. Several colleagues provided valuable comments. However, this paper represents the author's opinion, and not that of any institution with which he is affiliated.

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CANCER RISK ANALYSIS AMONG MEDICAL DIAGNOSTIC X-RAY WORKERS IN CHINA[1]

Ji-Xian Wang[2], Ben-Xiao Li[2], Zhi-Wei Gao[2], Jun-Xu[2]
Jing-Yuan Zhang[2], Takashi Aoyama[3], Tsutomu Sugahara[3]

[1] This work is an analysis of data collected by National coordinating Research Group of Dose-Effect Relationship in Medical Diagnostic X-ray workers in China

[2] Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin 300192, P R China

[3] Health Research Foundation, Kyoto Japan

Abstract To provide the evidence and related rules of human malignant tumors produced by prolonged exposure to low level ionizing radiation. The cancer incidence (1950-1990) among 27011 medical diagnostic X-ray workers was compared with that among 25782 other medical specialists employed between 1950 and 1980 in China by means of O/E system. A significantly elevated risk of cancer was seen among diagnostic x-ray workers (RR=1.1,95%CI:1.0-1.2,P<0.05) Significantly elevated risks were seen for leukemia and cancers of skin, female breast, liver and esophagus, the RR being 2.3, 5.0, 1.6, 1.3 and 4.4 respectively. The RR for leukemia was higher for X-ray workers who began employment before 1970 and also for those who were young when employment began. The patterns of risk associated with length of service and with age and calendar year of initial employment suggest that the excesses of leukemia, skin cancer and female breast cancer were due to occupational exposure to X-rays. The ERR and EAR for leukemia and solid cancer were calculated roughly.

1. INTRODUCTION

For providing evidence and related rules of human carcinogenic hazards produced by protracted low-dose ionizing radiation, a nation-wide survey on cancer incidence among diagnostic X-ray workers in China was organized in 1981, and the second, third follow-up were conducted in 1986 and in 1991, respectively. The current analysis included the three times survey and covered the observation period from 1950 to 1990.

2. SUBJECTS AND METHODS

A detailed account of the characteristics of the study population and methods of survey, cancer ascertainment and analysis were given in the earlier reports[1,2].

2.1. Study population

The study population consisted of 27,011 diagnostic X-ray workers employed between 1950 and 1980 in major hospitals in 24 provinces of China The radiation workers included both radiologists and technicians The comparison population consisted of 25,782 surgeons, physicians and otolaryngologists working in the same hospitals during the same time period but who did not use X-ray equipment in their work

2.2. Methods of survey

The first survey in 1981 was a retrospective cohort study. The second and third follow-up were perspective cohort study. For workers who developed cancer, the date and basis of diagnosis were abstracted from their medical records. Similarly, information on date and cause of death was obtained from the medical records of those who died. Cancers were coded according to the 8th revision of the International Classification on Diseases (ICD-8).

2.3. Data analysis

The cancer risk analysis were conducted by O/E system. Expected (E) numbers of cancers among the X-ray workers were estimated based on incidence rates of the comparison group. Standardized incidence rate ratios (RR) were calculated using the age by sex by calendar time person years (PY) distribution among the exposed as weights. Ninety-five percent confidence intervals (CI) for the RR were calculated.

3. RESULTS

3.1. General situation

From 1950 to 1990, approximately 566,232 PYs of observation were accumulated and total 542 cases of cancer occurred among the X-ray workers, and 633,697 PYs and 580 cases among comparison group. Observed number of incident cancers (O), standardized Rate Ratios (RR) and the 95% confidence intervals for specific sites are shown in Figure 1. Cancer incidence among the diagnostic X-ray workers was 10% greater than expected based on incidence in the comparison group (RR=1.10,95%CI: 1.0-1.2, $p<0.05$).

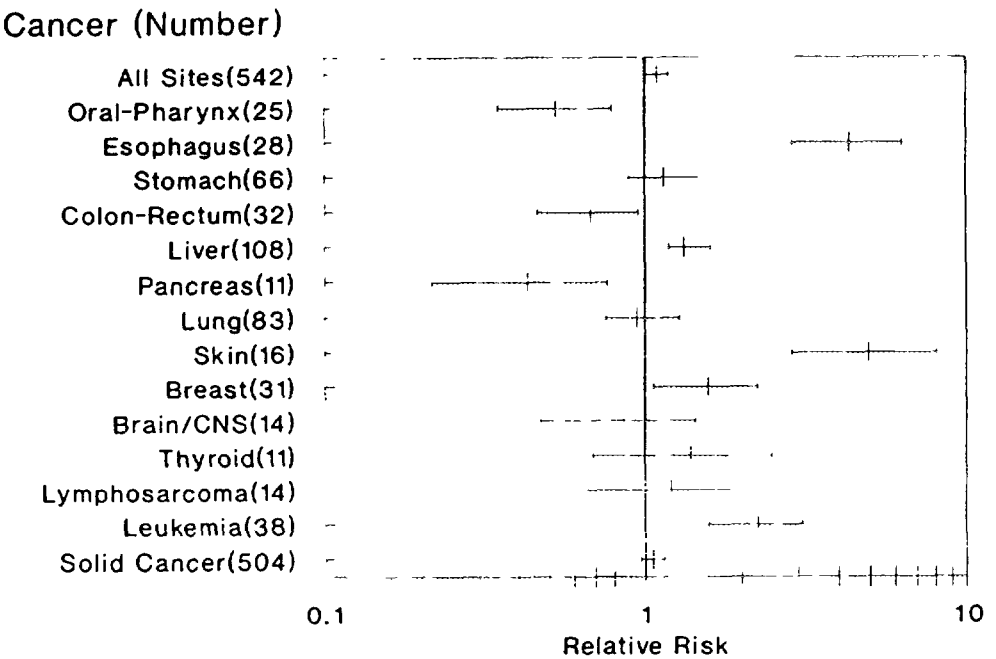

Figure 1 Observed number of incident cancers and relative risks among diagnostic X-ray workers. Shown are 95%CI.

Female X-ray workers had a lower risk of developing cancer in contrast with male X-ray workers and only breast cancer RR was significantly elevated.

An excess of leukemia and thyroid cancer were apparent only at age under 40, and for total solid cancer, skin cancer and female breast cancer, the significantly excess of risk were seen in age range 50-59, and the RR tend to decrease among X-ray workers who aged over 60.

During 1950-1990 total 38 cases of leukemia were observed among X-ray workers and 21 cases among comparison. All 59 leukemia were histologically confirmed. Lymphatic and myeloid leukemia occurred more often than expected among X-ray workers, RR was 4.8 and 2.8 separately. Total 9 cases of lymphocytic leukemia occurred among the X-ray workers only one was chronic lymphatic leukemia, the other 8 were acute. The myeloid leukemia were split near equally 13 cases of acute and 11 cases of chronic.

3.2. The relationship between cancer risk and years since starting X-ray work

Variation in the RR by years since first employment differed among cancer types. The relative excess of leukemia was appeared 5-9 years since first employment and was highest between 10-14 years, then decreased but still higher until 25 years and dropped to under the comparison level. On the other hand, the RR of breast cancer increased with increasing duration of employment and became significant after 25 years employment. The skin cancer excess occurred among workers who had worked with X-ray for at least 15 years. The RR for liver and esophagus cancers were elevated for almost all length since first employment.

3.3 The relationship between cancer risk and calendar year of first employment

The RR of leukemia and liver cancer were significantly elevated among X-ray workers who employed before 1970. The RR of female breast cancer significantly excess was only seen among X-ray workers first employment before 1960 (Table 1).

Table 1 Observed numbers of incident cancer among X-ray workers and RR for selected sites by calendar year of first employment

Site of Cancer	Calendar year of first employment					
	Before 1960		1960-1969		1970-1980	
	O	RR	O	RR	O	RR
Esophagus	15	5.1*	8	5.1*	5	4.2*
Liver	54	1.7*	29	1.5*	25	0.8
Skin	9	3.3*	4	4.2*	3	7.1*
Breast	13	1.8*	9	1.4	9	1.5
Thyroid	6	2.0	3	1.2	2	0.8
Leukemia	17	2.1*	17	3.7*	4	1.0

*: $P<0.05$

3.4 The relationship between cancer risk and age at first exposure

For leukemia and thyroid cancer the highest RR was seen among workers who were aged under 25 years old at first employment and RR decreased with increasing age at first

employment. The highest RR for breast cancer was seen among women who were aged 25 to 29 at first employment (Table II).

Table II Observed number of selected cancers among X-ray workers and RR by age at first employment

age at first employed	Leukemia		Thyroid		Breast		Skin		Esophagus		Liver	
	O	RR	O	RR	O	RR	O	RR	O	RR	O	RR
<20	5	5.38*	2	3.45	0	0.00	2	15.38*	1	3.14	6	1.25
20-	18	4.39*	5	2.03	10	1.54	2	2.60	6	4.38*	29	1.32
25-	6	1.25	3	1.48	12	2.62*	7	6.80*	4	2.31	31	1.25
30-	8	2.33*	1	0.76	7	1.97	4	6.35*	9	7.69*	21	1.45
35-	1	0.51	0	0.00	1	0.41	1	3.33	1	1.22	11	1.40
40-	0	0.00	0	0.00	1	0.74	0	0.00	7	6.80*	10	1.41
Total	38	2.25*	11	1.40	31	1.55*	16	4.97*	8	4.35*	108	1.33*

*: $P<0.05$

The analysis on patterns of risk associated with length of service and with age and calendar year of initial employment suggest that the excesses of leukemia, skin cancer and female breast cancer were due to occupational exposure to X-rays.

3.5 Risk estimation

Based on the tentative collective dose estimation by physical and biological methods (detailed results will be reported elsewhere), the preliminary excess relative risk (ERR) and excess absolute risk (EAR) for cancer incidences were calculated roughly. The ERR is 15.63 per Sv (95%CI: 7.38 ~ 26.13) for leukemia and 0.67 per Sv (95%CI: -0.33 ~ 1.67) for solid cancer. The EAR of leukemia is 4.65 per 10^4 PY Sv (95% CI: 2.19 ~ 7.75) and 5.21 per 10^4 PY Sv (95%CI:-2.80 ~ 13.99) for solid cancer. The values were compared with the data of Japanese Atomic Bomb Survivors[3,4] and Nuclear Industry Workers[5].

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RESEARCH WASTE MANAGEMENT PROGRAM - AN ACTION PROPOSAL

COSTA RAMOS, A; ESPÓSITO, I
Radioactive Waste Management Coordination
Superintendence of Licensing and Control
Brazilian Nuclear Energy Commission

XA9745659

Abstract

The Brazilian Nuclear Energy Commission plan: ed, prepared and established a Research Waste Management Program, started in 1996, in order to map, to analyze and to solve the common problems in the research field. The specific study done included a large number of academic institutions. The procedures, results and operational methodology used by the Team linked to the Program , in one of the research institutions studied where corrective actions were implemented to avoid unnecessary dose to the public, will be discussed in this article.

1. INTRODUCTION

In Brazil, scientific researches with radioactive material, are developed, mainly in as public and private universities as well as public research establishments and private enterprises and are related to medical and biological field[1].

To ensure protection of human health and environment, now and in the future, the Brazilian Nuclear Energy Commission(CNEN) established a program named "Research Waste Management Program(PROGER)" , in order to control and to optimize the management of the wastes generated by the radiological research labs and avoid dissemination of radioactive material into the environment and the public.

2. PROCEDURES

The starting action for the Program consisted of preparation of specific questionnaires about waste management, and its distribution by mail, among academic institutions of all country.

The questionnaires distributed broached questions about: trends of researches; description of the use of radionuclides; radionuclides more frequently in use; types of radioactive waste generated; amount of radioactive waste generated; radioactive waste management executed; the current disposal of the radioactive waste; provisory deposit for radioactive waste; radiological experience of the personnel and the on-going Radioprotection Service.

An Operational Team was selected in CNEN's staff to plan and prepare corrective actions in the cases when it might be necessary.

3. RESULTS

A number of 123 questionnaires were distributed, covering 48 scientific and academic institutions. A total number of 174 researches labs answered and sent back the questionnaires to CNEN.

The Operational Team started its functions, at the end of 1996, by a cooperation agreement with a research institution located in Rio de Janeiro Federal University. This institution was selected and contacted taken into account their location, nearby of CNEN's headquarters, and the possibility to train all the personnel of CNEN's team at the same time in the tasks of this special case of radioactive waste management, and to train the personnel of the Radioprotection Service of the University in waste management too.

The selected institute had 13 labs. developing researches with radioactive materials and one radioactive waste storage room. An overview of the 13 labs condition linked to radiological waste generation might be seen in Table 1.

After a analysis of the lab conditions and in the storage room, the CNEN's Team established the goals to be accomplished with the implementation of the PROGER in the institution:

01) **Inspection and technical visit :**

A interaction between the generator and the inspection service is strongly recommended, to carry out the identification and documentation of principal duties, tasks and difficulties to implement the correct waste management.

02) **Radioprotection Service:**

A Radioprotection Service, according a CNEN's specific regulation[2], is a service in charge of the execution and maintenance of a radioprotection plan, include a radioactive waste management plan. In fact, the development and improvement of a Radioprotection Service in the institutions is important to ensure continuity in the work developed after a corrective action.

03) **Storage and segregation of radioactive waste:**

Storage for decay is the best method to be used in the research waste case, due the low level of activity and the short half-life of the majority of radionuclides used. Therefore after the storage the waste can be released on urban garbage system and sanitary sewerage system within the specific clearance limits.

Segregation is a fundamental action for waste management and allows for a correct inventory of the waste[3].

04) **Biological and organic radioactive wastes:**

Radioactive waste of biological materials must be managed with particular care due their potential hazards. A special strategy for the correct management of this waste is necessary in order to carry out a safe handling, processing, storage and disposal.

Organic radioactive wastes require special management that take into account both their radioactivity and their chemical content, because the organic radioactive waste can have besides its radioactivity detriment a chemical detrimental effects[4].

05) **Removal of wastes which needs to be disposal:**

A safety and correct handling and packing of the wastes which needs disposal or special care, as Carbon-14(C-14), tritium(H-3), Cesium-137(Cs-137) or Cobalt-60(Co-60)[5] should be provide by the Team.

06) **Safety culture of each lab with the non radiological aspects of safety:**

In several research labs investigated , the principal problem is not due to the radiological risk, but due the chemical hazard and the absence of personnel training in this field[6].

07) **Educational Program:**

It is strongly necessary to provide specific education to researches, in order to homogenize the actions and procedures[7].

08) **Environmental monitoring:**

It's recommended the establishment of a environmental monitoring program when we have quantities of radionuclides released into the environment like in this case.

4. OPERATIONAL METHODOLOGY

The main problem founded on the institution was related to the radioactive waste storage room, where, during 6 years, all types of waste was storage without the necessary care.

To solve this problem a control point and a segregate area was prepared: the floor was covered with a plastic film; the area around was monitored, signalized and isolated; steel drums of 200 litters were lined with plastic bags to put the segregate wastes inside; the access was restricted; the Security Service of the University was advised and the public (students, employees and professors) too.

The categorization of the solid waste in accordance with practical experience took into account the fact that the waste were a combining of gamma and beta emitters, and so it was possible to use the radiation count rate of the waste to classify it[8] The categories selected was showed in Table 2

The waste were segregate slowly once that part of it didn't have any tag to identify the activity of the contents Most part of the waste were pure beta emitters, including soft beta like Sulfur 35(S-35) and Tritium (H-3) and in order to avoid mistakes in the segregation works, all soft beta emitters were include in the category of radioactive waste to be analyzed better in the future All the waste of C-14 and H-3 were storage separately to be removed to a temporally deposit of CNEN

The corrective actions spent 72 working hours to segregate the waste, to remove it, to clean up and prepared the new storage room The CNEN's Team used the same procedures of the segregate actions in the Goiânia's Accident[9] The amount of waste put out like common garbage, storage for decay and collected for a CNEN's institute is shown in Table 3 The quantities of personnel protection material, dump steel drums, plastic bags, and other materials used in the operational actions is shown in Table 4

The liquid waste management applied in the institution nowadays is under investigation, because although the volume of soluble liquid waste released by each lab individually into the sewerage system be in accordance with the Brazilian specific regulation[10], it's necessary more data about the total volume of the sewerage system and the total volume of aqueous waste released by all labs of the institution, to make a more refined evaluation of the on-going situation concerning the Brazilian regulation

The volume of organic liquid waste is small when compared with aqueous radioactive waste Most part of the organic waste is composed of scintillation liquids from radiochemical analysis such as toluene, and were storage for future treatment like, for instance, fractionation to recover the toluene

5 CONCLUSION

Most part of the established goals for the actions on this institution were reached

1) The interaction with the researches were positive and promising,
2) The training of the Radioprotection Service was very good and the exchange of experiences very useful,
3) The necessary actions to segregate the waste were and improved The levels of the radiation measures(cps) inside the storage room decrease twice, and nowadays is the same of the currently background in the surrounding area,
4) The main problem of the actions were related to the biological and organic wastes The researches of the institution are trying together with the CNEN's staff, to find the better solution for this specific problem,
5) The removed wastes were composed mainly of C-14 and H-3, due to there half-life and the difficult of detection,
6) Instructions for safety behavior inside a chemical lab were distributed,
7) The educational program to researches is being implemented by seminaries given by the CNEN's staff
8) A environmental monitoring program might be established in order to ensure the radiological safety around the installation

The main results of this Radioactive Waste Management Program - PROGER is master by practice of segregation, storage, monitoring and others actions, the correct and applicable radioactive waste management in scientific researches institutions in Brazil

It is clearly necessary to improve and to expand the PROGER to all country, to avoid unnecessary exposure, and to reduce the probability of the so called stochastic effects of low doses[11] in the academic institutions

TABLES

BIOCHEMISTRY LABORATORYS	RADIONUCLIDES IN USE	WASTE TYPES*
Nº 01	S-35; C-14; H-3	SW, LW
Nº 02	Ca-45; C-14; S-35; Fe-55; Fe-59; H-3; I-125; P-32	SW, LW
Nº 03	H-3; C-14; S-35; P-32	SW,LW
Nº 04	Cr-51; H-3	SW,LW
Nº 05	P-32; Ca-45; Sr-90	SW,LW
Nº 06	P-32; Ca-45; C-14; H-3	SW,LW
Nº 07	H-3	SW,LW
Nº 08	P-32	SW,LW
Nº 09	P-32	SW,LW
Nº 10	H-3; C-14; S-35; P-32	SW,LW
Nº 11	P-32; I-125; S-35	SW,LW
Nº 12	P-32; Ca-45; H-3	SW,LW
Nº 13	H-3; P-32	SW,LW
TOTAL 13 Labs	H-3; C-14; P-32; S-35; I-125; Cr-51; Ca-45; Fe-55; Fe-59	

TABLE 1

INSTITUTION LABS., WASTE OVERVIEW

* SW - solid waste / LW - liquid waste

CATEGORY	RADIATION MEASUREMENT(RM) ON THE SURFACE OF WASTES (CPS)	REMARKS
Common Garbage	R.M.= Background*	β, γ emitters
Waste to decay more	R.M >Background	β, γ emitters
Waste to storage	R.M.>>3xBackground	β, γ emitters

TABLE 2
ADOPTED CATEGORIES OF SOLID WASTE

*200 cps = background counting rate

CLASSIFICATION	QUANTITY (V=liter)•	REMARKS
Common Garbage	20000	
Waste Storage	1000	For decay
Waste Removed	1200	C-14; H-3 and Sr-90

TABLE 3
TOTAL QUANTITY OF WASTE

•The waste were evaluated in liters due the total volume used of plastic bags with wastes after segregation

PROTECTION EQUIPMENT	QUANTITY
Disposable overall	20
Disposable masks anti-dust	20
Disposable overshoe (pair)	20
Steel dump drums 200 liters	10
Rubber gloves (pair)	20
Plastic bags 200 liters	100
Plastic sheet (m^2)	30

TABLE 4
PROTECTION EQUIPMENT

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Health effects study of the nuclear industry workers in Japan

Epidemiological Study Group of Nuclear Workers (Japan)[1]
Presented by Tamiko Iwasaki

Institute of Radiation Epidemiology
Radiation Effects Association
1 -9 -16, Kajicho, Chiyodaku, Tokyo 101 Japan

Abstract

To clarify the effects of low-dose and low-dose-rate exposure to the human body, study on the health effects of the nuclear industry workers in Japan was conducted since 1990 by the Institute of Radiation Epidemiology, the Radiation Effects Association, which had been entrusted by the Science and Technology Agency of the Japanese Government.

In the first phase analysis between 1986 and 1992, the study population was selected from among persons who were engaged in radiation work at nuclear power plants and associated facilities, and registered in the Radiation Dose Registration Center for Workers. The cohort consisted of 114,900 persons who satisfied the criteria of nationality, age, sex, etc. The average follow-up period was 4.6 years, and the average cumulative dose per person was 13.9 mSv. The total number of deaths among the study population was 1,758, including 661 deaths due to all malignant neoplasms.

The Standardized Mortality Ratio of various death causes was compared. Furthermore, the cohort was grouped by five different dose levels, and the O/E was calculated to test whether there is a trend for the death rate to increase with dose.

Among nuclear workers no significant increase in deaths nor any relationship with radiation dose was found, except the pancreatic cancer with 10 - years lag. Since many previous studies of nuclear industry workers have demonstrated no significant association between exposure dose and pancreatic cancer, we cannot immediately conclude a causal relationship between with radiation.

Introduction

Although it has been well established that radiation exposure after high doses causes an increased risk of cancer in many organs, there remain many important questions about the effects of low-dose chronic exposures. Recently, a direct assessment of the carcinogenic effects of long-term low-level radiation exposure in humans can be made from studies of cancer risk among workers in the nuclear industry, and some reports already published[1-4].

In these circumstances, an epidemiological study of radiation workers at nuclear power plants and associated facilities in Japan had been initiated by the Institute of radiation Epidemiology, the Radiation Effects Association, under the trust of the Science and Technology Agency of the Japanese Government[5].

Materials and Methods

1. Characteristics of the cohort

114,900 persons who had been registered in the "Radiation Dose Registration Center

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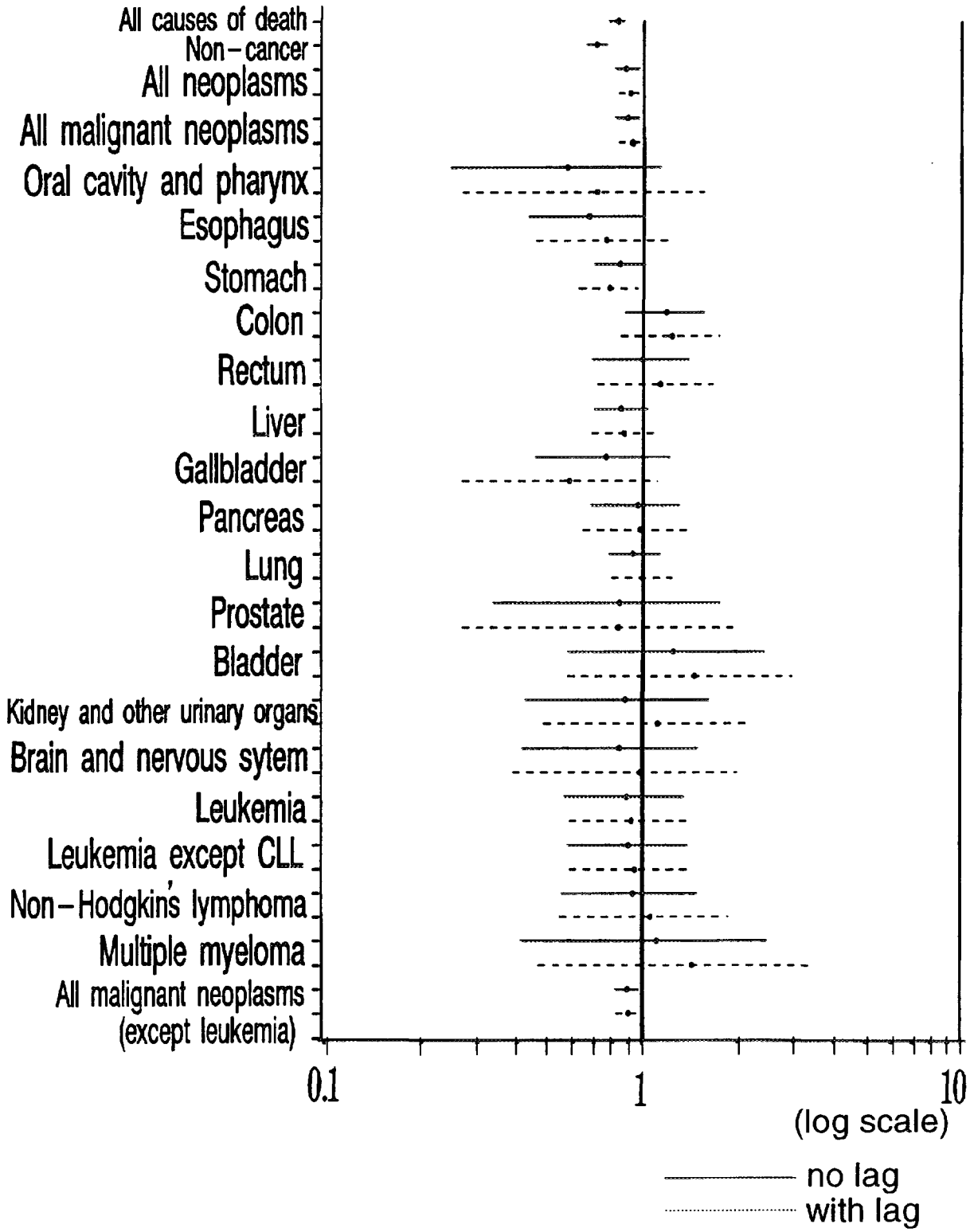
[1] Y.Hosoda, T.Iwasaki, M.Kuba, S.Kudo, Y.Kumatori, S.Kusumi and T.Miyake (IRE) H.Matsudaira (Res.Develop.Corp.), M.Kaneko (TEPCO), T.Yoshimura (Univ.Occup. Environ.Health,Japan), S.Akiba (Kagoshima Univ), M.Minowa and T.Tango(Inst.Public Health), M.Murata (Chiba Cancer Center), Y.Yoshimoto (RERF).

SMRs of various death causes for nuclear workers in Japan, with 95% confidence intervals, using Japanese male as the standard population.



for Workers" (RADREC) as of March 1989 were selected, and they met the following criteria: (1) persons who had engaged in actual radiation work, (2) male, (3) Japanese nationality, (4) persons who the vital status happened to be issued within five years of the record keeping, (5) age range within the 20- to 85-year-old.

The underlying cause of death was identified by using of the magnetic tapes of National Vital Statistics supplied by the Japanese Ministry of Health and Welfare. In the cohort, there were 1,758 deaths including 661 of all malignant neoplasms.

The mean follow-up period per member was 4.6 years and the total of person-years was 528,540. The mode of the year of birth was in the 1950s, and the mean age as of 1986, when follow-up began, was 39 years.

2. Exposure dose

Exposure doses associated with radiation work for this study were obtained from the annual dosimetry records combining the external and internal dose, for each member of the study population filed in the RADREC from 1957 to 1992. The distribution of cumulative dose groups in the cohort was about 70% at less than 10 mSv and 2.7 % at more than 100 mSv. The mean cumulative dose per individual was 13.9 mSv, the total population dose of the cohort being 1,598.5 person-Sv.

The dosimetry records filed in RADREC reflect changes over time in the concept of radiation dosimetry, the unit of measurement of dose, technical advances in the method of dosimetric measurement, evaluation of exposure dose, and also reflect methodological differences between the respective nuclear power companies. It was reviewed whether the records were adequately consistent to consider the records to be uniform. The results indicated that all aspects of the records were appropriate and proper, and the records were adequately consistent for use in this study.

3. Statistical analysis

External comparisons: The cause-specific death rate by 5-year age groups for Japanese males in general for the period 1986 - 1992, in accordance with the total follow-up period in this study, was taken to be the standard death rate for this purpose. Significant tests for the SMR (Standardized Mortality Ratio) were two-tailed in view of a possible healthy worker effect.

Internal comparisons : The cohort was grouped by cumulative exposure dose into 5 dose categories, i.e., less than 10, 10-, 20-, 50-and 100 mSv or more. The ratio of the actual observed number of deaths to expected deaths, i.e., the O/E ratio, was obtained. Further, one-tailed p values were calculated using score test statistics to test for any trend of an increase in death rate with cumulative dose. In the calculation of score test statistics, the mean cumulative dose was used to represent each dose group.

III. Results

The SMR of all causes of death is 0.83 (95% CI: 0.79 -0.87), and that for non-cancer 0.72 (0.67 - 0.77). For all neoplasms including benign neoplasms and neoplasms of an unspecified nature, the SMR was 0.89 (0.82 -0.96) without lagging and 0.92 (0.84 - 1.01) on a 10-year lag. The SMR of stomach cancer was 0.79 (0.63 -0.97) on a 10-year lag. The SMRs were not significant for any of the other neoplasms (see Figure).

Examination of death rates by cumulative dose groups showed no statistically significant difference for any cause of death. Only the trend in the death rate was significantly found for malignant neoplasm of the pancreas with 10-year lag (p=0.043).

IV. Discussion

The death rates in the cohort due to the following causes of death were found to be significantly lower than in the general population: all causes, non -cancer causes excluding

external causes, all neoplasms, malignant neoplasms, malignant neoplasms other than leukemia, and stomach neoplasm. In stomach neoplasm, the death rate on a 10 - year lag was also significantly lower. These are well known as a "healthy worker effects".[6]

Although a statistical association of pancreatic cancer to radiation dose was noted in the present study, many previous studies of nuclear industry radiation workers have demonstrated no significant association between radiation dose and cancer of the pancreas. The exception is the most recent study of Hanford workers (1945 - 1986) which showed a significant association of cancer of the pancreas with dose on a 2-year lag but not on a 10-year lag. As a result of various considerations, the authors felt that no causal relationship could be inferred[1]. Also the results of atomic bomb survivors[7]and BEIR V Report[8] cite the pancreas to be a relatively radio-insensitive organ. Neither have the 1990 recommendations of ICRP[9] assigned any specific tissue weighting factor to the pancreas. After considering these scientific findings, the statistically significant association noted between cancer of the pancreas and dose in the present study can not be immediately judged as indicating a causal relationship with radiation.

Since the mean follow-up period was only 4.6 years, and the cases of various death causes were relatively small in the present study, further study should be continued to obtain more precise results.

ACKNOWLEDGEMENTS

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INCIDENCE OF THYROID CANCER AMONG CHILDREN OF THE UKRAINE IN 1996 AS COMPARED TO PREVIOUS POST-CHERNOBYL YEARS

Tronko, M.D., Bogdanova , T.I., Likhtaryov, I.A.* Institute of Endocrinology and Metabolism, Acad. Med. Sci. Ukraine. Research Centre for Radiation Medicine, Acad. Med. Sci. Ukraine, Kyiv, Ukraine*

A B S T R A C T

In 1996 a high incidence rate of thyroid cancer has persisted in Ukraine among children aged under 15 years, which averaged, according to preliminary data, 0.44 case per 100 thousand children's population. The geographical distribution of thyroid cancer cases in children of Ukraine is mainly related, as in previous years, with the most affected regions following the Chornobyl accident. The highest incidence of thyroid cancer (over 80%) was observed in those patients who were aged under 5 years at the moment of the accident, being the most radiosensitive age group. Among thyroid tumors removed in 1996, as in previous years, papillary carcinomas prevail, which are characterized by marked invasive properties.

Based upon preliminary data of statistical reports from regions of Ukraine and according to the results obtained at the Institute of Endocrinology and Metabolism, Acad. Med. Sci. Ukraine, 51 cases of thyroid cancer were registered in children aged under 15 years in Ukraine. Out of 51 cases of thyroid cancer in children under 15 years, 48 children were included in the Register, because 3 children were born after the Chornobyl accident (in 1987, 1989 and 1993).

We have pointed out in our previous investigations that for the period 1986 to 1995, 257 cases of thyroid cancer in children were registered in Ukraine, 41 and 44 cases being registered in 1994-1995, respectively [1 - 3]. In 1996, as compared to previous years, a high incidence rate has persisted in the above-mentioned age group of patients. These data are being supplemented with information on patients having been operated out of the Institute of Endocrinology and Metabolism.

The average incidence per 100 thousand children's population in Ukraine may be estimated only approximately, until complete data are received from all regions of Ukraine. However, even a preliminary analysis evidences a slight increase of this rate as compared to 1994-1995, and, so far, it makes 0,44 case per 100 thousand or 4,4 cases per one million children's population.

The highest incidence of thyroid cancer, as in previous years, is observed among children from the most affected regions as a result of the Chornobyl accident: Kyiv, Chernihiv and Zhytomyr oblasts, where the incidence per 100 thousand children exceeds the average rate for the Ukraine by 9.6 (4.25), 3.5 (1.54) and 2.5 (1.03) times, respectively.

The percentage of cases for six northern regions, as compared to the total number of cases for the whole Ukraine, makes 72.9 %.

If we additionally compare data for 1996 with those for previous years, taking five-year periods of observation, we may see a progressive and marked increase in northern regions over the post-Chornobyl years. So, for 5 years preceding the Chornobyl accident (1981 to 1985), thyroid cancer incidence among children of 6 above-mentioned northern regions of Ukraine was 6 times as low as for the other 21 regions. After the Chornobyl accident, the situation becomes opposite: in 1986 to 1990 the incidence for the 6 affected regions exceeded that for the rest of Ukraine by 2 times, in 1991 to 1995 - by 8.5 times, and in 1996 (according to preliminary data) - by 11 times.

Furthermore, it should be stressed an increasing number of cases of thyroid cancer among children who have been evacuated from the Chornobyl raion. In the first 5 years after the Chornobyl accident, as stated in our previous report, one case of cancer, and for the next 5 years, 11 cases of cancer were registered among such children. In 1996 (only for one year !) 5 children were operated upon, who had been evacuated from the cities of Prypyat, Chornobyl and neighbouring villages. Such indices are very alarming.

Such an alarming situation is confirmed by calculations of excessive incidence among children from the most affected regions as regards their thyroid irradiation dose.

Analysis of relationship between radiation doses and thyroid cancer in children who were operated upon in 1986 to 1995, shows that in the majority of cases (80.0 %) they were exposed to a thyroid dose less than 0.3 Gy, in 9.0% of cases - to 0.3 to 1.0 Gy, and in 11.0% of cases - to 1.0 Gy or more.

Furtherly, and analysis has been performed in the oblasts which have been the most affected following the Chornobyl accident: Kyiv, Chernihiv, Zhytomyr, Cherkasy, Rivne oblasts, as well as city of Kyiv. Using average exposure doses for each of the raions of above oblasts, several dose zones were established.

For each dose zone, incidence and excessive incidence of thyroid carcinoma in children under 15 years at the time of surgery, have been calculated. An analysis has been made for two-year periods of observation: 1986-1987, 1988-1989, 1990-1991, 1992-1993, 1994-1995.

As it was shown by an analysis of excessive incidence in indicated dose zones as compared to estimated spontaneous levels, the most significant increase in excessive incidence (more than by 100 times) was observed in 1992 to 1995 in children with a thyroid dose more than 1 Gy [4].

The distribution of above-mentioned children according to their age at the moment of the accident showed that over 80 % of them were aged under 5 years in 1986, and thus belonged to the age group which was the most sensitive to the radioiodine effect. It should be stressed that before 1995 the children who had been exposed at the age under 5, represented on the average no more than 40% among children who have had thyroid cancer in the following years.

Thus, in 1996 a marked increase in thyroid cancer incidence among children aged under 15 years has persisted in Ukraine.

The distribution of thyroid cancer cases in children of Ukraine, according to data of statistical analysis is, as in previous years, geographically related with those of Ukraine regions that have been the most affected as a result of the Chornobyl accident.

The highest incidence of thyroid cancer (over 80%) is noted among patients who were aged, at the time of the accident, under 5 years, i.e. in the most sensitive to radioiodine effect age group.

The situation for the first half 1997 may be estimated only according to the data obtained at the Institute of Endocrinology and Metabolism, Academy of Medical Sciences of Ukraine. Over this period, 19 children aged under 15 years were operated upon at the Institute. Out of them, 18 children have been operated for the first time (newly registered cases), and one children has been operated for a local relapse of cancer and relapse of regional metastases of thyroid cancer.

Pathomorphologically, 45 thyroid carcinomas have been studied, which were removed in children at the Surgical Clinic of the Institute of Endocrinology and Metabolism in 1996. Verification of diagnoses was carried out according to W.H.O. Classification [5].

Among the above-mentioned cases, 92.4% were found to be papillary carcinomas, 1.9% were follicular carcinomas, 1.9% were metastases of medullary carcinoma in lymph nodes (because of a grave condition, the primary tumor had not been removed in a girl), a low-differentiated thyroid carcinoma was found in 1.9%, and an anaplastic carcinoma -

in 1.9% of cases. These data show that in 1996, as before, in most cases papillary carcinomas were noted in children and adolescents of Ukraine.

A histological study of papillary carcinomas revealed a prevalence of tumors measuring more than 1 cm diameter. Only in one case the tumor was less than 1 cm diameter and it was identified as a papillary microcarcinoma. 92% of tumors were non-incapsulated, in 58% infiltration of soft tissues surrounding the thyroid was noted. In 73% there were signs of spreading of tumor within the gland limits. A so-called multifocal growth, when tumoral loci were identified in relatively unchanged thyroid areas distant from the main tumor, was noted in 50%.

A typical papillary carcinoma was found in 20% of cases, in 30% of cases a follicular structural type of papillary carcinoma was noted, in 28% - a solid variant, in 4% - a diffuse-sclerosing variant of papillary cancer, and 18% of tumors had a mixed follicular-solid structure.

Signs of invasion of papillary carcinoma cells into lymphatic vessels were observed in 65% of observations. In addition, a circulatory invasion was found in 45% of cases.

Metastases of papillary carcinoma usually affect regional lymph nodes. Morphologically, they are registered in 60% of cases. In such a situation, the tissue of lymph node is often completely substituted by the metastasis which has a structure either of a typical papillary cancer or of a follicular or solid variant of the latter. More often, papillary, follicular and solid areas took place at the same time. Psammoma bodies, hemorrhages, sclerotic changes may be observed in tumor metastases into lymph nodes.

Thus, among thyroid tumors, as in previous years, papillary carcinomas prevail, which are characterized by signs of aggressive behavior, what is evidenced by marked invasive properties of these tumors.

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Evaluation of apoptosis and apoptosis proteins as possible markers of radiation at doses 0.1-2 Gy, in comparison to the micronucleus assay in three cell lines

Alicja Jaworska, Dept. Radiation Medicine, Norwegian Radiation Protection Authority, Pilestredet 46B, 0167 Oslo, Norway
Paula De Angelis, Institute of Pathology, University of Oslo, The National Hospital, Pilestredet 32, 0027 Oslo, Norway

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ABSTRACT

In recent years the interest in apoptosis as possible indicator of radiation damage has increased. Studies have been done to examine the induction of apoptosis after ionizing radiation using morphological criteria, characteristic DNA damage pattern(ladders),early DNA damage using flow cytometry and/or expression of the proteins involved in apoptosis. But the picture which emerges from these investigations is unclear. Some researchers suggest that apoptosis studies can be used as potential assays of biological dosimetry, others doubt if apoptosis can be used as a marker of irradiation at all.
Most studies have been done using relatively high doses of radiation. In this study we focus on apoptosis induction after relatively small doses (0,1- 2 Gy).We detected apoptosis with the in situ terminal deoxynucleotidyl transferase assay by flow cytometry, and measured the expression of proteins that regulate apoptosis (Bcl-2, Bax, P53) with Western blotting. As comparison we used the cytokinesis-block micronucleus assay as a reference. The studies were carried out in three lymphoid cell lines: the mouse lymphoma L5178Y resistant and sensitive cell lines widely used in radiobiological studies, and the human pre-B cell leukemia Reh cells.
Our results indicate that we can not consider the examined parameters of apoptosis as markers of radiation in these cell lines.

1. INTRODUCTION

Together with the increasing knowledge about the molecular mechanisms of radiation sensitivity and radiation induced-apoptosis the interest in possibilities of using apoptosis and the gene products which are involved in signalling pathways leading to apoptosis as possible indicators or markers of radiation damage has also increased.(1,2,3).
In many lymphoid cells lower doses of irradiation are believed to cause cell death via apoptosis. In some lymphoid cells apoptosis occurs within hours after irradiation. Others undergo delayed apoptosis ie, cells divide before they ultimately die by apoptosis(4).
In this work we wanted to determine if there was any relationship between apoptosis, expression of apoptosis-related proteins (Bcl-2, Bax, P53) and the micronucleus test in two mouse lymphoma cell lines: L5178Y-R relatively resistant to X-ray (Do=1Gy), L5178Y-S sensitive to X-ray (Do=0.5Gy) which have been used as radiobiological model system(5), These have recently been studied for protooncogene expression after irradiation(6). We have also used human pre-B leukemia Reh cell line which expresses high levels of antiapoptotic Bcl-2 protein.

2. MATERIALS AND METHODS

2.1. Cell culture and irradiation

Cell cultures were maintained in RPM1/1640 medium with 10% FCS (5% CO_2 at37°C). Exponentially growing cells were irradiated in 10 ml flasks(T25) with 0.1, 0.5, 1 and 2Gy of X-rays (250V, 12mA, 3mm Al, dose rate 1 Gy/min) at room temperature.

2.2. Detection of apoptosis -Terminal deoxynucleotidyl transferase (TdT) assay

The procedure was modified from Gorczyca et al (7). Briefly, at 0, 24, 48 and 72 h after irradiation $5x10^6$ cells were fixed in 1% paraformaldehyde and post-fixed in absolute methanol at -20°C. To detect apoptosis, cells were incubated in TdT solution (5 units in 50 µl) with biotin 16-dUTP (Boehringer Mannheim) as a substrate for 30 min at 37°C, washed and the cell pellets stained with streptavidin-fluorescein (Amersham) made up in PBS plus 0.1% Triton X-100 and 3% fat-free milk. After 30 min incubation at 4°C and washing with PBS plus 0.1TritonX-100 the cells were treated with 100µg/ml RNAase (Boehringer Mannheim) and stained with propidium iodide PI (5µg/ml) for total DNA content. Red fluorescence from PI bound to DNA and green fluorescence from the labelled DNA ends were measured for 10^4 cells in a FACS Vantage laser flow cytometer (Becton-Dickinson,CA,USA). Percentages of apoptotic cells were calculated from bivariate distributions of DNA content versus FITC fluorescence.

2.3. Western blotting

After irradiation cell cultures were incubated for 4 or 24 hours and $2\text{-}3x10^7$cells were used for extracts preparation(method from Research Application, Santa Cruz Biotechnology,In). Protease inhibitor cocktail tablets(Boehringer Mannheim) were added to these extracts. Cell extracts were diluted 1:4 in standard Western blotting sample buffer.and run on 12% SDS-PAGE gel at 60V, 30mA for 14 hours. Blots were stained for Bcl-2 and Bax and p53 proteins using rabbit polyclonal antibodies from Santa Cruz Biotechnology,Inc: (bcl-2(ΔC21)and bax(p19) and p53(E-19). Antibody bound proteins were detected with biotinylated donkey anti-rabbit Ig, streptavidin alkaline phosphatase and developed with a BCIP/ NBT system (Amersham).Kaleidoscope prestained standards(broad range) from Bio-Rad were used as molecular weight standards.

2.4. Cytokinesis-block micronucleus assay

The method was performed according to Fenech (8) with modifications for generation time, cytochalazyn B(cytB) concentrations, and mitotic delay. Briefly L5178Y-S cells were incubated with 1.5µg/ml cytB for 17-24h, L5178Y-R with 3µg/ml for 17-19h, and Reh cells with 3µg/ml cytB for 44h. For each cell line 2-3 series of experiments were performed.

3. RESULTS AND DISCUSION

The TdT flow cytometric results confirmed that L5178Y cells undergo delayed apoptosis as was earlier published(9). Significant apoptosis at doses lower than 2Gy were found only in the X-ray sensitive L5178Y cell line(t-test, $p<0.05$) (Figure 1a.b.). The effect was most pronounced after 24h after irradiation.

In Reh cells we observed a marked variation in the number of spontaneous apoptotic cells in controls, and significant apoptosis was only seen after 24hours and 2Gy of X-rays (Fig 1c.) in the irradiated cells ($p<0.05$).

Western blotting studies demonstrated high levels of expression of the antiapoptotic Bcl-2 protein in Reh cell line, and lower level of expression of Bax, thus the ratio Bcl-2/Bax favours Bcl-2. In contrast in L5178Y cells had high levels of Bax protein in both sub-lines, but Bcl-2 expression could only be detected in the radiation sensitive L5178Y-S.

We did not observe any changes in the amounts of these proteins at 4 or 24 hours following irradiation at doses 0.1-2Gy. In L5178Y cells we also determined p53 expression. P53 was detected in the control cells, and no changes in p53 expression were seen after irradiation as above. These lines have a mutation in exon 5 at codon 170 of the p53 gene(10). The proteins recognised by the p53 antibodies used were both wild type and mutant .

Surprisingly, the micronucleus assay studies on these cell lines (Table I) for the low doses do not show any differences between cell lines which may indicate that this assay is not a measure of intrinsic sensitivity but rather is a good estimator of the dose.

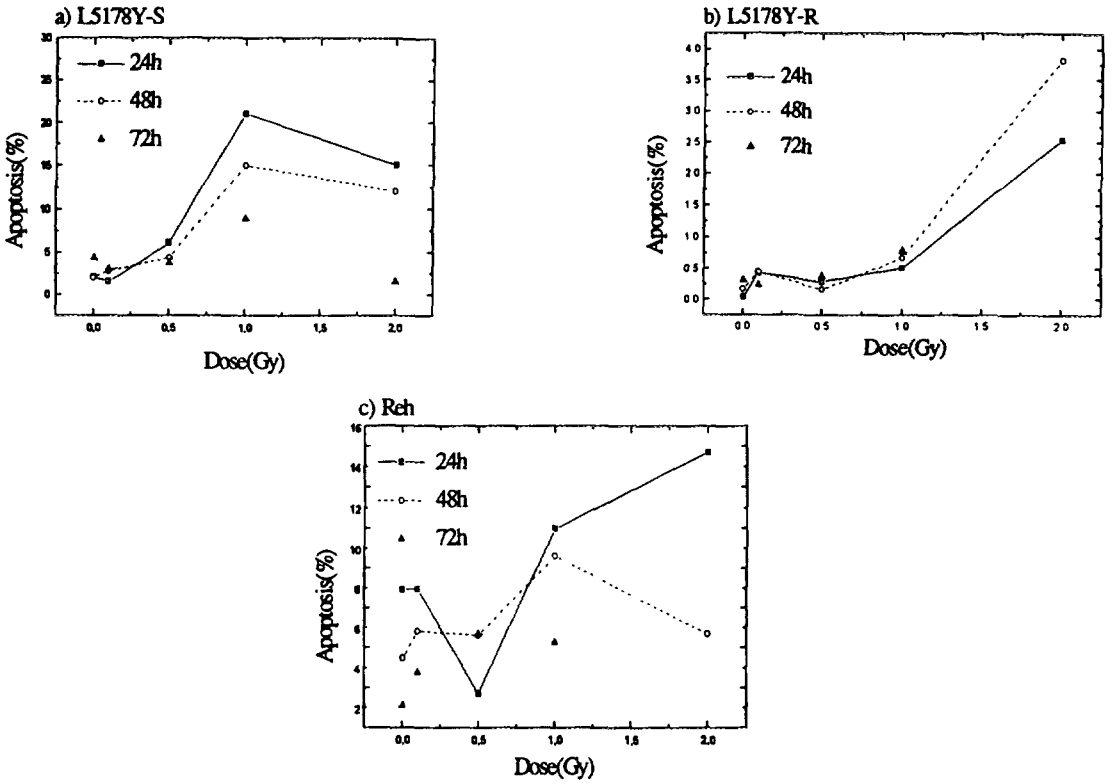

Figure 1.

Radiation induced apoptosis in L45178Y-S(a), L5178Y-R(b), and Reh(c) cells 24, 48 and 72h after irradiation with doses 0.1- 2 Gy of X -ray (250kV, 12mA, 3mmAL, dose rate 1Gy/min.).Apoptosis was measured using a flow cytometric TdT assay.

Table I

Frequency of micronucleus in three cell lines after X-ray irradiation with doses 0.1-2Gy. Each value represents results from 2-3 series of experiments

Dose (Gy)	Micronucleus/1000 cells ± SD		
	L 5178Y-S	L5178Y-R	Reh
Control	11.5 ± 3.4	8.0 ± 4.6	11.8 ± 5.1
0.1	17.0 ± 6.80	24.5 ± 8.7	21.5 ± 6.8
0.2	23.3 ± 7.00		
0.3	38.7 ± 12.8		
0.4	41.3 ± 16.8		
0.5	42.7 ± 4,20	49.5 ± 7.9	49.0 ± 17.8
1.0		85.0 ± 6.2	77.5 ± 20.2
2.0		190.0 ± 50.3	116.7 ± 21.0

Overall, neither the numbers of apoptotic cells nor the expression of apoptosis-related is proteins can serve as dose estimators in the above lines and at the doses studied. This is in agreement with the available literature which points out that it is not possible to predict a cell's tendency to undergo apoptosis from the expression of p53, the bcl-2 family of proteins and c-myc protein(11). Nor is apoptosis reliable indicator of radiation sensitivity(3). Therefore we disagree with the recent proposal that radiation-induced apoptosis has potential as a biological dosimeter(12).

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Analysis of cancer mortality risk among workers of a research uranium metallurgy division in France

JEJATI Hélène[1], LAURIER Dominique[1], TIRMARCHE Margot[1], GIRAUD Jean-Michel[2]

XA9745663

[1] Institute for Protection and Nuclear Safety, Human Health Protection and Dosimetry Division, Risk Assessment and Management Department. IPSN, B.P. n°6, F 92265 Fontenay aux Roses Cedex, France.

[2] Medical Adviser of CEA, 31-33 rue de la Fédération, F 75752 Paris, Cedex 15, France.

Abstract

This cohort study has been undertaken in response to a suspected cluster of cancers mentioned by workers involved in research activities concerning the metallurgy of uranium. The studied population included all persons having worked between 1950 and 1968 at the Metallurgy Division of the French Atomic Energy Commission (CEA). Exposures were registered on an individual annual basis. For analysis, they were grouped in three categories: use of chemicals agents (Benzene, beryllium, alcohols, solvents...), manipulation of radioactive materials (uranium, thorium, fission decay products), and exposure to external radiation.

This relatively small cohort included 356 workers followed up to December 1990. Out of observed deaths, 21 were from cancer. Total mortality from cancer was less than expected from national rates (Standardised Mortality Ratio = 0.73). Cancer mortality did not increase with duration of exposure to external radiation or with duration of manipulation of radioactive materials. Risk of cancer was increasing with the number of years of exposure to chemicals.

The small size of this cohort limits the conclusion of the observed results. The purpose, despite this lack of power, was to answer a worry of the workers, more than to estimate a clear dose-response relationship linked to a specific cancer site. The effect studied here is "all cancers", a distinction of the different sites being uninformative because of the very small number of cases observed. Nevertheless, this study suggests some routes for further research: it highlights the importance of considering concomitant exposures like chemical ones in studies of nuclear workers.

1. INTRODUCTION

This epidemiological follow-up has been undertaken in response to a suspected cluster of several cases of cancer in 1983-1984 among workers from the Metallurgy Division of the French Atomic Energy Commission (CEA). These workers were involved in research activities concerning the metallurgy of uranium. In the framework of their occupational activity, they were manipulating uranium and other radioactive materials, and were also using chemicals.

The aim of this study was to screen for an increased risk of cancer mortality related to occupational exposure.

2. MATERIAL AND METHODS

The studied population included all subjects who had worked at the Metallurgy Division for at least one year between 1950 and 1968. Follow-up was completed up to December 1990. The dates and causes of deaths were obtained from the occupational medicine staff of CEA. Causes of deaths were coded according to the ninth International Codification of Deaths. The observed number of deaths from cancer were compared with the expected ones based on French national rates with adjustment for age, sex and calendar time and expressed by the Standardised Mortality Ratio (SMR).

Information on occupational exposure was obtained by a qualitative approach, from medical files and collective memory. Several meetings were organised with retired workers to discuss and precise individual yearly exposure (collective memory). For each worker, exposure to more than 30 different products was reconstructed per working year in a qualitative way (exposed/not exposed). For the analysis, these exposures were grouped in three categories, reflecting three different types of activity: use of chemicals (Benzene, ketones, beryllium, alcohols, solvents...), manipulation of radioactive materials (uranium, thorium, fission products), and exposure to external radiation (β, γ, X). Quantification of exposure was expressed by the number of years of exposure to each of the main components. Individual dosimetric records were also used to assess quantitatively the cumulative exposure to external radiation. Relationship between risk of cancer and exposure was examined using 3 methods: Poisson trend test, external Poisson regression modelling, using national rates of mortality as external reference, and internal Poisson regression modelling [1]. Only those results showing good agreement between the three methods were considered as significant.

3. RESULTS

3.1. Mortality

The cohort included 356 workers. Mean age at entry into the cohort was 30 years. Mean duration of follow-up was 30.4 years. The total number of person-years was 10,850. 24 subjects (6.7 %) could not be traced up to 1990. The observed number of deaths was 44. Cause of death was obtained for 31 cases.

For all causes of death, the studied population showed a strong « healthy worker » effect. The observed number of deaths from cancer (ICD 140-208) was 21. Total mortality from cancer was less than expected from the national rates of mortality (SMR = 0.73, Confidence Interval

$IC_{95\%}$=[0.49-1.06]). We found no evidence of any excess of cancers in the period 1983-1984. On the whole cohort, a significant excess of death was observed for multiple myeloma (SMR= 8.38, $IC_{95\%}$=[1.44-26.2]), but based on only 2 observed deaths.

3.2. Exposure-Mortality relationship

Of the 356 included workers:

- 191 have been exposed at least one year to chemicals, with a mean duration of exposure of 12 years.
- 255 manipulated radioactive materials at least one year. The mean duration of exposure was 11 years.
- 262 have been exposed at least one year to external radiation. The mean duration of exposure was 11 years. Mean dosimetric cumulative exposure was of 8.7 mSv (from a minimum of 0.4 to a maximum of 85.2 mSv)
- 20 % were never exposed to any of the materials from the three groups. 45 % were exposed in the three groups for at least one year.

When studying relationship between number of years of exposure and risk of cancer mortality, the three methods showed a high degree of agreement (Table I). No increase of cancer mortality was observed with the duration of exposure to external radiation. An increase with the duration of manipulation of radioactive materials was not consistent among the three methods. An increase of the risk of cancer mortality was observed with the number of years of positive exposure to chemicals (Table I).

Table I: Tests of a linear relationship between number of years of exposure and risk of cancer mortality

	Trend tests		**Poisson regression external ***		**internal ****	
	Chi-2	p	ERR	p	ERR	p
Number of years with						
exposure to chemicals	17.7	0.001	0.26	0.005	0.20	0.002
manipulation of radioactive materials	4.69	0.03	0.14	0.043	0.10	0.08
external exposure to radiation	1.51	0.22	0.05	0.276	0.03	0.42

*: using national rates of mortality from cancer as an external reference

**: stratified on sex, age and calendar year

ERR: excess relative risk (per year of exposure)

p: significance probability of the exposure-response relationship

4. DISCUSSION

The study was decided in response to questions coming from the workers of the Metallurgy Division, suspecting an excess of cancers in the period 1983-84. Despite its reduced size, this cohort study answers the following points:

(a) No excess of cancer mortality was observed on the whole follow-up period

(b) No cluster of cancers appeared in the period 1983-1984

(c) No increase of cancer mortality was observed with the duration of exposure to external radiation or with the duration of manipulation of radioactive materials.

On the other hand, two positive results were obtained:
(a) An excess of mortality from multiple myeloma was observed,
(b) The analysis suggested that exposure to chemicals might be a risk factor of cancer in the studied population.

When considering these results, we should remember the very small size of the study, and consequently its lack of power. Due to this reduced size, it was not possible to consider multiple exposures, nor to analyse separately the exposure to different chemicals. Also, we were not able to distinguish between different sites of cancer when analysing the exposure-effect relationship. For example, beryllium was included in the group of chemical exposures. This material has already been proposed as a carcinogen of lung cancer [2,3], but the size of our study was not sufficient to analyse this potential relationship. For multiple myeloma, the observed excess was based on only two cases. This excess is therefore susceptible to be a chance finding, but we have to note that a significant excess of multiple myeloma was also observed in some nuclear workers studies [4].

This study shows also the practical limits of such a precise reconstruction of past multiple exposures: what was possible here in a small population appears unfeasible on a large scale in cohorts of several thousands of nuclear workers. In our opinion, a nested case-control approach should be preferred when taking into account the influence of concomitant exposures on the dose-response relationship linked to external radiation in nuclear workers studies.

5. CONCLUSION

Due to the limited size of the study, conclusions have to be considered very cautiously. But it suggests some results that should be considered in further research on the risk of cancer among nuclear workers: particularly, it highlights the importance to consider exposures to chemicals in subgroups of nuclear workers.

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Analysis of personnel exposure of working with ionizing sources

Korenkov I.P., Sobolev A.I., Polskiy O.G., Verbova L.F.
(SIA"Radon")
Alexandrova A.I.
(RMAPO)

XA9745664

Abstract

Personnel exposures of staff of scientific, medicine and industrial enterprises to various ionizing sources were evaluated. All the significant data with close parameters were statistically united into groups. By the help The curves of overexposure probability of personnel were presented. It was shown that the probability curve, estimated from anticipated lognormal distribution of personnel exposures had the smallest errors.

At present, in terms of ICRP recommendation, base on conception non threshold exposure to ionizing sources, problems, related to processing of personnel exposures are significant importance for practical dosimetry. The problems include the methods of detection of doses from 0.01 mSv, the methods of accumulation of statistics information and choice of processing methods applied. We tried to analyze the level of radiation exposures of various occupational groups, working with ionizing sources and give recommendations for analysis of processing the information about occupational exposure.

We chose 70 enterprises, where the evaluation of individual doses of personnel were performed for more, then 10 years. Dosimeters sensitivity was in the range of 0.01mSv - 10 Sv. Exposure time was usually 1-3 months.

The first data 1985-1996 were grouped according to the type of exposure, professions, sorts of enterprises and years into subgroups for which statistical parameters of distribution were estimated and checked according to agreed-upon criteria for conformity with normal or logarithmic normal law. All selected subgroups are statistical samplings.

In process of grouping according to years, for getting statistical sampling six groups, namely medicine, scientific establishments and industrial enterprises separately for gamma and X-ray exposure were chosen.

For no subgroups distinct tendencies in average values were revealed. Average values of gamma irradiation for the last 10 years are in the range of 0.26 -2.6 mSv (average value 1.7 mSv/year), average values of X-ray exposures for the last 10 years are within 0.6 - 3.3 mSv (average 1.6 mSv/year). During forming the occupational subgroups we united the data for the total time period of observation. Average dose in subgroup amounts to the maximum for the scientists of medical institutions, in process of work with X-ray radiation and minimum values can be observed in the subgroups of the others, who work with gamma sources and include managers of institutions, leaders of sectors and individuals with the occupation, which has no relation to the subgroups examined.

As a rule the data are in correspondence with lognormal law, however, as it was mentioned before, in separate cases this rule is broken and the data do not correspond to any of above mentioned laws.

Very low doses (0.1-0.15 mSv/year) and unreasonably high ones (more then 20 mSv per quorter), which result into distortion of distribution of exposures were revealed.

Values, exceeding 15-20 mSv/year, for all the enterprises and institutions under consideration represent seldom occasional outliers (total number of which along the base amounted to not more than 2%), which can be governed both by mistake of operator or failure in the apparatus operation during detector analysis, and real overexposure (due to violation the safety rules or deliberate exposure of detector), each

case demands revealing the true reasons. The attempts to evaluate the degree of influence of all these errors to the type of radiation distribution law demonstrated, that exclusion of large deviations, more than 15 mSv/year, brings the data into correspondence to lognormal law of distribution.

Availability of the values less than 0.4 mSv in the annual data is interpreted by incomplete initial information, the data include the information for 1-2 quarters, for example. Exclusion of low values can deteriorate the data correspondence to lognormal distribution, that is why the values not more, than 0.4-0.5 mSv/year can be excluded from the total number of values.

Processing of data obtained showed, that occupational subgrouping the data is not justified for gamma exposures in the medical institutions, because they belong to the single population. For the X-ray irradiation one should subgroup the scientists, all the rest belong to the single population both for gamma and for X-ray exposure.

Taking into consideration the occupations of different branches, we can conclude that subgroup of engineer and technical workers represents the same population for each type of radiation exposure. Scientists off all institutions are expedient to be united into one subgroup.

Subgroups, the distribution parameters of which belong to the same population according to statistical criteria, can be described by the united distribution law. Statistical parameters of such a law can be calculated by uniting the given logarithms of individual doses, included into these subgroups into one group, namely these parameters were used for evaluation of gaining this or that dose by the personnel.

Usually risk assessment of personnel ascribed to any group, is characterized by the single value, numerical equal to probability P of gaining radiation exposure during a year, equal or exceeding the permissible dose limit. However, for practical application except the risk value, it is important to predict any exposure of person, who belongs to a definite occupational group, and for this purpose it is useful to have all the probability curve P(D), where probability of gaining the dose, equal or exceeding value D, by the personnel of group is calculated as a unit minus integral within 0 - D of the probability density of lognormal distribution with the parameters of any group.

Curve variations during different thresholds of excluded rough deviations for normal and lognormal laws are different. In case of approximation of data left to normal law spread in probability curves within values of doses up to 5 mSv/year amounts to 10-25%. In case of approximation the data left to lognormal law, maximum difference between curves do not exceed 10%.

That is why to evaluate the probability of gaining the dose, not exceeding D by the person, one should originate from suggestion of lognormal distribution of data , as it results into comparatively small errors along the range of doses considered.

In terms of mentioned above we conclude:

1. It is possible to form authentically occupational groups within one branch or various branches with close distribution of personnel exposures.
2. Scientists of medical institutions gained maximum individual dose during the work in the area of X-ray radiation. Statistic authentical tendencies of variation in average annual individual doses in all separate occupation groups are absent.
3. During calculation of probable exposure of personnel from any group to radiation dose D<Dose limit, the best approximation to real dependence is lognormal distribution of doses. Low doses have more significant influence on the rigour of lognormal distribution of individual doses of personnel than abrupt high outliers.

Assessment of Radiation Dose Formation due to Hot Particles of Chernobyl Origin

Vladimir Demchuk[1], Vladimir Lutkovsky,[1] Oleg Bondarenko[2]

[1] - Chernobyl Branch of Ukrainian Research Hydrometeorological Institute, Radyanskaya Str. 72a, Chernobyl 225620, Ukraine

[2] - Radiation Protection Institute, Melnikova 53, Kiev, 253050, Ukraine

XA9745665

Abstract. The necessity to apply original data about the size and the activity distributions of hot particles has been arising at many post-Chernobyl research. Such researches include first of all (i) studying of migration processes at soil-water complexes, (ii) retrospective inhalation dose reconstruction for the population, and (iii) validation different scenarios of the Chernobyl accident deployment.

Results of this research show that the fuel matrix in soil can be considered as constant with accuracy 20-30% for transuranic nuclides and major of long-living fission products. Temporal stability of hot particles at the natural environment gives a unique possibility to use the hot particle size distribution data and the soil contamination data for retrospective restoring of doses even 10 years later the Chernobyl accident.

In present research the value of the integral of hot particle activity deposited into the lung was calculated using a standard inhalation model which takes into account the hot particle size distribution. This value normalised on the fallout density is equal to 0.55 Bq/(Bq·m^{-2}) for areas nearby the Chernobyl NPP.

1. INTRODUCTION

The peculiarity of the Chernobyl accident was that a most part of radioactivity released the emergency reactor was in the hot particle form [1].

Hot particles are meant all classes of radioactive particles (i) of condensation type (caesium and ruthenium), and (ii) of fuel type having the radionuclide contents similar to that of burnt out fuel. Hot particles represent a potential hazard to human, of which there are principally two aspects.

Firstly, after deposition in (or on) the human body, hot particles produce huge local doses. This can make a micro injury inside different organs (or on skin) as well as contributing to late (carcinogenic) effects.

Secondly, hot particles are "repositories" of a large amount of transuranic radioactivity which is encapsulated inside them. The solubility of hot particles and the degree of mechanical destruction determine the biologically accessible fraction of transuranic nuclides. Thus it forms the additional source of transuranic elements intake through the food chain or dissolution inhaled hot particles.

2. METHODS

Identification of hot particles and measurements of their size and activity distribution are carried out by well known and worked out methods of the emulsion autoradiography (X-ray film PM-B, PM-1) for the beta component [2] and solid-state nuclear track detection (SSNTD) (films of LR-115 and CR-39 types) for the alpha component [3].

The lower level of detection (LLD) for the emulsion autoradiography is about 0.1 Bq/particle after the exposure time of 96 hours. In this way the minimal registered size of à hot particle is about 0.05 μm. The SSNTD method is able to identify a hot particle and provides simultaneous measurement of its size and activity, and also gives information about its radionuclide contents refusing destroying of a particle. The LLD of the latter method is 0.1 mBq/cm^2 after one week exposure time.

In contrary to methods above a standard radiochemical analysis destroys particles and is only able to give the total amount of radionuclides in a sample. Additionally radiochemistry of soil is laborious enough and can be hardly made as an automatic procedure.

3. FORMATION OF RADIOACTIVE CONTAMINATION AFTER THE CHERNOBYL ACCIDENT

Primarily the radioactive pollution of the environment took place by air transport of radionuclides and their deposition onto the surface. In the bulk radionuclides were departed to the air in a form of dispersed fuel particles and their mixture with inactive carriers. The fuel component of the release comprised dispersed fuel matrix of UO_2, UO_3, U_3O_8 and other. Inactive component contained a complex mixture made from graphite, building materials of the reactor, materials used for overwhelming devastated areas of the reactor.

Gases departed the active zone of the reactor were mostly isotopes of Kr and Xe. Some elements sublimated from the active zone and then deposited onto the surface as mononuclide particles. Among those there were mostly isotopes of I and partially of Cs and Ru. A formation of such mononuclide particles occurred at condensation centres which may have been particles of dust, smoke etc. The caesium particles prevail in the region of less than 1-2 μm whereas fuel particles comprise mostly the region above. The ratio of the fuel component to the condensation component is in the range 5-8 for the near zone [4].

Fuel particles in the main were forming contamination of the near zone whereas gaseous and vapor components and partially fine fraction of fuel particles were contributing contamination of the far zone. Proceeding the analysis of the structure, forms and mapping density of radioactive pollution of the near zone, it can be assumed that the hot particles were a main radiation factor of polluting the atmosphere and of forming inhalation doses of the population after the Chernobyl accident.

The pollution of the zone in vicinity of the NPP was formed basically by hot particles which radioactive contents coincides with the structure of burnt out fuel. In addition there were met ruthenium (1-3%) and caesium (10-20%) types of particles.

By the 8th year after the accident the portion of the caesium activity aggregated in hot particles is 40-80%. It should be taken into account that at the moment of the initial explosion the departing particles were already depleted by caesium. Changes of the hot particle dimensions structure in time is insignificant. Seven years of research from 1989 to 1994 gives the value of these changes about 10-20%. Processes of hot particle mechanical destruction in soil and selective leaching of radionuclides from them have been insignificant relatively to the rate of vertical migration. Thus the fuel matrix in soil can be considered as approximately constant (with accuracy 20-30%) for transuranic nuclides and major of long-living fission products.

The vertical activity distribution of soil 8 years after the accident basically (90-95%) is condensed in the higher layer of 5-10 cm. Only trace amounts of caesium and strontium are tracked below 10 cm. The activity distribution depends locally on a soil type and water

regime. The number of hot particles varies from 70-80% in the top 0-2 cm layer down to 1-3 % in the 6-8 cm layer. Below 10 cm hot particles are observed hardly.

4. RETROSPECTIVE ASSESSMENT OF HOT PARTICLE INTAKE INTO THE LUNG

The spatial distribution of airborne hot particles during earliest fallout with regard to HP dimensions and activities is very important and in the same time is the least investigated side of the entire HP problem. The information about this distribution based on direct measurements almost completely absents. Such a sort of situation forces to face to indirect methods to make HP lung intake estimation [5].

In most simple way, the intake model looks as follows. Suppose, a human situated in damage territory all the time of radioactive ground trace formation (with accuracy about "human behavior coefficient" which approximately equals to 0.5). Human lung may be considered as a filter system into falling down radioactive dust.

The amount (or the integral activity) of radioaerosols of a given size I deposited in the respiratory tract can be determined by two alternative ways

$$I = vS \cdot CT = kQ \cdot CT \qquad (1)$$

where S - effective lung capacity of aerosol retention (m^2), v - sedimentation velocity of particles (m sec^{-1}), Q - respired volume (m^3 day^{-1}), k - coefficient of aerosol deposition into the lung, C - concentration of aerosols (particle m^{-3} or Bq m^{-3}), T - time.

For aerosols of a wide size range their size distribution P_r should be taken into consideration

$$S_r = \frac{P_r k_r Q}{v_r}. \qquad (2)$$

Then the effective lung capacity of aerosol retention becomes the integral through all range of dimensions r

$$S_{eff} = \int S_r dr. \qquad (3)$$

Thus it means that the fallout density $\grave{A}$ (Bq·m^{-2}) could be applied for calculation of the integral hot particle activity I deposited into human lung during an accident

$$I = AS_{eff}. \qquad (4)$$

One practical example could demonstrate the application of such an approach. The data of soil fallout may be approximated by log normal distribution and thus the geometric dimensions distribution P can have the following look

$$P_r = \frac{1}{\sqrt{2\pi}Sr} \exp\left(-\frac{1}{2}\left(\frac{\ln r - \ln X}{S} \right)^2 \right).$$

For the particular area inside Chernobyl NPP Exclusion Zone we have recently found: X = 2.23 μm, S = 0.32. It means that for Q = 30 m^3 day^{-1}, the value of effective retention capacity S_{eff} obtained after integration is equal to S_{eff} = 0.55 m^2. Thus the integral I of HP

activity deposited into the lung normalised on the fallout density A numerically equals I/A = 0.55 Bq/(Bq·m^{-2}).

5. DISCUSSION

Results of this research show that the fuel matrix in soil can be considered as constant with accuracy 20-30% for transuranic nuclides and major of long-living fission products. Temporal stability of hot particles at the natural environment gives a unique possibility to use the hot particle size distribution data and the soil contamination data for retrospective restoring of doses even 10 years later the Chernobyl accident.

Approximately by convention, whole the period of inhalation doses formation could be divided by two stages:

1. Short-term period of primary air pollution directly from the destroyed active zone (April - May 1986).
2. Period of secondary atmospheric pollution in result of re-suspension.

The first period distinguishes by high concentration of primary radioactive particles and availability of a plenty short-living radionuclides in air.

An important feature of that stage was that hot particles massively irradiated (by beta emitters) lung of many people could not have been subsequently found inside their bodies because of relatively fast removal from top compartments of lung (during several days). However calculations show that these hot particles could make a main contribution in inhalation dose for a broad group of the population. In present research the value of the integral of hot particle activity deposited into the lung was calculated using a standard inhalation model which takes into account the hot particle size distribution. This value normalised on the fallout density is equal to 0.55Bq/(Bq·m^{-2}) for some areas inside the ChNPP Exclusion Zone.

The second stage is stretched in time by now. It has been attributed with considerably lower intensity of radioaerosol sources (some orders of magnitude). Main dose forming radionuclides has been caesium, strontium and actinides. The hot particle size distribution has been conditioned on soil grain properties. The source of secondary airborne hot particles has been the soil surface, plants, buildings etc.

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Notification of Occupational Lung Cancer Caused by Ionizing Radiation in the Czech Republic

XA9745666

Evžen Hrnčíř

Occupational Diseases Clinic, Third Medical Faculty, Charles University, Prague, Czech Republic

Abstract

In the Czech Republic decisions on the occupational character of lung cancer which could be caused by ionizing radiation are based on the probability assessment. Cases are considered occupational when according to the calculation based especially on data of the patient's exposure there is at least 0.5 (in some cases even 0.4 - 0.5) probability (PC) that the disease was caused by professional exposition to alpha radiation of the radon decay products. Coefficients derived from epidemiological surveys carried out in miners of the uranium industry are used for this calculation. New surveys provide new data for calculations. The principle of assessment of the occupational character of lung cancer in working people should be unified on an international scale.

Key words

lung cancer, ionizing radiation, occupational disease

* * *

Non-medical exposures to major doses of ionizing radiation or biologically relevant contamination of the organism by radioactive isotopes are extremely rare in the Czech Republic. Acute radiation syndrome has not been described in this country and the inpatient department established in one hospital in Prague 35 years ago for decontamination of people has never been used for this purpose.

On the other hand, there are many working people in the Czech Republic who are repeatedly exposed to relatively small amounts of ionizing radiation. This applies in particular to uranium miners and uranium mill workers. They inhale while working the decay products of radon (^{218}Po, ^{214}Po), the alpha radiation of which can cause lung cancer.

In the Czech Republic about 6500 new cases of lung cancer are detected every year (the incidence in 1996 was 101/100 000 in men and 33/100 000 in women). No doubt, in the majority in the development of the disease a decisive role was played by other causes than ionizing radiation, above all cigarette smoking, contamination of the environment, immunological and genetic mechanisms. In individual cases, however, clinical or laboratory examinations cannot reveal the cause of the disease. Some cases of lung cancer can be, however, according to law, notified as an occupational disease and the worker is entitled to appropriate damages, the sum depending on the used compensatory system. (As a rule the worker gets a lump sum corresponding roughly to thirty monthly mean wages in the Czech Republic and subsequently he receives a permanent monthly pension and some other allowances). Therefore the decision on

the occupational character of the disease is of great importance.

The List of occupational diseases which is an appendix of the Government decree no. 290/1995 contains item III/6: Lung cancer caused by radioactive substances. According to this regulation lung cancer can be notified as an occupational disease only in the case it has developed in the course of work where "such exposure to radioactive substances by inhalation has been proved which according to contemporary medical knowledge causes disease".

Evaluation of the occupational character of lung cancer as practiced by clinics for occupational diseases in the Czech Republic is based on the probability principle. The calculation is made according to the recommendation issued by the Ministry of Health in 1991 [1]. It is based on knowledge of the hygienic conditions of the workplace and the exposure period. First the intake (H_i) of the decay products of radon (alpha emitters ^{218}Po and ^{214}Po) in different years is assessed. This is expressed in WLM units (working level month) where 1 WLM stands for the inhalation of the latent energy concentration of $1.3 \cdot 10^5$ MeV/l for a period of 170 hours which corresponds to the intake of the radon decay products of $2.65 \cdot 10^{10}$ MeV absorbed in bronchial epithelium. Then the additional risk (R) (i.e. the increase of the lung cancer rate due to the alpha radiation) is assessed according to the following equation:

$$R = \sum_{i=1}^{n} (H_i \cdot C_i)$$

where C_i is the relative risk coefficient given in table I
n is the number of years of the worker's exposure

Table I

Relative risk coefficients C

age when started risk work (years)	time which elapsed between exposure and diagnosis of lung cancer (years)		
	0-4.9	5.0-14.9	15 and more
≤ 29	0/WLM	0.057/WLM	0.0285/WLM
30 - 39	0/WLM	0.035/WLM	0.0175/WLM
> 40	0/WLM	0.021/WLM	0.0105/WLM

The relative risk coefficients were assessed on the basis of epidemiological studies implemented in uranium miners before 1985 [2]. At present, results of more recent surveys are available and therefore a change of the relative risk coefficients C is contemplated, while preserving the principle of assessment of additional risk R.

The ratio of causal relationship of irradiation on the development of lung cancer (PC) (i.e. probability of causation) is calculated from the equation:

$$PC = \frac{R}{R + 1}$$

If the assessed value of PC is greater than 0.5, the clinic of occupational diseases notifies lung cancer as an occupational disease and the patient is paid full damages by his employer. If the PC value is lower than 0.4, the condition is evaluated as non-occupational and the patient does not receive any damages. If the calculated PC value is between 0.4 and 0.5, the clinic of occupational diseases considers, when deciding on the occupational character of lung cancer, further factors, in particular cigarette smoking and the possible exposure to other cancerogenic factors in the working environment.

The numbers of people in the Czech Republic where occupational diseases clinics certified lung cancer as an occupational disease in 1986 - 1996 are listed in table II.

Table II

Number of cases notified as occupational lung cancer in the Czech Republic

year	number
1986	95
1987	102
1988	79
1989	85
1990	75
1991	85
1992	71
1993	92
1994	77
1995	55
1996	67

Workers not granted by clinics of occupational diseases the occupational character of their lung cancer because of a low PC value frequently ask a court of law for revision of the matter. The recommendations of the Ministry of Health concerning the occupational character of lung cancer are not mandatory for the court. That is why the court decides very frequently that lung cancer is an occupational disease despite a very low ratio of causal association of irradiation (PC), usually by stating that it is not possible to rule out completely that the disease was caused by ionizing radiation. There are no records on the number of cases of lung cancer which were thus granted an occupational character. The majority of physicians do not agree with the mentioned attitude of the

court. (If it were used consequentially every case of lung cancer in any worker could be considered an occupational disease. Everybody is always exposed at any workplace at least to small amounts of ionizing radiation. It can never be ruled out that these doses caused his or her disease.)

It is obvious that the principle which is applied in the Czech Republic to compensate for lung cancer, i.e. that if the occupational character is accepted the patient receives full damages or if it is not accepted, he does not receive anything, has its pitfalls. There are some variants which could be used when compensating for the disesase (as well as other diseases which can be evaluated only on the basis of the probability principle) [3]. It seems to be useful for specialists from different countries to unify their views of this matter. International organizations would use their opinions as a basis for recommendations how to proceed in the evaluation, notification and compensation of lung cancer caused by ionizing radiation.

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"LA SITUACIÓN ACTUAL DEL SISTEMA DE MAGNITUDES OPERATIVAS ICRU EN MÉXICO"

José T. Alvarez Romero.
Departamento de Metrología.
Gerencia de Aplicaciones Nucleares en la Salud.
ININ.
Salazar, Edo. de México, México.

RESUMEN.

Se presenta un panorama del desarrollo del sistema de magnitudes dosimétricas empleadas con fines de Protección Radiológica (PR). Finalmente se argumenta la necesidad de la implementación de el sistema de *magnitudes operativas ICRU* en México.

1.- INTRODUCCIÓN.

Es conocido que las técnicas que involucran el empleo de las radiaciones ionizantes son herramientas poderosas por sus aplicaciones en la industria, medicina e investigación. Sin embargo su empleo tiene asociados riesgos, los cuales hay que evaluar con objeto de prevenirlos y limitarlos.

La rama del conocimiento que nos permite evaluar los mecanismos de deposición de energía y de ahí estimar los efectos producidos por la radiación, tanto en la materia inerte como animada, es la dosimetría. En esta *el sistema de magnitudes operativas ICRU* es empleado con fines de protección radiológica (PR). Cuyo propósito es hacer una estimación de la *Dosis Equivalente Efectiva* H_E y/o de la *Dosis Efectiva E* ; propuestas en los *sistemas de limitación de dosis* ICRP 26 e ICRP 60, respectivamente.

La discusión que presentaremos a continuación **es válida estrictamente para dosimetría de haces externos con fines de protección radiológica en maniquíes que simulan el tórax humano**[1] .

2.- SISTEMA DE MAGNITUDES DOSIMETRICAS.

2.1.- Magnitudes Dosimétricas Propuestas por el ICRP.

La Comisión Internacional de Protección Radiológica (ICRP) desde 1928 hasta la fecha, ha publicado recomendaciones en protección radiológica tanto para trabajadores ocupacionalmente expuestos como de el público en general. Recomendaciones que han evolucionado hasta lo que se conoce como *sistema de limitación de dosis*, cuyo propósito es evitar los *efectos determinísticos* y limitar la aparición de los *estocásticos*.

Dada la necesidad de introducir una magnitud dosimétrica que con fines de protección radiológica que nos permita estimar *efectos estocásticos* y más particularmente los relacionados con la inducción de cáncer. En 1976 ICRP, publicó las recomendaciones denominadas ICRP 26, que entre otras define el *sistema de limitación de dosis*, donde establece

[1] Aunque los conceptos se pueden extender a otros órganos como extremidades y piel.

los valores límite de 50 mSv/año (POE) y 5 mSv/año (público en general). Límites válidos tanto para exposiciones producidas por campos externos como internos al cuerpo humano.

Es interesante hacer notar que en la publicación ICRP 26, jamás definió la H_E, sino es hasta 1978 en las llamadas recomendaciones de Estocolmo que el ICRP aclara que la magnitud dosimétrica sobre la cual basó sus recomendaciones se simbolice como H_E, y se le denomine : *Dosis Equivalente Efectivo*. Esta situación creo muchas confusiones las cuales desafortunadamente han persistido hasta la fecha. De hecho es importante hacer notar las diferencias que existen entre H y H_E, y establecer la forma correcta de estimar la H_E , ya que ambas magnitudes no son medibles.

Posteriormente, de una revisión de la dosimetría de los bombardeos atómicos en Japón se determinó una corrección de los modelos dosimétricos y epidemiológicos que sustentaron al ICRP 26, conduciendo a un nuevo *sistema de limitación dosis* dado por el ICRP 60 en 1990. Este establece nuevas recomendaciones y definiciones, entre otras define la *Dosis Efectiva E*, en sustitución de H_E y una reducción a los valores del *sistema de limitación de dosis* para E de 20 mSv/año (POE) y 1 mSv/año (público en general).

Finalmente en 1996 el ICRP en su publicación 74, suministró un conjunto de *factores de conversión* que permiten relacionar el *sistema de magnitudes operativas ICRU* con las magnitudes dosimétricas de los *sistemas de limitación de dosis ICRP*.

2.2 El Sistema de Magnitudes Operativas ICRU.

En 1985 la Comisión Internacional sobre Unidades y Medidas en Radiación (ICRU), publicó el ICRU 39, donde propone el *sistema de magnitudes operativas*:

Las *magnitudes dosimetricas ambientales*: la *Dosis Equivalente Ambiental* $H^*(d)$ y la *Dosis Equivalente Direccional* $H'(d)$; y las *personales*: la *Dosis Equivalente Individual Superficial* $H_s(d)$ y la *Dosis Equivalente Individual a Penetrante* $H_p(d)$.

Más tarde, en 1988 el ICRU publica el reporte ICRU 43, donde se da la justificación física del sistema de magnitudes operacionales propuesto. La cual consiste en comparar los valores obtenidos por simulación de Montecarlo, en diferentes *maniquíes* (MIRD-5, Adam, Eva, *Esfera ICRU*) con diversos ángulos de incidencia, energía y tipo de radiación, para: $H^*(d)$, $H'(d)$, $H_s(d)$ y $H_p(d)$ con respecto a H_T, H_E. También da información de *coeficientes de conversión* para obtener los valores de las *magnitudes operativas* respecto de la X, K o la *fluencia*.

En 1992 el ICRU publica el ICRU 47, donde simplifica las magnitudes personales a una sola: la *Dosis Equivalente personal* $H_p(d)$. Además establece los procedimientos de medida para realizar y reproducir las *magnitudes operativas* en los diferentes instrumentos empleados en PR. Especificando en detalle los *factores de conversión* y los distintos *maniquíes* que se deben emplear en las *pruebas tipo* y calibración de los dosímetros personales.

Finalmente en 1992 el ICRU 51, unifica el sistema de magnitudes dosimétricas ICRU con el *sistema de limitación de dosis ICRP 26 y 60*, vía el *sistema de magnitudes operativas ICRU*. Aclarando la relación que existe entre los factores Q, Q_T y W_R.

3.- IMPLEMENTACION Y ADOPCIÓN DE LAS MAGNITUDES ICRU .

A continuación presentamos algunos hitos relevantes en normativas reguladoras en PR, tanto México como a nivel internacional respecto a las magnitudes dosimétricas:

- En 1988, se publica en Diario Oficial de la Federación el Reglamento General de Seguridad Radiológica, el cual se basa en las recomendaciones del ICRP 26.

- El OIEA se pronunció sobre el posible rol que la red de laboratorios Secundarios de Calibración Dosimétrica (SSDL), pueda jugar en la implementación de el *sistema de magnitudes operativas*. [1].

- A finales de 1991 la Comisión de Electrotécnia Internacional (IEC), publicó la norma IEC-1066, sobre dosimetría personal y ambiental, donde se hace uso explícito del *sistema de magnitudes operativas ICRU.*

- En 1993, se actualiza norma sobre dosimetría personal ANSI N13.11 (USA), donde el punto relevante es el la aceptación del *sistema de magnitudes operativas* para realizar el servicio de dosimetría personal en los Estados Unidos.

- La Comisión Nacional de Protección Radiologica y Medidas (NCRP) de Estados Unidos, público en 1995 el reporte 122, donde recomienda la medición en los dosimétros personales de la magnitud operativa *Hp*, como la magnitud adecuada para estimar E o H_E.

- El Organismo Internacional de Normalización (ISO) publicó los proyectos de actualización de la norma ISO 4037-I.II.II, sobre calibración de dosímetros personales y de área, donde se adopta el *sistema de magnitudes operativas ICRU.*

- A finales de 1995 y todo 1996, se propusieron un conjunto de proyectos de Normas por parte de Secretaria de Salud, con el objetivo de reglamentar en México las aplicaciones de las radiaciones ionizantes en sus diversas modalidades: radiodiagnóstico, medicina nuclear y radioterapia. Desafortunadamente, en este conjunto de proyectos y normas, en la parte correspondiente a PR, no se hace mención alguna al *sistema de magnitudes operativas ICRU.*

- La Comunidad de países Europeos, desde finales de la década de los Ochenta ha sido la promotora de la adopción del sistema de magnitudes operativas, por ejemplo en Inglaterra el servicio de PR en sus plantas nucleares es realizado en base a la magnitudes ICRU.

4.- PERSPECTIVAS Y CONCLUSIONES.

Concluyendo, H_E y E no son magnitudes medibles, no obstante ellas evalúan el riesgo de presentarse los efectos estocásticos por exposición a la radiación ionizante; tampoco H es una magnitud medible, pero determina la efectividad biológica de los diferentes tipos de radiación en PR; por lo tanto, estas magnitudes deben estimarse vía modelos de cálculo.

De tal manera que las condiciones de su simulación deben corresponder lo más posible a las condiciones de uso y calibración radiológica de los instrumentos (*pruebas tipo*). De ahí que sea necesario contar con métodos y/o procedimientos para establecer las relaciones entre las magnitudes dosimétricas medibles (D, K, X o Φ) y las que no lo son. Siendo esta relación suministrada por el *sistema de magnitudes operativas ICRU.*

Dados los antecedentes mencionados, algunos profesionales dedicados a la protección radiológica, vemos la necesidad de convocar a las principales instituciones nacionales que tienen que ver con el uso y reglamentación de las radiaciones ionizantes, a una suma de acciones conjuntas que tengan como propósito lograr la implementación en México del llamado *sistema de magnitudes operativas ICRU.*

- Pedir al SSDL-ININ-México la trazabilidad a éste sistema de *magnitudes operativas*; y en especial de manera prioritaria para radiación γ, dado su amplia aplicación en la República Mexicana.

- Pedir a las instituciones de investigación y enseñanza que ofrezcan cursos de postgrado en Física Médica, la inclusión dentro de los planes de estudio el tema de las *magnitudes operativas.*

- Pedir a las instituciones reguladoras o docentes (que acrediten o impartan cursos de PR) la *actualización de los programas de estudio*, de tal forma que incluya tema de *las magnitudes operativas*, con el propósito de *capacitar y actualizar* adecuadamente a los encargados y responsables de PR.

- Pedir a las instituciones reguladoras involucradas en la expedición de normativas con fines de PR, modifiquen las normativas existentes y consideren en sus proyectos de normas el uso de este *sistema de magnitudes operativas.*

Es preocupante observar que ninguno de los organismos nacionales involucrados en los anteriores puntos se ha pronunciado por la adopción del *sistema de unidades operativas ICRU*, sin embargo, *ha habido pronunciamientos por adoptar las recomendaciones del ICRP 60.* Esta situación es muy grave ya que antes de adoptar una reducción en el *sistema de limitación de dosis,* es necesario implementar el sistema de *magnitudes operativas ICRU*, puesto que éste es la única manera confiable de poder cumplir con dichos *sistemas de limitación de dosis.*

El hecho de proponer la adopción en México de el *sistema de magnitudes operativas ICRU* es una decisión meditada, ya que es necesario contar con información confiable para realizar estudios epidemiológicos sobre los efectos de la radiaciones ionizantes a bajas dosis.

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EVALUATION OF IRRADIATION DOSE OF THE POPULATION IN REPUBLIC OF MOLDOVA FROM NATURAL AND ARTIFICIAL SOURCES

A.Andriesh[1], I.Bahnarel[2], A.Buzdugan[1], Iu.Chiruta[2], A.Hustuc[2]
[1)] Academy of Sciences, Nr 3/2 Academiei str., Chisinau MD-2028, Republic of Moldova
[2)] National Scientific Center for Hygiene and Epidemiology, Nr 77a Asachi str., Chisinau MD-2028, Republic of Moldova

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Abstract
Irradiation of the population in Republic of Moldova is a result of joint action of two categories of sources, natural and artificial.

1. Natural irradiation

Natural irradiation refereed to collective doses represents the main source of the irradiation of the population, and determines the natural background of the irradiation of the population in Republic of Moldova. Because of the increased level of the technologic component of natural irradiation (discharges in the environment of the products of burning of the fuel at thermo-electric power stations and transport, building materials including these, which contains industrial wastes, etc.), it is necessary to reevaluate periodically the values of the exposure to natural radioactive background, in accordance with evolution of the dozimetric methods and measurement equipment and technologies.

Exposure which is caused by cosmic radiation (for ionizing and neutronic components) has been estimated by means of Bouville formula. The equivalent of the effective dose, due to external gamma irradiation has been calculated on the bases of averaged specific concentrations of U-238, Th-232 and K-40, which have been determined by means of gamma multichanal spectroscopy in representatives samples of soil from the territory of the Republic of Moldova. We have used the following parameters according to UNSCEAR recommendations: 1.3 for the ratio internal/external irradiation, 0.8 for internal occupancy factor, 0.2 for external occupancy factor and 0.7 Sv/Gy for dozimetric factor.

For Republic of Moldova for average latitude and height we have estimated the exposure due to cosmic component of radiation to be 0.35 mSv/year and the exposure due to gamma-terrestrial component to be about 0.376 mSv/year. When estimating these parameters we have taken the value 0.8 for the buildings screening coefficient and 0.8 for the occupancy factor. So, one individual of the population from the Republic of Moldova receives in averaged the effective dose equivalent about 0.726 mSv due to cosmic irradiation and terrestrial gamma-irradiation, which represents about 29% from the overall natural irradiation. It was determined that about 50% of the terrestrial irradiation is caused by radioactive components of Th-232. Investigation of the content of natural radionuclides in food products has been performed both in separate dishes and standard menus. The effective dose equivalent have been estimated with application of standard dose coefficients, recommended by ICRP-30.

The major contribution to internal irradiation is due to ingestion of K-40 and long-lived descendent of Radon, Po-210, with 0.162 mSv/year and 0.084 mSv/year respectively (Table 1). The effective dose equivalent per caput, due to the annual ingestion of natural radionuclides is approximately 0.266 mSv/year. In order to evaluate the irradiation of the population in Republic of Moldova due to inhalation of Radon, Thoron and their descendants with short lifetime, we have examined the main materials, used in Moldova for buildings construction. We also have carried out measurements of the dose growth and the concentration of Radon and Thoron in 374 flats, representing all types of buildings. Investigation of the content of natural radionuclides in building materials has been performed by means of multichanall gamma spectroscopy. The concentrations

of Radon descendants' with short lifetime (Pb-218, Pb-214, Bi-214) and of Thoron (Pb-212, Bi-212) have been determined by means of aspiration of aerosols on the filter, with subsequent multiple measurements of the radioactivity of particles deposited on the filter. Measurements of the influx of the dose have been carried out with an universal dosimeter.

Table 1
Internal irradiation caused by the ingestion of natural radioactive elements in the period of 1989-1993 in the Republic of Moldova

Radioactive elements	Integrated averaged activity, (Bq/year)	Dose factor, (mSv/Bq)	EDE (mSv/year)
K-40	29931	0,0054	0,162
Ra-226	16,0	0,610	0,009
Pb-210	23,0		
Po-210	20,0	1,58	0,084
Th-232	2,3	2,6	0,006
U-238	6,6	0,75	0,005
TOTAL			0,266

Table 2
Irradiation related to inhalation of descendants of Radon and Thoron* with short lifetime

The source	Space	Concentration of descendants (Bq/m^3)	EDE (mSv/year)	
			internal	external
Rn-222 + descendants	in the house	24	1,195	
	in the open air	5,3		0,094
			1,289	
Rn-220 + descendants	in the house	0,8	0,196	
	in the open air	0,08		0,017
			0,213	
Total			1,391	0,111
			1,502	

*) The equivalent concentration in equilibrium of Radon.

The investigations confirmed that the main part of specific radioactivity of natural radionuclides gives building materials made from industrials wastes (ashes, slag, etc.) In this case the activity exceeds the maximal admitted level by 1.4-2 times, and it is always higher then the activity of local natural limestone materials (sand, gravel, stone, etc.).

Utilization of materials made from industrial wastes (ashes, slag, etc.) in buildings construction leads to an additional exposure of the population to radiation due to an increased concentration of Radon, Thoron and their descendants with short lifetime. All the local materials used for production of construction materials exhibit a radioactivity below the actual standard levels.

Maximum concentration of Radon in rooms air has been registered in the houses which have been built with utilization of industrial waste materials (ashes, slag, etc.) The highest dose growth (83 nGy/h) have been also detected in that rooms, which have been built with utilization of industrial waste materials.

We have estimated the value of EDE per caput related to inhalation as 1.50 mSv/year which represents 60.0 % of the natural background (Table 2). When determining these parameters we have used the dosimetric parameters recommended by UNSCEAR: internal occupancy factor 0.8 and external occupancy factor 0.2 The irradiation caused by the descendants of Thoron is 6 times lower as the irradiation caused by the descendants of Radon (Table 3).

2. Irradiation from artificial sources

The individual doses, related to exposure to artificial sources of irradiation are very different. In most of the cases their magnitudes are rather low, but sometimes, for example in the case of nuclear accidents, irradiation caused by these sources is hundred or thousands of time higher than the irradiation caused by natural sources. One such an example is the Chernobyl accident. The main artificial sources of irradiation in republic of Moldova are: medical radioactive diagnosis, nuclear medicine, radiotherapy, radioactive depositions and professional irradiation. The magnitudes of the irradiation doses, related to medical radiological X-ray procedures differ essentially from one country to another, they even differs in the framework of the same country, from one radiological service to another. The average annual EDE related to medical radiological diagnosis has been evaluated to be about 0.588 mSv/year. This value shows that radiological diagnosis constitutes the main source of artificial irradiation of the population. It occupies a separate place not only because of the magnitude of population irradiation dose but also because exposure of the population by these sources is not controlled by the legislation of the Republic of Moldova.

A significant role to ambient pollution in Republic of Moldova have played the nuclear accidents. The Chernobyl accident had a major impact on the ambient. Because of meteorological conditions the discharge of radioactive materials in the ambient affected large areas in Europe including all the territory of Republic of Moldova. The discharge of enormous quantities of radioactive substances has lead to contamination with radioanuclides of ambient and of food products which determined an additional internal and external irradiation of the population in Republic of Moldova.

The major weight in the overall irradiation of the population in Republic of Moldova after the Chernobyl accident belongs to the period of first year after the accident. So, the EDE for the 1st year after the accident was estimated to be about 3.478 mSv for infants and 1.73 for adults. These figures represent overestimated values of the irradiation because they include irradiation due to consumption of the milk in May 1986 with an enhanced content of radioactive Iodine-131. The minimum values of EDE (for the period May - June 1986) are estimated to be 2.387 mSv for infants and 1.53 for adults (with the condition of elimination of the milk from the food menu). After 1986 the annual average EDE has decreased considerable to 0.034 mSv in 1990, which represented less than 1% from total irradiation of the population of Republic of Moldova. In Republic of Moldova the exposed medical personnel constitutes more than 90% from total personnel of Republic of Moldova exposed to ionizing radiation.

Investigation of radioprotection and of radiological service, of nuclear medicine and radiotherapy in medical units have been carried out with application of general and individual dozimetry methods with utilization of dosimeters LTD model. The average annual DE per caput associated to professional irradiation in the Republic of Moldova constitutes < 0.001 mSv/year. These data show that medical irradiation in the Republic of Moldova constitutes the main source of irradiation from artificial sources. The major weight (about 60%) of medical irradiation represents medical radiological diagnosis, which constitutes also one the of main sources of irradiation of the population. The final results of estimation of population irradiation in Republic of Moldova from natural and artificial sources are presented in Table 3.

Table 3
The annual averaged effective dose equivalent for the population in Republic of Moldova

Source of irradiation	Average annual EDE (mSv/year)			(%)
	internal irradiation	external irradiation		
A. Natural				
- cosmic irradiation	-	0.35		10.1
- gamma terestrial	-	0.376		10.8
- ingestion (K-40, U-238, Ra-226)	0.266	-		7.7
- inhalation (Radon, Thoron +descendants)	1.502	-		43.3
SUBTOTAL:	1.768	0.726		
			2.494	71.9
B. Artificial				
- medical radiological diagnosis	-	0.588		16.9
- nuclear medicine	0.007	-		0.2
- radiotherapy	-	0.38		10.9
SUBTOTAL:	0.007	0.968		
			0.975	28.0
C. Professional irradiation	-	0.001		< 0.1
TOTAL: Republic of Moldova	1.775	1.695		
			3.47	100.0

3. Conclusions

1. The average annual EDE for the population in Republic of Moldova constitutes 3.447 mSv.
2. The major weight in population irradiation (~71.9%) refers to natural sources.
3. The main natural source of irradiation is Radon, and the main artificial source of irradiation is medical radiological diagnosis.

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What is "ionizing radiation"?

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Manfred Tschurlovits, Atominstitut der Österreichischen Universitäten

Stadionallee 2, A-1020 Wien, Austria

Abstract

The scientific background of radiation protection and hence "ionizing radiation" is undergoing substantial progress since a century. Radiations as we are concerned with are from the beginning defined based upon their effects rather than upon the physical origin and their properties. This might be one of the reasons why the definition of the term "ionizing radiation" in radiation protection is still weak from an up to date point of view in texts as well as in international and national standards. The general meaning is unambiguous, but a numerical value depends on a number of conditions and the purpose. Hence, a clear statement on a numerical value of the energy threshold beyond a radiation has to be considered as "ionizing" is still missing. The existing definitions are, therefore, either correct but very general or theoretical and hence not applicable. This paper reviews existing definitions and suggests some issues to be taken into account for possible improvement of the definition of „ionizing radiation".

1. Introduction and background

Ionizing radiation as we are concerned with is from the beginning defined upon the causation of certain effects rather that on their physical properties of the sources. In the very beginning, standards were concerned with either x-rays or radiation- (rather radium) sources /NB 31/, and there was little need to coin a common term for the effects of these sources. Later a more consistent approach was required as the standards were dealing with both x-ray and radioactive radiation sources. Therefore, a common term was needed to describe the radiation the standards are concerned with in a more general form as this was done by "ionizing" as by ICRP 1955. At this time there was no real need for a more precise definition than on the ability of a certain radiation to "ionize". Although other issues undergo an enormous development with time, the definition of ionizing radiation remained unchanged. This might be one of the reasons why the definition of the term "ionizing radiation" is still weak in texts as well as in international and national standards. The general meaning is unambiguous, but all definitions avoid consistently a clear statement on a numerical value of the energy threshold beyond a radiation is to be considered as "ionizing".

Occasionally, other definitions were made in order to fulfil particular requirements, e.g. for measuring quantities. Since the recent European Standards introduce a new definition, it seems due to review the basis of the definitions. This is because in radiation protection standards dealing with "ionizing radiation", a clear statement what radiation in terms of energy they are concerned with is still generally avoided. This might be acceptable in scientific texts or papers, where a scientific dispute and a case oriented interpretation can be expected. However, this does not apply to legal issues as international or national standards, where a legal and pragmatic interpretation is carried out by definition.

2. Some more or less recent definitions on ionizing radiation and their properties

The following definitions and statements can be found in some relevant standards and textbooks. Original supplementary paragraphs to the definitions are in italics.

ICRP 1955: Ionizing Radiation: electromagnetic radiation (x-ray or γ-ray photons or quanta), or corpuscular radiation (α-particles, β-particles, positrons, neutrons and heavy particles) capable of producing ions.

BEIR (1980): Radiation is **directly ionizing** if it carries an electric charge that directly interacts with atoms in the tissue or medium by electrostatic attraction. **Indirect ionizing** radiation is not electrically charged, but results in production of charged particles by which its energy is absorbed. *It takes about 34 eV of energy to produce a ionization. Most human exposures to radiation are of energies of 0.05 - 5 million electron volts (MeV) - energies at which many ionizations occur as the radiation passes through cells.*

ICRU 33 (1980): *Ionization* is a process in which one or more electrons are liberated from a parent atom or molecule or other bound state. Ionizing radiation consists of charged particles (for example, positive or negative electrons, protons or other heavy ions) and/or *uncharged* particles (for example, photons or neutrons) capable of causing ionization by primary or secondary processes. *However, the ionization process is not the only process by which energy of the radiation may be transferred to a material. A second important phenomenon is excitation, a process which can also have physical, chemical, or biological consequences. A radiation, such as low energy photons, may be ionizing in one medium but not in another. Hence, the choice of a suitable cutoff, below which a radiation is considered as non-ionizing, will depend on circumstances. The definitions given in this report apply to a specified fixed cutoff value where relevant.*

DIN 6814 (1980) Ionisierende Strahlung ist eine Strahlung, die aus Teilchen besteht, die ein permanentes *Gas* unmittelbar (direkt) oder mittelbar (indirekt) durch Stoß zu ioniseren vermögen. Der Begriff „Teilchen" umfaßt in dieser Norm Korpuskeln (Teilchen und Ruhemasse) und Photonen (Teilchen ohne Ruhemasse). *Eine bestimmte Teilchenenergie als Grenze zwischen nichtionisierender Strahlung (zum Beispiel sichtbares Licht) und ionisierender Strahlung läßt sich nicht angeben, da die zur Stoßionisation benötigte Energie auch von der Art des ionisierten Gases abhängt. Die in der Radiologie angewendeten Strahlungen haben im allgemeinen Teilchenenergien oberhalb 1 keV und gehören dehalb eindeutig zu den ionisierenden Strahlungen.*

ATTIX (1986) Ionizing radiations are generally characterized by their ability to excite and ionize atoms of matter with which they interact. *Since the energy needed to cause a valence electron to escape an atom is of the order of 4 - 25 eV, radiations must carry kinetic or quantum energies in excess of this magnitude to be called "ionizing". As will be seen, this criterion would seem to include electromagnetic radiation with wavelengths up to about 320 nm, which includes most of the ultraviolet (UV) radiation band (~ 10 - 400 nm). However, for practical purposes these marginally ionizing UV radiations are not usually considered in the context of radiological physics, since they are even less capable of penetrating through matter than is visible light, while other ionizing radiations are generally more penetrating.*

Austrian Standards ON A6601 (1995): Ionisierende Strahlung: Photonen- oder Teilchenstrahlung, die in einem *Gas* durch Stoß direkt oder indirekt Ionen erzeugen kann. *In dieser Definition wird Strahlung mit einer Energie über 5 keV als ionisierende Strahlung festgelegt. Eine physikalische Abgrenzung zu nichtionisierender Strahlung ist nicht möglich, weil die Ionisation vom Material abhängig ist.*

INTERNATIONAL BASIC SAFETY STANDARDS (1996) For the purpose of radiation protection, radiation capable of producing ion pairs in biological material(s).

EURATOM Guideline (1996): Ionizing Radiation: The transfer of energy in the form of particles or electromagnetic waves of a wavelength of 100 nm or less or a frequency of 1.10^{15} Hz or more capable of producing ions directly or indirectly.

It can be seen that some definitions are most general, some refer to a certain material or to certain conditions. The definitions referring to a gas are intended mainly for the purpose of measuring external radiation.

Regarding the most recent EURATOM definition, it can be concluded:

a) ionizing radiation is not a transfer
b) since ionization is by mainly by collision processes, an energy corresponding to a wavelength has to be converted to a kinetic energy of particles. This calculation leads to the following numerical figures. A wavelength of 100 nm corresponds to:
   * 6 eV for electrons
   * about 10^{-7} eV for neutrons (corresponding to a temperature of <1 K) and protons
   * even less for α-particles
   * 12,4 eV for photons.
c) the wavelength chosen is just the border to radiation which is considered as non-ionizing.

The EU- definition seems not applicable also for some other reasons because the standards covers at the low energy end a much smaller range of energy than the definition of ionizing radiation. It is not advisable to include radiations with certain properties into standards without guidelines applicable for these properties. Since a definition in a formal standard shall keep the possibility of misinterpretation from a formal point of view as low as possible, this definition has to be changed. A definition as in the Intenational BSS is sufficient and reasonable for that purpose and should be adopted as it is.

3. Proposal

This paper is not intended yet to suggest a reasonable final definition, but some aspects regarding the low energy end will be addressed.

The most pragmatic approach for defining a lower energy cutoff is to take just the binding energy as the energy required to produce an ion pair. The lowest binding energy is in the order of 4 eV for some elements as Cs, Rb, K, Na, Li, which are not relevant for biological effects. Elements being more important as H, C, O, N have corresponding energies of about 12 eV. However, a particle carrying an energy numerical equal to the binding energy is unable to produce ions, because the incident energy E produces in competing processes ions, excited states, and subexcitation atoms, the yield between the competing processes being energy dependent. For example, it has been shown (ICRU 31 p. 29) for electrons in air that the energy required to produce an ion pair in air is about 33 eV for a particle with an incident energy of 100 eV or more, but more than 1 keV for a particle with an incident energy of less than 15 eV.

However, from a scientific point of view, the present situation as described above is not satisfactory, and an agreement on a numerical value has to be found. However, a single figure will not meet all requirements. This is because a sequence of processes take place until a ion pair which might be relevant for a **possible biological effect** is produced under given circumstances.

a) The energy of the initial radiation must exceed the binding energy of the valence electron E_0 of a relevant atom.
b) Only a certain fraction of the initial energy leads to ionization
c) The initial radiation must be capable to penetrate the relevant material (as air and body tissue) to reach the site where the ionization might take place.

d) Ionization takes place only with certain probability (as the cross section for indirect ionizing radiation).
e) The density of the material have to be taken into account (as biological tissue is different than gases)
f) Geometrical and exposure conditions influence the energy required to produce ionization

The requirements of **measurements** of external exposure lead to different constraints than the conditions above. The situation is quite similiar to different approaches of operational and limiting dose quantitites)

Conclusions

It was shown that the present definitions of „ionizing radiation" are either general and hence vague or not applicable. It is therefore required to define for certain exposure conditions well founded definitions to satify both radiological as well as measuring requirements

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"LOW DOSE" AND/OR "HIGH DOSE" IN RADIATION PROTECTION: A NEED TO SETTING CRITERIA FOR DOSE CLASSIFICATION

Mehdi Sohrabi
National Radiation Protection Department &
Center for Research on Elevated Natural Radiation
Atomic Energy Organization of Iran, Tehran

ABSTRACT

The "low dose" and/or "high dose" of ionizing radiation are common terms widely used in radiation applications, radiation protection and radiobiology, and natural radiation environment. Reading the title, the papers of this interesting and highly important conference and the related literature, one can simply raise the question; "What are the levels and/or criteria for defining a low dose or a high dose of ionizing radiation?". This is due to the fact that the criteria for these terms and for dose levels between these two extreme quantities have not yet been set, so that the terms relatively lower doses or higher doses are usually applied. Therefore, setting criteria for classification of radiation doses in the above mentioned areas seems a vital need. The author while realizing the existing problems to achieve this important task, has made efforts in this paper to justify this need and has proposed some criteria, in particular for the classification of natural radiation areas, based on a system of dose limitation.

In radiation applications, a "low dose" is commonly associated to applications delivering a dose such as given to a patient in a medical diagnosis and a "high dose" is referred to a dose in applications such as radiotherapy, mutation breeding, control of sprouting, control of insects, delay ripening, and sterilization having a range of doses from 1 to 10^5 Gy, for which the term "high dose dosimetry" is applied [1].

In radiation protection and radiobiology, although the terms "low dose" and "high dose" are frequently used, they have been rather vaguely defined, mainly based on the domain of the application and the researcher's interest. Some criteria used for the term "low dose" include: dose levels experienced with typical occupational (below allowable dose limits) and medical diagnosis exposures [2]; or 1 mSv y^{-1}, the dose limit for public as a practical meaning of low level neutron monitoring [3]; or a small cumulative dose, e.g. under 10 rem (0.1 Sv) [4]; or low dose effects such as single traversal of charged particles through individual cells [5]; or low dose radiation cancer risks for doses < 20 cSv (rem) [6]; or doses above background levels yet below that which could induce acute effects usually associated with cell death [7]; or a dose level below which control of radiation exposures would be deliberately and specifically curtailed which must be below any established limit for specific practices, known as *"de minimis dose"* [8]; etc.

On the other hand, the term "high dose" in radiation protection and radiobiology has been considered a level for which the radiation risk is clearly detrimental, the scene being dominated by the detrimental effects, e.g. death via the acute radiation syndrome [9]. By considering a "low dose" in the ranges given above, and a "high dose" when the effect is detrimental, the range between them has not yet been classified and the doses between are usually referred relative to a "low dose" or a "high dose" level. Even the term "low dose" in radiobiology based on a single traversal of a charged particle through the nucleus of a cell, while it can be considered a "low dose" when averaged over the whole volume, it will be a "high dose" when only mass of the volume of the affected area around the trajectory of the particle is concerned.

The term "high level" has also been commonly applied to natural radiation environment, where the potential exposure is even few times higher than that of normal background areas. For example, the exposures even between 15 to 30 μR h^{-1} with small peaks between 35 and 45 μR h^{-1}, as it is in Fichtelgebirge, Germany, have been considered high [10], as compared to 9 mR h^{-1} in some areas in Ramsar, Iran [11]. This has been a common practice based on which at least four international conferences on high level natural radiation areas (HLNRA) have been organized [12]. Using the term "high level" is in fact not always a justified practice and it can cause radiophobia among public living in areas not having high enough exposures to be classified as a real HLNRA. So, for biological and epidemiological studies, it has been also necessary to set criteria for classification of natural radiation environment based on potential exposures and/or internal and external exposures of the public.

For a HLNRA, some criteria have also been proposed. For example, a HLNRA has been characterized as an area where one or more parameters such as the exposure rate over an extended area, long-term alpha activity ingested or inhaled, radon concentration of potable water, and ^{222}Rn and ^{220}Rn levels in air are higher than certain levels, and a population higher than 1000 [13,14]. The NCRP has used the term "unusual exposure", i.e. a level different from the mean with concerns for values above the mean [15].

For a radon prone-area, the criteria given by ICRP include an area with more than 1% of dwellings having radon concentrations more than 10 times the national average value [16]. The NRPB in UK has used the term "affected area" rather than "radon-prone area" and has expressed it as an area within which a certain percentage of present and future dwellings might exceed a predetermined action level and from which certain consequences would follow [17]. Also Scott [18], selecting one of the three concepts for radon-prone areas he proposed, defines a radon-prone area as an area where the average risk (radon concentration) to public is high enough to justify an action program.

The above criteria or definitions more or less have classified only two extreme classes of "low" and "high" doses with no levels defined between them. Also, the levels should be defined specific for each area including: (i) radiation applications, (ii) radiation protection and radiobiology, and (iii) natural radiation environment. One approach is to classify the whole dose range into four dose classes: e.g. "low dose", "medium dose", "high dose" and "very high dose". Setting such criteria will provide: (1) Standardized levels for dose classes for harmonized worldwide studies, (2) Proper classification of; (i) radiation applications for implementation of regulatory practices; radiation protection and radiobiology for harmonized radiation effect studies and for proper setting of criteria for protection of workers and public, and (iii) natural radiation environment for biological and epidemiological studies and risk assessment, implementation of remedial actions, prevention of radiophobia, and uniform protection of public, (3) Establishment of a regulatory system and framework for implementation of regulatory practices, and (4) Worldwide harmonization of radiation protection implementation and regulatory practices.

In radiation applications, the four dose classes, for example, may be defined based on type of sources, type of applications (e.g. medicine and industry), and potential exposures involved. In radiation protection and radiobiology, the four dose classes may be defined: for example, up to the ICRP dose limit for workers as a "low dose"; from this level to a dose of a few hundred mGy from which measurable health effects can be detected as a "medium dose"; and from this level to a dose where health effects are clearly shown as a "high dose", and above this level which can considered lethal as a "very high dose". The above are just some examples given and further research are underway for more specific classifications.

For natural radiation areas, another criteria have been proposed [19,20], applying the annual global average effective dose of 2.4 mSv y^{-1} from normal background areas of UNSCEAR [21], as well as the ICRP dose limits [22], based on which four dose classes have been defined as follow:

1. A "low dose natural radiation area" (LDNRA) or a "low level natural radiation area" (LLNRA); an area or a complex of dwellings where the cosmic radiation, and cosmogonic and terrestrial radionuclides in soil, outdoor air, indoor air, water, food, etc. lead to exposures and/or radioactivity levels causing an internal and/or external public exposure, which falls below or is equal to two times the average global annual effective dose from natural sources given for example by UNSCEAR [20]; i.e. 2 x 2.4 = 4.8 or $\approx$ 5 mSv y^{-1} or a dose level $\leq$ 5 mSv y^{-1}. No remedial action is recommended for such LLNRAs although some simple measures can always mitigate the national average annual effective dose.
2. A "medium dose natural radiation area" (MDNRA) or a "medium level natural radiation area" (MLNRA); an area or a complex of dwellings where cosmic radiations, and cosmogonic and terrestrial radionuclides in soil, outdoor air, indoor air, water, food, etc. lead to exposures and/or radioactivity levels causing an internal and/or external public exposure which is higher than the upper limit for LLNRA, or 5 mSv y^{-1}, but it falls below or is equal to a pre-established level or limit; for example the dose limit of 20 mSv y^{-1} for radiation workers [21]. A remedial action is required to be implemented within a time frame to be determined; for example within 5 years.
3. A "high dose natural radiation area" (HDNRA) or a "high level natural radiation area" (HLNRA); an area or a complex of dwellings where cosmic radiation, and cosmogonic and terrestrial radionuclides in soil, outdoor air, indoor air, water, food, etc. lead to exposures and/or radioactivity levels causing an internal and/or external public exposure which is higher than 20 mSv y^{-1}, the upper limit for a MLNRA, but it falls below or is equal to, for example, 50 mSv y^{-1}, the former ICRP dose limit for radiation workers. A remedial action should be implemented subject to a regulatory control within a time frame to be calculated; for example within one year.
4. A "very high dose natural radiation area" (VHDNRA) or a "very high level natural area" (VHLNRA); an area or a complex of dwellings where the cosmic radiation, and cosmogonic and terrestrial radionuclides in soil, outdoor air, indoor air, water, food, etc. have exposures and/or radioactivity levels to lead to an internal and/or external public exposures higher than the upper limit for a HLNRA; i.e. 50 mSv y^{-1}. Evacuation is recommended as the first step in the remedial action program to be enforced by a regulatory authority.

Based on the criteria proposed, some areas in the world known as HLNRA have been tentatively classified as LLNRA or MLNRA. The criteria can also be easily applied as a regulatory framework and a system for implementation of remedial actions, and for biological and epidemiological studies. They can also be directly applied to define radon-prone areas and to classify them accordingly.

In conclusion, the above proposals are just examples so that other criteria may be further proposed; yet they are open for criticism, improvement, and/or approval to be used as criteria for worldwide use. Further research are underway by the author.

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THERMODYNAMIC THEORY OF PHASE TRANSITION IN BIOSUBSTANCE FROM EXPOSURE TO LOW DOSES OF IONIZING RADIATION

V.D.Rusov, T.N.Zelentsova

Odessa State Polytechnic University
1, Shevchenko av., Odessa, 270044, Ukraine

The synergetic conception of biophysical action of ionizing radiation low doses is offered and on its basis the universal theoretic-analytical expression for functional dependence "dose - effect" in the all range of doses is received. And in the field of low doses the behavior of this dependence is a consequence of phase transition of the first kind in dose-sensitive microvolume and carries the brightly expressed parabolic character, which qualitatively precisely describes all known and most carefully executed experiments in this field.

The analysis of the modern concepts and approaches to an estimation of biophysical action of low doses ionizing radiations has shown, that nowadays there is no uniform standard concept of biological action of low doses ionizing radiations. Used for an estimation of genetic risk of low doses of models based on linear thresholdless concept, carry extrapolation character, have not a strong biological substantiation and enter into the contradiction with available experimental data. The analysis experimentally of observable reactions of a cell to an irradiation allows to make a conclusion, on the one hand, that the laws of an output radiate-induced of biological damages in the field of low doses are characterized by the brightly expressed nonlinearity and have universal character (Fig.1), differing for different objects by meanings of doses, with which there is a change of character of dependence and which are determined by their sensitivity to external influences. With other - to allocate the basic laws, i.e. experimental invariants, observable in problems connected to a quantitative estimation of biological action of low doses ionizing radiations [1]:

- Presence "dose-independed" of a site (II) on a universal curve (Fig.1);
- Linearity of both sites I and III on Fig.1;
- The presence of multiaberrated cells, which number on the order is more expected with low doses;
- Presence at chromatin of the fixed number of conformational conditions, and in the field of low doses the phase transition "globule-ball", connected with decondensation of chromatin, results in increase of a diameter of cell nucleuses [2];
- Even the small change of quantity antiions in a cell is critical for processes of active or passive their transport through membranes, that accordingly results in change of permeability of membranes, which, in turn, can become initiating event causing transition of chromatin in a new stationary condition with inclusion of systems of a reparation of biological infringements.

It is obvious, that the basic experimental laws of an output radiate-induced effects in sensitive microvolume in the field of low doses ionizing radiations as against classical microdosimetry, operating in conditions of stationary processes, are predetermined as changes in time of the geometrical sizes of sensitive microvolume, and changes of their under action ionizing radiations. I.e. in the field of low doses classical microdosimetry has serious restrictions and should be replaced by the concept **nanodosimetry** - microdosimetry in environments with changeable parameters.

Thus, a subject of nanodosimetry should be study of energy absorption fluctuation in sensitive microvolumes and analysis of formation of the appropriate spatial - temporary distributions of the absorbed energy and their characteristics in environments with changeable parameters.

Experimentally revealed in the field of low doses conformational transition, and in the field of low doses the phase transition "globule-ball", caused by decondensation of chromatin, the theory of statistical physics of macromolecules connects to phase transition of the first kind (PT1) [3].

Thus it is accompanied by jump of volume ΔV with increase of temperature, and jump of entropy ΔS, describing a degree of absorption body of the latent heat. Size of jumps ΔS and ΔV rather small, as it is known, that PT1 "globule-ball" is close on the character to PT of the second kind which $\Delta S \to 0$ and $\Delta V \to 0$.

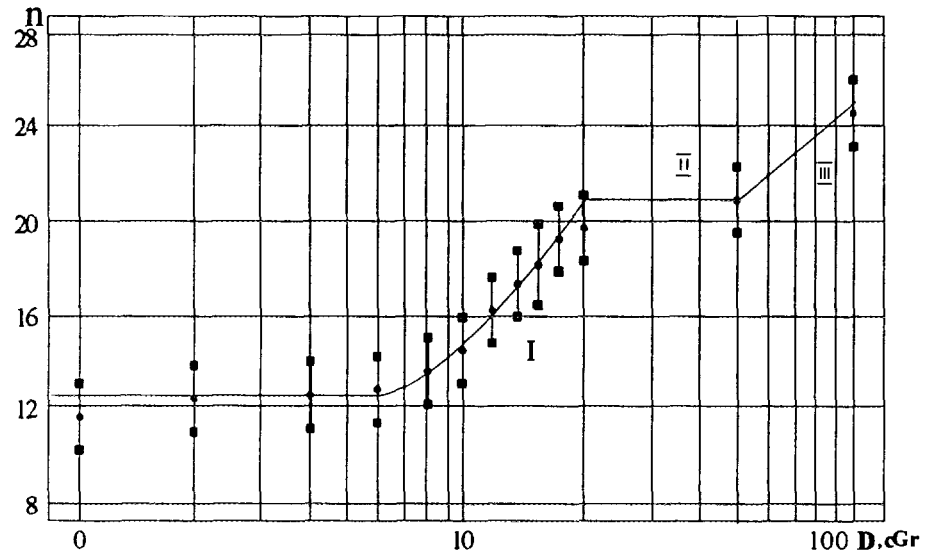

Fig. 1. A universal curve of formation of radiate-induced biological damages in the field of low doses.

The thermodynamic theories allowing quantitatively to describe of change of properties of substances in the vicinity PT1 with small jumps of entropy, close to PT2, is the Landau's theory. This theory concerns only to PT with changes of symmetry within the limits of one (only crystal or only liquid) condition of substance, that is characteristic for discussed microdosimetrical a situation.

In the Landau's theory of the order parameter η, dependent on temperature, contacts to symmetry of substance. Thus in one of phases (as a rule, in a high-temperature phase) the system is not ordered and $\eta=0$. In the ordered phase (it is usual low-temperature) $\eta \neq 0$. Then in conditions, when the properties of phase transition are considered with imposing on a body of an external field h, which physical nature is not principle (in our case, for example, it is a dosing field of ionizing radiations D), and which action depends on value of parameter η for the thermodynamic description PT1 in a case of centresymmetric disorder phase decomposition of thermodynamic potential $\hat{O}(\eta,T)$ on order parameter has (with addition of the member - $hV\eta$) a kind

$$\hat{O}(\eta,T)=\hat{O}_0(T)+\alpha\eta^2+\beta\eta^4+\gamma\eta^6-hV\eta \qquad (1)$$

where $\hat{O}_0(T)$ - meaning of potential in an initial phase; $(\alpha=\alpha_0(T - T_0)$ - by virtue of a minimum $\hat{O}(\eta,T)$, i.e. requirement $\partial^2\hat{O}/\partial\eta^2 > 0$; $\beta<0$, as the character (feature of transition) PT is deter-mined is familiar of factor with η^4 (for PT1 it is negative); and for stability of system the member with η^6, where $\gamma>0$, is necessary to take into account.

The addition to decomposition of the member of a kind - $hV\eta$, according to the theorem of differentiation on parameter, provides performance of a ratio for average meaning

$$V\langle\eta\rangle = -\partial\hat{O}(P,T,h)/\partial h .$$

Then the connection of order parameter (with a field h) is described by the equation of a condition)

$$\partial\hat{O}/\partial n=2\alpha\eta+4\beta\eta^3+6\gamma\eta^5-Vh = 0 , \qquad (2)$$

where $h=D=z_1\langle n\rangle/\varepsilon(d/R_p)$, and role of order parameter $\eta=\rho - \rho_{cr}$ plays connected to an external field macroscopic value ρ - density of nuclear chromatin.

It is necessary at once to note, that the thermodynamic theory does not put a question on a nature of the mechanism causing transition, and simply enters a pair connected variable (in our case, for

example, N and DV for cell nucleuses) and in the equation of a condition, which contains these variable, includes the members of the lowest order.

One of the basic purposes of the present research is the development of the practical recommendations on experimental identification such as phase transitions of the first kind with presence and in absence of an external field [4].

THE ANALYSIS of MODEL η^6 an EXTERNAL FIELD.

With construction of thermodynamic potential $\hat{O}(\eta,T)$, external field, describing influence, (DV) on phase transition, it is necessary to take into account, that the role of order parameter is played macroscopic value η (change of density nuclear chromatin). In this case account of an external field is reduced or to addition to thermodynamic potential of the member η(DV), where DV - the field connected variable η (the equation of a condition then has a usual kind $d\hat{O}/d\eta=0$), or potential is left constant, and the equation of a condition accepts a kind $DV=d\hat{O}/d\eta$.

Let's consider influence of an external field on phase transitions of the first kind, proceeding from expression for potential (1).

Let's note first of all, that already as much as weak field results that parameter η (becomes distinct from of zero in the whole area of temperatures, and, as the consequence, is washed away a discrete point PT on some temperature interval. Let's estimate the order of size of this interval from the requirement hV

$$(T - T_0) \cong D^{2/3} \frac{\gamma^{1/6} |\beta|^{1/6} V^{2/3}}{\alpha_0} \qquad (3)$$

For quantitative research of transition we write a condition of balance

$$2\alpha\eta + 4\beta\eta + 6\gamma\eta = DV \qquad (4)$$

The equation (4) allows to construct the diagrams of dependence of order parameter η from temperature $\alpha=\alpha_0(T-T_0)$ and from a field DV, which are submitted on Fig.2a and Fig.2b.

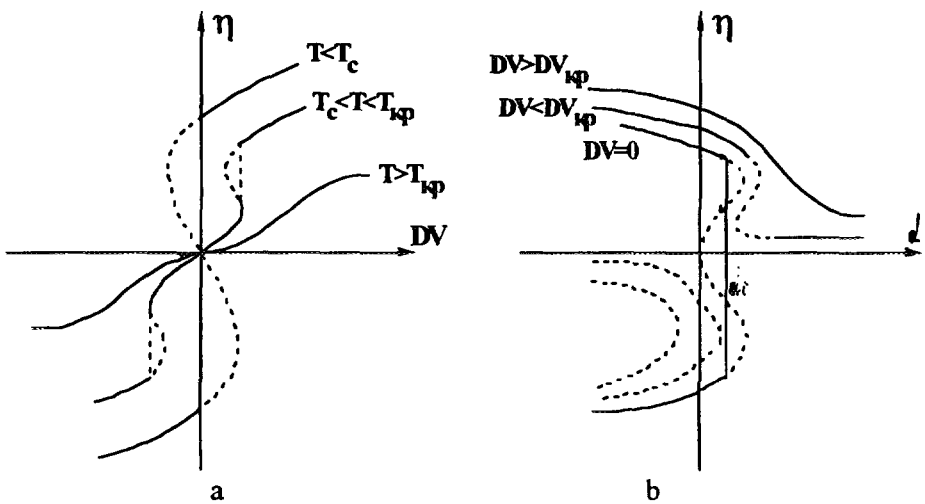

Fig.2. Dependence of parameter η from an external field DV for potential $\hat{O}(\eta,\dot{O})$ (a) and temperature dependence of parameter (for various meanings of a field D (DV > 0) (b). Continuous lines - steady condition, shaped - unstable condition.

The analysis of the diagrams η(DV) and $n(\alpha)$ allow to allocate three temperature intervals:

- $T>T_{cr}$, where T_{cr} is temperature, with which there is an excess on function $\hat{O}(\eta)$. In this interval of temperatures the value η smoothly varies with change of a field and PT is impossible what with meanings D;
- $T_c<T<T_{cr}$, where the T_C - temperature PT1 in absence of a field (D = 0). In this interval on the diagram there are sites with a negative susceptibility $\chi = (\partial\eta/\partial(DV)\ T,\ DV\to 0$, that answers

unstable condition. Hence, in this interval with achievement of some meaning of an external field DV, there will be PT1;

- $T<T_C$ jump of parameter η is observed in a zero field.

The meanings of parameters $\alpha_{cr}$and $(DV)_{cr}$ are from conditions:

$$\partial^2\hat{O}/\partial\eta^2=0,$$
$$\partial^3\hat{O}/\partial\eta^3=0,$$

which answer occurrence of a point of an excess a curve $\hat{O}(\eta)$.

These two equations together with the equation of a condition (4) give system for a finding α_{cr} and $(DV)_{cr}$, from which following meanings easily turn out:

$$(DV)_{cr} = 16\gamma(|\beta| / 5\gamma)^{5/2},$$
$$\alpha_{cr} = 3|\beta|^{2/5}\gamma, \qquad (5)$$
$$\eta^2_{cr} = |\beta| / 5\gamma.$$

To construct the phase diagram in variable α, DV, we shall copy expression for potential $\hat{O}(\eta,T)$ (1) and equation of a condition (4), using expressions (5), in a dimensionless kind:

$$\hat{O}^*=15\alpha\eta^{*2}-5\eta^{*4}+\eta^{*6}-16\eta^*(DV)^* \qquad (6)$$
$$15\alpha^*\eta^*-10\eta^{*3}+3\eta^{*5}-8(DV)^*=0 \qquad (7)$$

The expression (7), into which any sizes describing the given substance do not enter, means some kind of the law of respective condition: dependencies $\eta(\alpha)^*$ (change of density) for dose-sensitivity microvolumes (cells) of one biochemical nature in various fields $(DV)^*$ ionizing radiations differ only in scale of temperature

The basic advantage of the thermodynamic theory of biophysical influence of low doses consists in its mathematical simplicity and in an opportunity of an establishment of connections between various macroscopic parameters of dose-depended phase transition in cell sensitive microvolume.

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ENFORCEMENT OF RADIATION SAFETY STANDARDS AND EXPERIENCE IN THE REGULATORY CONTROL OF EXPOSURES

T.N. Krishnamurthi
Health and Safety Division
Atomic Energy Regulatory Board
Mumbai, India

Abstract

Regulatory provisions for radiation protection and their enforcement in India are discussed in this paper. The rules and regulations framed for radiation safety cover all the nuclear fuel cycle activities as well as the application of radiation sources in industrial, medical and research institutions. The enforcement aspects and experience in the control of exposures are presented.

1. Introduction

Nuclear fuel cycle facilities and industrial, medical and research institutions, using radioactive materials and radiation generating equipment, are the major areas, where regulatory controls are exercised in respect of radiation safety. Nuclear fuel cycle activities in India extend over mining and milling of uranium, processing of thorium, reactor fuel fabrication, operation of nuclear power plants and research reactors, spent fuel reprocessing, recycling of plutonium, decommissioning of nuclear plants and radioactive waste management. Outside of the nuclear fuel cycle, important radiation installations that are brought under regulatory control are gamma irradiators, industrial radiography devices, industrial and medical x-ray equipment, teletherapy machines, medical linear accelerators, brachytherapy equipment, nucleonic gauges and high energy research accelerators. Regulatory consents for these installations are issued, after detailed safety review, in the form of an authorisation for operation or a licence or type approval of equipment or registration. It is estimated that there are about 42000 radiation workers in the country and their occupational exposures are controlled as per the dose limits, stipulated by the regulatory body and are monitored.

2. Regulatory Provisions for Radiation Safety

The national infrastructure required to enforce the radiation protection standards is identified in the IAEA Basic Safety Standards (BSS) [1]. For the control of occupational exposures, the BSS specify the various requirements such as classification of radiation areas and their supervision, use of personal protective equipment, work place monitoring, individual monitoring, maintenance of exposure records, responsibilities and duties of employers and workers. In India, many of the existing legislations fulfill the objectives of the BSS. Some of these legislations were framed 20 years ago that they need changes to incorporate the recommendations of ICRP-60 publication [2] and the BSS of IAEA. In addition, the Competent Authority for radiation protection has published many Codes, Guides and Standards and has also issued Safety Directives, which are binding on the nuclear fuel cycle plants and the users of radioactive materials and radiation generating equipment.

The Atomic Energy Act 1962 provides the basic regulatory framework for all activities related to the atomic energy programme and the use of ionizing radiation in India. The following rules were promulgated under the provisions of the Act :

(i) Radiation Protection Rules, 1971
(ii) Atomic Energy (Working of Mines, Minerals and Prescribed Substances) Rules, 1984
(iii) Atomic Energy (Safe Disposal of Radioactive Wastes) Rules, 1987
(iv) Atomic Energy (Control of Irradiation of Food) Rules, 1996
(v) Atomic Energy (Factories) Rules, 1996

These rules adequately cover radiological safety and specify the requirements of licensing or authorizations, powers to revoke or modify the licences, the duties and responsibilities of Radiological Safety Officers, their qualifications, radiation surveillance procedures, powers of inspection of radiation installations, sealing and seizure of radioactive material.

The Atomic Energy Regulatory Board (AERB), constituted in November 1983, exercises the regulatory and safety functions envisaged under the Atomic Energy Act 1962. Chairman, AERB has been designated as the Competent Authority to enforce the Rules stated above. Some of the other important functions of the Regulatory Board are as follows :

(i) Development of safety codes, guides and standards for siting, design, construction, operation, quality assurance and decommissioning of the nuclear or radiation installations;
(ii) Ensuring compliance with the above regulatory documents by all installations;
(iii) Safety review of the installations for licensing or authorization for specific stages of development of the installations with the aid of design basis and safety reports, results of commissioning tests, quality assurance checks, operating limits and conditions and emergency preparedness plans;
(iv) Stipulation of acceptable limits of radiation exposure to occupational workers and members of the general public and acceptable limits of environmental release of radioactive materials;
(v) Review of training, qualification programme and licensing of operating personnel of the plants;
(vi) Enforcement of Rules and Regulations promulgated under the Atomic Energy Act 1962 for radiation safety;
(vii) Review of operating experience of the plants in the light of radiological and other safety criteria and evolvement of safety policies and
(viii) Keeping the general public informed on issues of safety significance.

3. Regulatory Control of Radiation Installations

AERB enforces radiation safety requirements in institutions using radiation generating equipment or radioactive materials for industrial, medical and research applications. After detailed technical review including quality assurance aspects and measurement of relevant safety parameters, AERB issues Type Approval for radiation generating machines and equipment containing radioactive sources. AERB also issues licences for gamma irradiators and particle accelerators after a review of the siting considerations, design and operational safety features. For all these radiation installations, AERB approves appointment of Radiological Safety Officers, after a review of the qualifications of the applicants and specialised training undergone by them. Issuance of "No objection certificates" for import of equipment containing radioactive substances and radiation generating machines is also undertaken by AERB after examining the applications.

Regulatory requirements for radiation safety are contained in the Radiation Protection Rules 1971. The Rules have provisions empowering the Competent Authority to notify appropriate surveillance procedures. The following surveillance procedures have been notified by the Competent Authority.

(i) Industrial Radiography (Radiation Surveillance) Procedures, 1980
(ii) Radiation Surveillance Procedures for Safe Transport of Radioactive Materials, 1987
(iii) Radation Surveillance Procedures for Medical Applications of Radiation, 1989

In addition, AERB has issued Safety Codes on medical diagnostic x-ray equipment; telegamma therapy equipment; brachytherapy sources and equipment; nuclear medicine laboratories; transport of radioactive materials and emergency response planning and preparedness for transport accidents involving radioactive materials. These codes are supplemented by Safety Guides, published by AERB. Users of radioactive materials and radiation generating equipment are required to comply with these Safety Codes and Guides.

India is one of the few countries which have already taken steps to implement the recommendations contained in the ICRP-60 publication [2], which forms the basis for dose limitation in the BSS of IAEA [1]. Safety Directives were issued from 1991 onwards, reducing the annual occupational dose limit in a phased manner from the previously enforced limit of 50 mSv till 1990. The current dose limits are as follows: (i) the occupational dose to a worker during the five year period 1994-98 shall not exceed 100 mSv and (ii) the dose in any single year of this block shall not exceed 30 mSv.

4. Regulatory Control of Nuclear Fuel Cycle Plants

In the case of nuclear fuel cycle facilities, radiological safety is one of the key areas reviewed by the Regulatory Board for authorisation of the plants for operation. The plant has to submit site related data and analysis important to radiation safety, emphasizing those site characteristics which may influence the design and operation of the plant. Site evaluation report should include information on the interaction of the plant and the environment. Design and operational features provided primarily for protection of the operating personnel from radiation hazards should be submitted for review along with design basis and safety analysis reports. These include containment and ventilation systems, layout and zoning for contamination control, radiation shielding, radiation monitoring systems, personnel monitoring programme, radioactive waste management schemes, post-accident monitoring system, environmental monitoring programme and emergency response plans for on-site and off-site actions. The review also covers the adequacy of trained manpower and training in radiation protection for plant and health physics personnel.

After the plant is authorised for operation, the Regulatory Board reviews the periodic reports on plant performance and radiation safety status and also reports on safety related unusual occurrences. Installations are inspected at periodic intervals by a team of experienced engineers and health physicists. Violations of Technical Specifications in respect of radioactive discharges to environment are examined. AERB is empowered to impose restrictions or suspend operation of the facility in case of non-compliance with AERB's directives, serious violations of safety norms or an unusual occurrence of serious safety significance. Re-commencement of operations after suspension will be permitted only after a detailed review and approval by the Regulatory Board.

Health Physics Units are established at all nuclear facilities to monitor the radiation safety status. These units are administratively independent of the plant management and this scheme ensures total independence in the discharge of their functions. The health physicists are covered by a qualification scheme and are required to pass written examinations, field checklists, walk-through tests and a viva-voce before they are licenced to perform health physics work at the plants.

Environmental Survey Laboratories (ESL) are set up at major nuclear sites for surveillance of environmental radioactivity. Such units have been established at nuclear power plant sites, uranium mining and milling site, fuel fabrication site, monazite/ thorium processing site and at nuclear research centres, where many nuclear facilities are operating. The ESLs carry out comprehensive monitoring of radionuclide content in different environmental matrices from aquatic, atmospheric and terrestrial domains to estimate intake of radionuclides through inhalation and ingestion routes and dose to members of the public.

The periodic reports issued by the Health Physics units and the ESLs on the radiation safety status of the plant and the environment are reviewed by the Regulatory Board.

5. Dose Limits and Control of Exposures

AERB has issued a Radiation Protection Manual for Nuclear Facilities. Recommendations of ICRP-60 [2] and ICRP-61 [3] publications have formed the basis for regulation of radiation exposure of plant personnel as well as members of the public. The Manual lays down guidelines for investigation of over- exposures. Exposure limits to workers in the event of an emergency and intervention levels for various countermeasures in an off-site radiological emergency are provided in the document. All nuclear fuel cycle facilities have implemented the provisions of the Radiation Protection Manual. A summary of dose limits and constraints as stipulated in the Manual is given in Table - I. In addition, a number of Codes, Guides and Manuals have been prepared to provide specific guidance to design and operation of nuclear power plants. These documents cover the areas of nuclear and radiation safety.

TABLE - I

Category	Life-time Effective Dose limit (Sv)	Dose constraints (Cumulative) for medical review (Sv)	Dose constraints (Cumulative) (mSv)	Annual Effective Dose limit (mSv)	Annual equivalent dose limits: Lens of eye (mSv)	Skin (mSv)	Extremities (mSv)
Radiation worker *	1	0.5	100 (in 5 Yrs.)	30	150	500	500
Apprentices and trainees	-	-	-	6	50	150	150
Temporary worker	-	-	-	15	75	250	250
Member of public	-	-	-	1	15	50	-

Note : * For pregnant woman, 2 mSv to abdomen for remainder of pregnancy.

TABLE - II

DISTRIBUTION OF OCCUPATIONAL EXPOSURES

Institutions and year	No. radiation Workers	No. of workers exceeding Annual dose of: 20 mSv	30 mSv	35 mSv	40 mSv	50 mSv
Nuclear Power Plants						
1995	9851	31	1	0	0	0
1996	10090	98	3	0	0	0
Industrial						
1995	5325	25	5	5	5	4
1996	5296	19	7	6	6	6
Medical						
1995	15822	37	11	8	7	7
1996	16069	12	5	4	2	2
Research						
1995	2327	0	0	0	0	0
1996	2397	0	0	0	0	0

6. Analysis of Radiation Exposures

Dose distribution amongst the radiation workers of nuclear power plants and industrial, medical and research institutions handling radioactive materials and radiation generating equipment are presented in Table - II for the years 1995 and 1996.

A standing committee reviewed the radiation exposures exceeding 20 mSv in a year. The cases from nuclear power plants were mostly found to be genuine exposures. In the case of other institutions, most of them were from medical x-ray and industrial radiography units. Critical review of the circumstances and technical factors revealed that in 1995, only 42% of the cases were genuine. About two-thirds of the non-genuine cases were due to negligence of the workers. In many instances, the workers have inadvertently left their personnel dosimeters in the work place. The dosimeters were thus exposed when the workers were not actually in their work places. There were few instances of defective work place layout or work practices. The pattern of over-exposures in 1996 also was almost identical. Better supervision, discipline and education were recommended for controlling the exposures.

7. Conclusion

AERB has established a competent national infrastrucure to enforce radiation protection standards in all nuclear and radiation installations in the country with the result that the occupational exposures of radiation workers have registered a decrease continuously over the last several years. The experience acquired over the years point to further improvements in the radiation safety status of the plants, operating personnel and the public.

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EVALUACION DE LAS ENFERMEDADES ASOCIADAS A LA EXPOSICION PROFESIONAL DE LAS RADIACIONES IONIZANTES

Autor: Ileana Frómeta Suárez
Médico especialista 1er Grado en Higiene
Dpto. Higiene de las Radiaciones. Instituto de Medicina del Trabajo.

RESUMEN

Se realizó un estudio retospectivo de todos los casos atendidos en el IMT por presentar patologías atribuida a la exposición de las radiaciones ionizantes, durante 1990-1995.Se describe la incidencia de estas enfermedades estudiadas y su relación con otros factores. Se constatópredominio de las patologías del sistema hemolinfopoyético en individuos que laboran en radiologídiagnostica.

INTRODUCCION

La Vigilancia Médica a trabajadores ocupacionalmente expuestos permite la evaluación de su estado de salud y se apoya en la realización de examenes médicos pre-empleos y périodicos. Estos estudios masivos se fundamenta en investigaciones médicas con el objetivo de detectar tempranamente desviaciones o desordenes en órganos y tejidos que son particularmente sencibles al daño radiacional como resultado del trabajo con radiaciones ionizantes.1

Dentro del Sistema Nacional de Salud, el Instituto de Medicina del Trabajo (IMT), se desempeña para todo el país como centro de referencia de la atención médica de enfermedades y accidentes que pudieran estar relacionados o no con las condiciones de exposición laboral[2]. En este trabajo se presenta un estudio de todos los casos de trabajadores estudiados con sospecha de presentar patologías de origen radiogénico, se describe la incidencia de estas enfermedades, se determina la existencia o no de relación entre el tiempo de aparición de las patologías descritas con el tipo de fuente, tiempo de exposición y los niveles de dosis registrados durante su vida laboral.

MATERIAL Y METODO

Para la realización del presente trabajo se revisaron todas las historias clínicas(HC) de aquellos trabajadores que bajo sospecha de presentar enfermedades asociadas a la exposición por las radiaciones ionizantes fueron ingresados para estudios especializados en la sala de Enfermedades Profesionales del IMT, durante el período de 1990 a 1995. De las HC se registraron datos referentes a la edad, sexo, profesion, años de exposición, tipo de fuente, diagnostico al ingreso, diagnostico definitivo al egreso y evolución al tratamiento impuesto. Las afecciones estudiadas fueron divididas por grupos calsificatorios. Se estimaron las dosis equivalentes acumuladas y anual promedio para cada individuo durante su vida laboral. Se procedió a un análisis estadistico para cada parámetro analizado.

RESULTADO Y DISCUSION

20 casos fueron estudiados y atendidos durante 4 años en sala. Las patologías encontradas (Tabal I) fueron distribuidas en cinco grupos clasificatorios: enfermedades hematológicas, oftalmológicas, dermatológicas, de tiroide y los casos por estudios especiales por posible contaminación(Cs-137, I-131).

Tabla I.**Distribución de afecciones encontradas según grupos clasificatorios.**

Afecciones por Grupos	No. casos %	Casos por profesion I II III IV V VI
Enferm. Hematológicas Anemias Leucopenias Trombocitopenias	11 55 4 5 2	 4 3 1 1 2
Enferm. Oftalmológicas catarata Trast. nervio optico	2 10 1 1	2
Enferm. Tiroides Adenoma Folicular Nodulo	2 10 1 1	 1 1
Enferm. Dermatológicas Capilaitis cutánea	1 5 1	 1
Estudios por cont. por Cs-137 por I-131	4 10 2 2	 2 2

Nota: I:Tec Rx; II:enfer.Rx; III:radiologo; IV: Tec.radiofisica; V: Tec.geofisica VI: Defectoescopista.

Las enfermedades del sistema hemolinfopoyético se reportaron como las mas frecuentes para el 55% del total, seguidas por los casos ingresados por posible contaminación con un 20%, y en menos cuantía aperecieron las patologías en tiroides y las enfermedades oftalmológicas. En cuanto a las entidades específicas encontradas es de señalar, que las leucopenías, anemias y trombocitopenia constituyeron las patologías mas frecuentes.

En la distribución de los casos según la categoria ocupacional presenta y el tipo de actividad sobresale el número elevado, de trabajadores que laboran en prácticas médicas, 17 que representa el 85% de la muestra. Atendiendo a su profesión, el 70% de los pacientes estudiados laboran expuestos a fuentes ionizantes empleadas en radiodiagnostico médico, profesiones distribuidas entre técnicos de Rx, enfermera y médicos radiológos, el resto representa solo el 30%.

Al analizar el comportamiento de las enfermedades en dependencia de la profesion y tipo de fuente de exposición se puede apreciar que el mayor número de las patologías estudiadas fueron las enfermedades del sistema hemolinfopoyético, estas se manifestaron principalmente en individuos que laboraron expuestos a fuentes de Rx -diagnostico Estos resultados coincide con lo reportado por otros autores[3,4,5].

El análisis de las patologías presentadas en dependencia a los años de exposición y a las dosis equivalentes promedio anuales recibidas se muestran en la tabla II. Se observa que las patologías estudiadas se manifestaron en trabajadores que recibieron una dosis total acumulada que osciló entre 4,58 mSv y 37,74 mSv durante su vida laboral. Estos niveles de dosis corresponden a actividades en condiciones normales de exposición y que se encuentran por debajo del límite de dosis anual establecido (50 mSv) para un año de labor con fuentes de radiaciones ionizantes.

Establecer un criterio que defina una relación entre la aparición de manifestaciones clínicas que anuncien una enfermedad de origen profesional y el tiempo laborado en condiciones de exposición en este estudio, no fué posible, ya que esta relación se comportó de forma variable y no definida en cada uno de los casos.

Tabla II.Distribución de las afecciones según años de exposición y dosis equivalentes acumuladas.

Enfermedad	Rango de dosis equivalente acumulada (mSv)	Años de exposición por caso.
Leucopenía	5,65 - 37.74	7/ 7/ 8/ 17/ 18
Anemia	5,60 - 14,15	8/ 12/ 17/ 18
Trombocitopenía	4,5 - 31,8	10/ 24
Catarata	8,93	14
Adenoma de T.	5,06	12
Nódulo de T.	6,25	10
Trast.nervio opt.	5,48	12
Capilaritis cutánea	9.1	23

De los pacientes atendidos, al 10% se le planteo ineptitud para continuar laborando en actividades que impliquen exposición. A los pacientes con leucopenía(2),anemia(2) y nodulo en tiroide requirieron temporalmente cambio de labor, el 65% se mantuvo en su puesto de trabajo sin hacerse ninguna recomendación al respecto[6].

CONCLUSION

Las enfermedades del sistema hematopoyético se presentaron como las patologías de mayor incidencia entre los trabajadores que laboran expuestos a fuentes de Rx diagnostico médico atendidos en el IMT durante 1990-1995.

La posible correlación entre la enfermedad presentada por los trabajadores con las condiciones de exposición a las radiaciones ionizantes no fué aceptada.

Se reafirma una vez más la importancia de los exámenes médicos como registros cronológicos en la detección precoz de las distintas manisfestaciones clínicas por labores en prácticas con radiaciones ionizantes.

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EXAMENES RADIOGRAFICOS NEGATIVOS EVALUACION DE LOS RIESGOS POR SU EXPOSICION

Frómeta Suárez I*.y Jerez Veguería S. F.**
* Médico especialista en Higiene
**Lic. radioquímica
Dpto. Higiene de las radiaciones.IMT

RESUMEN

La dosis individual de radiación por diagnostico radiológico, a pesar de ser baja, es una contribución importante por el número poblacional expuesto. En este trabajo se presenta un estudio realizado en el Hospital Clínico Quirúrgico "Manuel Fajardo" de Ciudad de la Habana, en el que se evaluó el comportamiento de los exámenes radiológicos negativos, su contribución a las dosis colectiva, así como el detrimento asociado a estas exploraciones.
Se reportaron 5486 casos con exámenes radiográficos indicados en un período de cuatro meses. Se individualizó información, clasificandose por tipo de examen radiográfico y en base al criterio de justificación, en positivos y negativos. Se estimó la dosis absorbida para órgano y tejido irradiado, dosis equivalente efectiva colectiva y la probabilidad de ocurrencia de cáncer fatal, no fatal y daño genético asociado a estas exploraciones.
La negatividad representó el 41 % de los exámenes practicados, para una dosis colectiva de 11.35 Sv.hombre, la cual constituye el 52.9 % de la dosis total aportada por todos los exámenes radiológicos de la población estudiada.

INTRODUCCION

El desarrollo alcanzado por la radiología médica y el incremento sostenido de esta practica en los últimos años, ha posibilitado que el diagnostico radiológico y la radioterapia constituyan en la actualidad la fuente principal de exposición de la población a las radiaciones ionizantes de origen artificial.
El uso cada vez mas frecuente de estas practicas, ha motivado que surja preocupación por la aparición de efectos estocásticos: neoplasias y daños genéticos como resultado de las exposiciones médicas. Esto a dado lugar a que la comunidad científica en materia de protección radiológica se pronuncie por la necesidad de proteger al paciente y limitar estos posibles efectos, promoviendo que estas practicas sean debidamente justificadas si realmente ofrecen beneficio al paciente [1,2].
En nuestro país, durante los últimos años se ha reportado un incremento significativo de exámenes por Rx- diagnostico, y con el criterio de que un alto porciento de estos en su prescripción médica resultan no justificados, pretendemos a través de este estudio conocer la incidencia de exámenes negativos en la practica radiológica, evaluar la dosis colectiva aportada por estos exámenes, así como estimar el detrimento a la salud derivada de estas exposiciones en una institución de salud.

MATERIAL Y METODO

El presente estudio fue conducido en el Hospital Clínico Quirúrgico "Manuel Fajardo" de Ciudad de la Habana con el registro de todos los pacientes con exploraciones radiológicas realizadas, indicadas por consulta externa, cuerpo de guardia y sala durante 12 semanas de 1993. Se

detallaron datos clasificandose por tipo de examen, frecuencia y número de radiografías realizadas.
En base al criterio de justificación para la indicación clínica del estudio radiografico fueron catalogados en positivos y negativos. Positivos se consideraron aquellos exámenes en los que se confirmo la indicación clínica con la información radiografica obtenida, y en los que se diagnosticó una nueva patología no esperada. Negativos, aquellas radiografías clinicamente sin contribución diagnostica y a los exámenes no útiles para establecer diagnostico por empleo de técnicas no adecuadas, defecto en el revelado, o mal estado de las películas.
El análisis se realizo a través de estudio por distribución de frecuencia, por tipo de examen y según la clasificación. Fueron considerados los órganos y tejidos mas irradiados en correspondencia a las técnicas radiograficas empleadas, estimándose para estos la dosis absorbida (mGy). Para el calculo de esta se utilizaron los datos dosimétricos, obtenidos del estudio "Dosis de radiación en pacientes por examen radiológico" [3], que se realizó paralelamente a este trabajo en dicha institución.
Se determinaron la dosis equivalentes, dosis efectiva y dosis efectiva colectiva para cada subgrupo de población expuesta en determinado órgano y tejido. Se evaluó comparativamente la contribución de los exámenes radiológicos negativos a la dosis efectiva colectiva.
Fue estimado el riesgo radiológico que asume esta población, derivado de estas exposiciones por exámenes radiológicos: negativos y positivos, expresado en la probabilidades de inducción de cáncer fatal, no fatal y efecto hereditario[4].

RESULTADO Y DISCUSION

El presente estudio indicó que 5486 pacientes se realizaron exámenes radiograficos, de ellos 2249 (41 %) resultaron negativos, y 3287 (59 %) de los casos resultaron positivos.
La frecuencia de los exámenes radiológicos practicados y el comportamiento de los índices de negatividad según el tipo de estudio radiológico se exponen en la tabla I, de ella se deriva que los exámenes de tórax representan una proporción elevada del total de las exploraciones radiológicos realizados, se destacan los elevados índices de negatividad reportados en los exámenes de colon por enema, urograma y tracto urinario simple (TUS), a pesar de la complejidad de estas técnicas radiograficas y de los criterios clínicos específicos para su indicación.Esta negatividad pudiera ser disminuida con una adecuada selección de criterios clínicos en la indicación.

TABLA I. COMPORTAMIENTO DE EXAMENES RADIOLOGICOS

Tipo de examen	Positivos		Negativos		Total
	No	%	No	%	exámenes
COLON p/ENEMA	101	38.9	158	61.0	259
UROGRAMA	133	46.6	152	53.3	285
TUS	150	43.8	192	56.4	342
EED	399	57.4	295	42.5	694
COLUMNA	435	59.5	295	40.4	730
TORAX	2019	63.5	1157	36.4	3176
TOTAL	3237	59.00	2249	41.00	5486

Los datos dosimétricos son mostrados en la tabla II. Las dosis en órganos para urograma resulta significativo por los altos valores registrados en testículos, ovarios y médula ósea, así mismo son comparativamente bajas las dosis obtenidas durante los exámenes de estómago, esófago y duodeno (EED), en comparación con lo reportado en la literatura [5,6,7]. La diferencia de dosis en estos exámenes es atribuida a la técnica empleada y a la proximidad de algunos órganos al campo irradiado.

TABLA II. DOSIS EN ORGANOS POR EXPLORACIONES RADIOLOGICAS

	DOSIS (mGy)					
EXAMEN	TESTICULOS	OVARIOS	PULMON	MEDULA	TIROIDE	INTESTINO
E.E.D	0.21	O.61	-	0.49	-	0.03
COLON	5.13	6.67	-	9.30	-	0.49
UROGRAMA	35.57	15.27	-	3.40	-	-
T.U.S.	2.46	5.82	-	-	-	-
TORAX	-	- 0.26	-	0.25	-	-
COLUMNA	0.99	- 2.12	0.79	1.11	-	-

La dosis efectiva colectiva aportada por los estudios radiograficos fue estimada en un valor de 21.58 Sv/hombre. La dosis derivadas de los exámenes radiológicos negativos reportaron un 11.35 Sv/hombre del total de la exposición, lo que representa el 52.9% de la dosis colectiva de esta población (tabla III) por lo que constituyen estos exámenes una contribución significativa importante al valor de la dosis colectiva obtenida.

TABLA III. DOSIS EFECTIVA COLECTIVA Y DETRIMENTO COLECTIVO

Dosis efectiva colectiva(SV-hombre)		Riesgo radiológico 10-2 Sv-1 No. de casos Cáncer fat.	No fatal	Efec. Genet
Expuestos a examenes negativos	11.35	-	-	-
Población total	21,5	1	-	-

La estimación de riesgo para esta población estudiada predijo que existe la probabilidad de que un caso de cáncer fatal sea atribuido por la exposición médica. No se reporto posible caso de cáncer no fatal y efecto hereditario. Para los expuestos por exámenes radiológicos que resultaron negativos en la expectativa no se estimo ningún caso, influyendo a nuestro criterio los bajos niveles de dosis registrados en órganos por tipo de examen, el tamaño de las muestra y los nuevos valores de los factores de riesgo propuesto por la ICRP [6].

CONCLUSIONES

Se reportó alto índice de negatividad, lo que indica la necesidad de profundizar las valoraciones clínicas, validas para la indicación de un examen radiológico.
Las dosis derivadas de exámenes radiológicos negativos incide significativamente en los valores de la dosis efectiva colectiva de la población.
Si bien la expectativa matemática para exámenes radiológicos negativos descartó la posibilidad de cuantificar los riesgos radiológicos en este estudio, no se descarta la existencia de riesgos individuales a menos que las dosis sean cero.

Es necesario promover entre los médicos facultativos los conocimientos y la cultura radiológica necesaria, para reducir el número de radiografías rutinarias y las dosis colectivas derivadas de estas exposiciones.

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CYTOGENETIC STUDIES ON NEWBORNS FROM HIGH LEVEL NATURAL BACKGROUND RADIATION AREAS OF KERALA COAST, SOUTH INDIA

Cherian, V.D., Kurien, C.J., Birajalaxmi Das, Karuppasamy, C.V., Ramachandran, E.N., Thampi, M.V., Joseph, B., George, K.P., Aravindan, K.V., Kesavan, P.C. and Chauhan, P.S.
Monazite Survey Project and Cell Biology Division, Biosciences Group, BARC, Mumbai, India.

ABSTRACT

The human population residing in the monazite bearing high level natural background radiation (HLNBR) areas of Kerala, along the South-West coast of India provides unique opportunities of assessing directly in man, the health effects of chronic low-level radiation exposure. The per capita dose received by this population is nearly four times the normal background radiation level. While this is the average dose, the radiation levels prevailing in these HLNBR areas are in the range of 1 to over 35 mGy per year. Chromosomal aberration studies in the lymphocytes of newborns and adults from these areas have been in progress for two decades. So far, 4156 newborn babies from HLNBR and 7321 from normal background radiation (NBR) areas have been screened for the incidence of chromosomal aberrations (dicentrics and rings). The mean frequency of dicentrics and rings did not show any significant difference between the newborns in the control and the HLNBRA population. Assessment of the frequency of micronuclei in cytochalasin-B blocked binucleated lymphocytes of 49 newborns from control areas and 131 newborns from radioactive areas also showed similar values. While an age-dependent increase in chromosome aberration frequency was observed in the adult samples from control and the study areas, the regression analysis of the data indicated a marginally higher slope for the samples from HLNBRA. Karyotype anomalies recorded so far among the newborns have not revealed any significant difference in the incidence of numerical (including Down syndrome) and structural alterations between the control and the exposed populations. A noteworthy observation, herein reported for the first time from any HLNBR area is that there is no discernible increase in the incidence of micronuclei and chromosomal aberrations in the peripheral lymphocytes of newborn babies hailing from HLNBR areas, where their ancestral generations have lived for several hundreds of years.

INTRODUCTION

There is growing scientific interest, as well as controversy, over the relationship between health effects in humans chronically exposed to low doses of ionizing radiation at extremely low dose rates over prolonged period of time. The usual approach for assessment of low level radiation hazard is to extrapolate linearly to zero dose from well documented effects observed with high doses at high dose-rates. However, the validity of such extrapolation has remained unestablished in the absence of any statistically reliable evidence of detrimental effects of radiation at low doses [1]. On the contrary, the accumulating evidence of radioadaptive responses, the mechanisms of which are being currently elucidated, shows that effects elicited by low and high doses of radiation are not only diverse, but can be entirely counteracting [2,3,4]. Therefore, direct human studies pertaining to low level radiation exposures assume profound significance and these are also more appropriate for consideration of risk assessment to occupational workers. The inhabitants of the high level natural background radiation (HLNBR) areas, a coastal strip situated along the west coast of Kerala State in South India, serve as an ideal population to evaluate the possible biological and health effects of low level chronic radiation in a large human population. The radioactivity of these monazite bearing HLNBR areas (about 55 km long and 0.5 km. wide) is primarily due to thorium (also traces of uranium) content ranging from 8-10.5%, the highest reported in the world. ^{232}Th and its decay products contribute to the

elevated background radiation levels. The radiation belt is frequently interrupted by stretches which do not contain monazite deposits and thus have normal background radiation (NBR) levels. Historical records of this coastal strip indicate that it has been inhabited for over several centuries. Eversince, the importance and necessity of assessing the biological and health impact of HLNBRA in the Kerala coast was emphasised in a WHO meeting in 1959 [5], several investigations pertaining to dosimetry, cytological and radiochemical studies on different plant species and demographic and health studies in human populations have been undertaken [6-10]. Gruneberg et al. in a comprehensive study found no evidence of any genetic effects in the black rats, (Rattus rattus) trapped from the monazite belt [11-12]. Dosimetric studies show the average background radiation level prevailing in this area to be around 4 times the normal, with a wide range from 1 to over 35 mGy per year.

A field laboratory located at site in Kollam, adjoining the HLNBR areas has been pursuing a comprehensive programme for assessment of biological and health effects of radiation on human population for several years. Studies on the incidence of chromosomal aberrations in lymphocytes of newborns and adults (including young, adult and aged group of men and women) from NBR and HLNBR areas , which form part of the continuing programme of the Monazite Survey Project, are summarised in this communication.

MATERIALS AND METHODS

Metaphase preparations were made from short term *in vitro* PHA stimulated whole blood cultures employing standard microculture techniques. The slides were coded and stained in lacto-aceto-orcein or Giemsa. About 80-100 well spread metaphases were scored for dicentrics, rings, acentric fragments, minutes, translocations, inversions as well as chromatid aberrations like gaps and breaks. The incidence of dicentrics and rings are presented here, while detailed analysis of the total cytogenetics data are underway for critical evaluation. All major chromosomal aberrations were cross checked by each of the five cytogeneticists engaged in this project. Micronuclei (MN) were scored in cytochalasin-B blocked binucleated lymphocytes using cord blood samples with standard procedures as reported elsewhere [4]. From the coded slides stained in Giemsa, about 5000 binucleate lymphocytes have been analysed for each sample.

RESULTS AND DISCUSSION

Studies in Newborns : The data on the frequency of dicentrics and rings from a total of 11477 newborns, with 7321 samples (628960 cells) analysed from NBR and 4156 samples (360089 cells) from HLNBR areas, available so far, have been presented in Table I. The frequency of dicentrics and rings per cell was 1.84×10^{-4} in NBR and 1.92×10^{-4} in HLNBR samples. Thus, the incidence of chromosome aberrations in the newborns do not indicate any significant difference between the samples from normal and HLNBR areas. Considering the fact that a substantially large number of newborns have been analysed, it is highly unlikely that further increase in sample size will basically alter the observed trend. However, categorisation of the newborns of the HLNBR areas showed a very marginal upward trend with increase in the radiation levels. Both from HLNBR and NBR areas about 77% pregnancies occurred in women below 25 years of age and 97% below 30 years. In fact, less than 0.5% deliveries occurred among women above 35 years of age.

TABLE I. DICENTRICS AND RINGS AMONG THE NEWBORNS

Area	No. of Samples	Cell Analysed	Dicentrics + Rings	
			No.	Frequency*
NBRA	7321	628960	116	1.84 ± 0.17
HLNBRA	4156	360089	69	1.92 ± 0.23

* Dicentrics and rings per cell ± S.E x 10^{-4}

Data on the incidence of micronuclei (MN) in cytochalasin-B blocked binucleated lymphocytes of newborns presented in Table II, also do not indicate any significant difference between the samples from NBR and HLNBR areas, the frequency of micronucleated cells being 1.14×10^{-3} and 1.12×10^{-3} per binucleate cell, respectively. A slightly higher frequency of MN was observed in the female babies as compared to the males, thereby suggesting, as reported by others that sex can be one of the variable affecting the spontaneous frequency of micronuclei. Although, reports on the frequency of MN in adults have been published in literature, there is a paucity of such data among the newborns. To our knowledge no report on chromosome aberrations or micronuclei in the lymphocytes of newborns has been published from any HLNBR area, so far.

TABLE II. MEAN FREQUENCY OF MICRONUCLEATED LYMPHOCYTES AMONG NEWBORNS.

Area	No. of Samples	Cells Analysed	No. of Micro-nucleated Cells	Frequency*
NBRA	49	239734	266 (311)	1.14 ± 0.76
HLNBRA	131	602001	657 (740)	1.12 ± 0.76

Figures within parenthesis denote total number of micronuclei. * Micronucleated cell per binucleate lymphocyte ± S.D x 10^{-3}.

Studies in adults : The limited data available so far from 582 adult subjects include 279 (47727 cells scored) from NBR and 303 samples (53092 cells) from HLNBR areas. The frequency of dicentrics and rings observed among the samples of different age groups of adults have been presented in Table III. The incidence of dicentrics and rings in the lowest age group (≤ 20) is slightly, but not significantly, higher in the HLNBR as compared to the NBR population. The chromosome aberration frequency increased from 7.07 ± 2.89 to 26.13 ± 6.16 in the NBR population and from 10.44 ± 2.46 to 27.78 ± 16.0 per cell x 10^{-4} in the exposed population across the different age groups. In the NBR samples, a marked increase in aberration frequency was observed in the age group of ≥ 60 yrs., while in case of HLNBR it was higher from 40 years onwards. The highest age group in HLNBR suffers from the limitation of small sample size at present. A linear regression analysis of the data (the frequency of dicentrics and rings plotted against increasing age) showed a reasonable correlation with slightly higher slope for the HLNBR samples ($Y = 0.3414 x + 2.8022$, correlation coefficient = 0.845) as compared to NBRA ($Y = 0.2977 x + 0.8112$, correlation coefficient, = 0.7552). The initial tendency for increase in dicentrics and rings in the ≤ 20 yrs. age group was not seen in the 21-40 yrs of age group. The age dependent increase in chromosome aberrations is in confirmity with the reports in literature.

TABLE III. DICENTRICS AND RINGS IN THE LYMPHOCYTES OF ADULT SUBJECTS OF DIFFERENT AGE GROUPS.

	N B R A			H L N B R A		
Age Group	No. of Samples	Frequency*	Mean Age ± S.D	No. of Samples	Frequency*	Mean Age ± S.D
<=20	47 (8484)	7.07 ± 2.89	15.3 ± 5.2	98 (17244)	10.44 ±2.46	13.9 ± 4.5
21-40	150 (25062)	9.98 ± 1.99	27.7 ± 4.8	150 (25561)	9.78 ± 1.96	28.2 ± 5.9
41-60	41 (7293)	9.60 ± 3.63	50.5 ± 5.5	48 (9207)	16.29 ± 4.21	48.4 ± 5.5
> 60	41 (6888)	26.13±6.16	72.9 ± 9.1	7 (1080)	27.78 ± 16.0	65.0 ± 3.7

Figures in parenthesis denote number of cells analysed. * Dicentrics and rings per cell ± S.E x 10^{-4}.

During the metaphase analysis for chromosomal aberrations in the newborns, both numerical and structural karyotype abnormalities (KA) were recorded. A total of 65 variants (31 numerical and 34 structural) have been scored among 11,477 newborns. The overall population frequency of KA is 0.56%, with 0.59% in NBRA and 0.53% in HLNBRA. Analysis of karyotypic variants is being pursued by G-banding to identify the inter and intra chromosomal rearrangements. The 8 cases of Down Syndrome, so far confirmed are all primary trisomies with an overall frequency of one DS in about 1640 births. However, the number of individual karyotypic anomalies is still too small, and a sufficiently larger data base will be required to make any reliable estimates. In this context, it is important to mention that the state of Kerala with highest literacy in India, has lowest infant mortality and smallest family size. The total number of births from the HLNBR areas are also less due to relatively smaller population size in the limited HLNBR areas than the NBR areas. The studies are designed to continue for the next several years to obtain a satisfactory number of live borns from HLNBR areas for rigorous comparisons.

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SCIENTIFIC RESEARCH AND REGULATORY CONTROL: AN INTERACTION THAT MUST BE REVIEWED

Yannick Nouailhetas, Arnaldo Mezrahi, Carlos E. Bonacossa de Almeida and Ana M. Xavier.

Comissão Nacional de Energia Nuclear (CNEN), Diretoria de Radioproteção e Segurança.
Superintendência de Licenciamento e Controle.
R. General Severiano 90, Botafogo, CEP 22294-900, Rio de Janeiro, RJ - Brazil

Abstract

The control of radiological impact, in Brazil, at nuclear facilities is based on radiological protection guidelines adopted by the Nuclear Energy National Commission (CNEN), following recommendations of the International Commission on Radiological Protection (ICRP), Publication 26. ICRP adopted "prudently", for radiological protection purposes, the hypothesis, in case of stochastic effects, of linearity dose/effect, without dose threshold, based on absence of conclusive data concerning the real behaviour of dose/effect curve. Additionally, the position of ICRP is not sustained specially considering as non existent individually accumulated doses, accumulated doses through generations and origin of radiation, either natural or anthropogenic. Brazil follows ICRP recommendations despite existing high background radiation areas. In absence of a definitive position, professionals of different areas, such as jurists and psychologists infer on "effects of radiation", no matter it exists. ICRP should: clarify as being just operational linearity hypothesis; consider that an excess of prudence can cause a non-sense public rejection to nuclear applications; incentive participation of different fields scientists to elaborate radiological protection procedures and radiological protection scientists to develop researches based on realistic data. Finally, it would be possible to achieve a new philosophy for public protection considering real risks associated with exposure to radiation.

The control of radiological impact, in Brazil, at nuclear fuel cycle (uranium) facilities and at processing plants of thorium is based on radiological protection guidelines adopted by the Nuclear Energy National Commission (CNEN), elaborated according the recommendations of the International Commission on Radiological Protection (ICRP), Publication 26 [1]. Thus, annual limits for effective equivalent doses for workers and individuals of the public as well as ALARA principle were established. Processes of Licensing, involving: Site Approval, License of Construction, Authorization for the Use of Nuclear Material and Authorization for Initial and Permanent Operations, are required by the Brazilian Regulatory Body, in each one of its stages. Reports of the Site as well as Preliminary and Final Safety Analysis Reports are demanded from the operators and they should contain the required information established in specific Norms [2-4]. The occupational and environmental monitoring programmes are periodically surveilled by CNEN. The scientific justification for the magnitude of the limits recommended by ICRP and for the effort to minimize the exposures, initially to "as low as reasonable achievable", gave rise to the adoption, for radiological protection purposes, of the hypothesis of linearity dose / effect, without dose threshold, in the peculiar case of stochastic effects. The prudence demonstrated by ICRP, when the hypothesis was adopted, was based on the absence, at the time of its adoption, of conclusive data related to the real behaviour of the dose / effect curve. Additionally, its posture contributed significantly to the promotion of the use of nuclear energy in the world [5].

Geologically, Brazil, a continental country, is characterized by presenting anomalies that create a significant variation in the exposure rates to which the public is submitted [6,7]. As in other areas of the world, in which high levels of natural radiation occur, if biological effect exists, it is not, at present, sufficiently significant to allow its characterization through scientific methodology. The origin of biological effects of radiation begins with the transfer of nuclear energy carried by photons, alpha and beta particles, during the decay process, to electrons of atoms that constitute biological molecules. If the transferred energy of the nuclear particles is higher than the binding electron energy of the target atom, the electron will be ejected of its orbit, giving origin to a pair of ions and to the induction of biological responses, independently of the origin of the radiation: either anthropogenic or natural [8]. According to ICRP, if the resulting effects of sub-clinical doses capable to induce deterministic effects, are cumulative, public living in an environment with high natural radioactivity would present a previous disposition to develop stochastic effects, potentially and linearly with the accumulated doses. If this public has to be additionally exposed to radiation from human activities, the " problem " would certainly be worsened. However, in the recommendations of ICRP, the base line for the management of doses in public considers both the individually accumulated doses and the accumulated doses through generations as non existent. Within this context, the dose management is restricted in public to anthropogenic activities. Even for public exposed to high levels of natural radiation, what means a considerable amount of dose accumulated over generations, the National Nuclear Energy Commission, following the recommendations of ICRP, is equally restrictive, i.e., never takes into account if public is being exposed to a lower or higher level of natural radioactivity. Considering that biological effects result from interactions that happen, in an individual and aleatory way, at atomic level, in each one of the cell that receives the radiation energy, independently of the origin of this energy, if natural or anthropogenic, the position of ICRP, on a scientific basis, is not sustained: the adoption of the hypotheses of the linearity dose / effect and the absence of dose threshold would imply that the probabilistic previous disposition of damage coming from natural exposures should be considered in the effort to protect public against harmful effects of the radiation originated from anthropogenic activities. The non inclusion of doses accumulated due to the natural radioactivity in the risk assessment is a strong indication that even adopting the hypothesis of the absence of dose threshold for probabilistic effects, aiming radiological protection, the ICRP has perfect knowledge that, in fact, the subject of the low doses continues open, with great probability that it does not result in any significant effect. This understanding corroborates to the fact that, with all the prudence demonstrated by ICRP regarding low doses from anthropogenic activities, if there were any suspect of effect due to naturally accumulated doses, this effect would be taken in consideration in the recommendations of that Commission.

Apart from the radiological protection principles, and its motivations, and analyzing the subject exclusively considering its scientific aspects, it can be stated that: (i) for doses lower than 200 mSv effects of radiation that result in damages to the health of individuals or public as a whole are not observed [6,9] (ii) for accumulated doses much greater than 200 mSv, over a life time period, higher rates of neoplastic illnesses were not confirmed [10]. On the contrary, there is evidence that some benefit could result from exposure to significant doses of radiation [11]. Besides the conviction that ICRP has perfect knowledge of the lack of scientific consistency of its recommendations, the available evidence in the specialized literature does not seem to be sufficient to the authorities in the field of radiological protection to trigger the reviewing of more than fifty years of "well established" posture. This situation reflects the isolation in which ICRP and correlated organisms have being maintained during decades. As a result, only few research institutions in the world have the knowledge on radiological protection, with only a small number of researchers having an idea of what "Sievert" means. The great majority of laboratories qualified to investigate the relationship dose / effect and to define new approaches, other than the "well known" epidemiologic studies, hereditary effects and cancer, believe firmly, corroborating the official position of the world authorities in radiological protection, that: (i) to any absorbed dose, a significant increment of probability is

associated with the risk of cancer development and (ii) this is a definitive position. The claim for research in this subject drops into emptiness, since the radiological protection principles just reach professionals of this specific area, for which the subject can be summarized by the sole observation of radiological protection guidelines. Unsurprisingly, the lack of a definitive position with respect to individual radiation exposure is being fulfilled by professionals of different areas, not related with radiation, such as jurists and psychologists. Those professionals undertake, then, the responsibility to evaluate the consequences of low radiation exposures. In the absence of an objective posture on the above mentioned effects, the jurist assume that the effects actually exist. Created the juridical fact, in the lack of technical basis, the justice should pronounce the sentence upon the compensation, needed or not, for a damage to the health arisen from radiation, according the judge approach [12]. Psychologists start to treat "radiophobic" patients, independently of any significant exposure, since the trauma is real [13,14].

Facing the evolution of the subject, ICRP should take an aggressive attitude, placing clearly for the scientific community that the hypothesis of the linearity dose / effect is just a operational hypothesis, that was established in order to allow radiological protection to accomplish its purpose: the use of nuclear energy without risk for the health. It should be clarified however, that the same prudence that allowed the mentioned use can result in non-sense public rejection to all nuclear applications. In order to avoid total discredit of the exact sciences, with respect to their positioning about the effects of the low radiation doses, ICRP should also incentive scientists, not directly linked to the radiological protection subjects to contribute for the elaboration of radiological protection procedures. From now on, the radiological protection should be no longer based on hypotesis but on data obtained through scientific methods: elaboration of realistic hypothesis followed by experimental tests and finally, the thesis that should be the basis for a brand new philosophy for protection of public against the real risks associated with exposure to ionizing radiation.

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FORMACIÓN Y COMUNICACIÓN: Nexo de unión entre el investigador, el regulador y el profesional

M. Marco (Instituto de Estudios de la Energía-Ciemat).

L. Arranz (Sociedad Española de Protección Radiológica).

Abstract

In a constant flow of new information over the past years, the relationship between scientific knowledge and the application of such knowledge has profoundly changed. Communication between the various professional sectors has to keep abreast with the rapid development in order to arrive at a common understanding of the researcher, the legislator, the expert and the public. Ways towards this end are described.

INTRODUCCIÓN

La relación entre el conocimiento científico y las aplicaciones de estos conocimientos ha experimentado en los últimos años cambios profundos. El flujo constante y novedoso de información en el campo de la biología, la protección radiológica y la seguridad, desde el investigador al técnico y regulador y desde éste a los especialistas y usuarios viene siendo constante en los últimos tiempos.

Los avances en el conocimiento de los efectos biológicos radioinducidos y sus mecanismos de acción en los seres vivos, ya sean deterministas o estocásticos, han conducido al desarrollo de nuevos coeficientes de riesgo para cánceres y efectos hereditarios debidos a la exposición a fuentes de radiación [1].

La difusión de las normas de P.R. especialmente los aspectos revisados en la normativa europea y su transposición a las nacionales, es uno de los objetivos más importantes de las actividades relacionadas con la comunicación y en especial con la formación.

En esta situación toman especial relevancia centros como el Instituto de Estudios de la Energía (IEE) y las Sociedades profesionales tales como la Sociedad Española de Protección Radiológica (SEPR) por el importante papel que juegan en los diferentes procesos de la comunicación desde una posición puente entre el investigador, el legislador, el profesional y el público.

Nexo con el investigador.

La seguridad en el uso de las radiaciones y los riesgos debidos a la exposición a las mismas, no es un concepto estático, su evolución corre paralela al mejor conocimiento sobre los fenómenos básicos. La formación unida sustancialmente a la investigación intenta transmitir estos avances entre el grupo de científicos y técnicos.

El IEE y la SEPR, han hecho un importante esfuerzo en identificar a los expertos nacionales del sector y en mantener un constante vínculo de comunicación con ellos a través de la organización de seminarios, workshops, debates o conferencias sobre temas puntuales y concretos, facilitando el intercambio de información entre los distintos grupos de investigación. Como ejemplo, podemos citar el curso sobre "Avances en radiobiología" organizado conjuntamente por la SEPR y el CIEMAT, en colaboración con el Consejo de Seguridad Nuclear en mayo de 1997. En él se ha analizado el estado actual del conocimiento de los efectos producidos en los seres vivos tras la exposición a dosis bajas y bajas tasas de dosis, profundizando en el conocimiento de los efectos estocásticos (cáncer y efectos hereditarios) [2].

Los estudios de estimación del riesgo de cánceres debidos a bajas dosis provienen de la información obtenida, de la exposición ocupacional y la debida a accidentes, de la investigación con animales, de la exposición médica, y la estimada a través de modelos extrapolados. La escasa información disponible procede en su mayor parte de estudios

epidemiológicos que presentan grandes incertidumbres. Estas se reducirán a medida que se conozcan mejor los mecanismos de respuesta de los tejidos a la radiación mediante la investigación sobre efectos celulares y moleculares.

Estos estudios a bajas dosis resultan de gran importancia para tres tipos de poblaciones, los trabajadores expuestos a radiaciones, los pacientes sometidos a diagnóstico médico (con especial énfasis, en las mujeres embarazadas) y la población.

Nexo con el regulador:

La información científica básica se utiliza como referencia para la elaboración de las normas de protección frente a los riesgos de la exposición a radiaciones ionizantes. Nueva información científica conduce necesariamente a la actualización del marco legal especialmente el que se refiere a la exposición a las radiaciones.

La sociedad demanda mayores acciones de educación y formación tanto inicial como contínuada. En este sentido, la SEPR y el IEE, en colaboración con otros organismos afectados, organizaron un debate abierto entre los profesionales de diferentes sectores, sobre las implicaciones de la nueva Directiva Europea de Normas Básicas de Protección Radiológica en nuestra legislación.

Los aspectos de especial relevancia tratados durante el seminario [3] se pueden resumir en:

- Ampliación del ámbito de aplicación a actividades laborales que supongan una exposición significativa de los trabajadores o del público a fuentes de radiación natural.

Los aspectos de especial relevancia tratados durante el seminario [3] se pueden resumir en:

- Ampliación del ámbito de aplicación a actividades laborales que supongan una exposición significativa de los trabajadores o del público a fuentes de radiación natural.
- Las intervenciones en situaciones de exposición prolongada.
- La exención y desclasificación de materias radiactivas.
- La rejustifiación de prácticas.
- La restricción de dosis como factor fundamental en la optimización.
- Los nuevos límites de dosis, la asignación de la dosis interna en términos de límites básicos.

Posteriormente se debatieron en foros los aspectos legislativos, los ocupacionales y del público.

AVANCES EN RADIOBIOLOGIA

- Bases de Biología molecular y celular.
- Lesiones moleculares del DNA.
- Radiación y cáncer.
- Efectos hereditarios.
- Dosimetría biológica.
- Accidentes y lesiones radioinducidas.
- Riesgos radiounducidos.
- Epidemiología.

PRESENTE Y FUTURO DE LA PROTECCION RADIOLÓGICA

- Presentacion de la nueva directiva europea. Aspectos más significativos.
- Nueva Directiva: su historia y problemática.
- Aspectos ocupacionales y del público.
- Aspectos legislativos.

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CYTOGENETIC EFFECTS OF IN VITRO IRRADIATION OF HUMAN SPERMATOZOA

R. MIRÓ, A. GENESCÀ, R. ÁLVAREZ, L. TUSELL, I. PONSA
Department of Cell Biology, Faculty of Medicine,
Universidad Autónoma de Barcelona,
Bellaterra, Spain

Abstract

The effects of human mutagens, clastogens and aneugens have been studied almost exclusively in somatic tissues. However, currently there is a considerable discussion about the potential of ionizing radiation to induce heritable germ cell mutations. While the various viewpoints remain controversial, one of the aims of germ cell cytogenetic studies must be to improve the ability to identify and estimate the actual genetic risk in humans.

One way to assess the risk of transmission of genetic anomalies by men occupationally or accidentally exposed to ionizing radiation is to determine whether there is a dose-related genetic damage in human spermatozoa.Cytogenetic analysis of human spermatozoa is possible after interspecific *in vitro* fertilization between zona pellucida-free hamster oocytes and human spermatozoa.Using this assay system we have analyzed the radiation induction of structural chromosome abnormalities in sperm derived complements at the first embryo cleavage, as well as the radiation induction of micronuclei and aneuploidy in two-cell hybrid embryos.

Induction of structural chromosome abnormalities

Using the interspecific *in vitro* fertilization system, we have established a dose-effect relationship for the cytogenetic effects of gamma-rays on human spermatozoa. Semen samples from three healthy men were irradiated at doses of 0.00, 0.10, 0.25, 0.50, 1.00, 2.00 and 4.00 Gy. We observed that human spermatozoa retained a high fertilization ability even after high doses of gamma-rays. This indicates that induced DNA lesions are accumulated in male germ cells and may be transmitted to the zygote without being selected against at fertilization.

A total of 340 chromosome complements derived from no-irradiated human spermatozoa and 987 complements from irradiated spermatozoa were analyzed after sequential uniform staining-G banding. Both, the frequency of spermatozoa with structural chromosome abnormalities and the incidence of such abnormalities per cell showed strong dose-effect relationships, that were best expressed by linear-quadratic equations: $Y=0.06413(\pm0.00475)+0.1982(\pm0.00833)D-0.00763(\pm0.00204)D^2$ and $Y=0.07385(\pm0.00838)+0.23329(\pm0.03124)D+0.02317(\pm0.00955)D^2$ respectively (Fig.1).

The incidence of structural abnormalities per cell showed a linear-quadratic dose-response relationship (with a positive quadratic coefficient), where the quadratic trajectory was only visible at the highest dose. The linear dose-response relationship for the induction of spermatozoa with structural abnormalities showed a saturation effect (negative quadratic coefficient). This saturation effect was very small, and it could only be detected at the highest dose. This effect could probably be due to the fact that, at increasing doses, the probability that a cell will be affected by more than one chromosomal abnormality also increases, although this will be counted as a single abnormal spermatozoon. This saturation effect has also been reported in a study about the cytogenetic effects of *in vitro* X- and γ-radiation on Syrian hamster spermatozoa (Tateno et

al., 1996). In a previous study about the cytogenetic effect of γ-radiation on human spermatozoa (Mikamo et al., 1990), the induction of spermatozoa with structural abnormalities was 1.5 higher than the one found in the present study, and no saturation effect was detected for the induction of spermatozoa with structural abnormalities. The reason for this apparent discrepancy could be that in the study of Mikamo et al. (1990) the maximum radiation dose was 1.11 Gy. At this dose, a small saturation effect like the one found in our study, can easily go unnoticed.

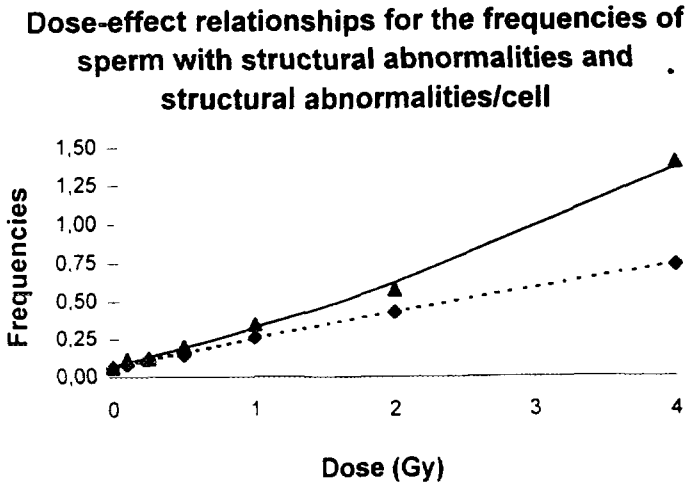

Figure1. Cytogenetic effect of gamma radiation on human sperm. Triangles and continuous line represent the frequency of human spermatozoa with structural abnormalities. Rombs and discontinuous line represent the frequency of structural aberration per cell.

Chromosomal aberrations may be categorized as to the number of breaks involved and the subsequent interactions among broken ends. Thus, structural abnormalities were classified as unrejoined and rejoined. Unrejoined structural abnormalities consist of such chromosome abnormalities as breaks, terminal deletions and acentric fragments, whereas inversions, translocations, dicentrics and rings are rejoined structural abnormalities.When analyzing separately both types of structural abnormalities, we found that the incidence of unrejoined lesions was four times higher than the incidence of rejoined anomalies. The induction of unrejoined abnormalities showed a linear, dose-dependent increase, whereas the incidence of rejoined abnormalities showed a quadratic, dose-dependent increase.

Induction of micronuclei

The analysis of human derived chromosomes at the first cleavage of the hybrid embryos, although useful, is very time consuming. Therefore in our laboratory we have developed a new assay system, which is faster and gives an estimate of the frequency of structural as well as numerical chromosome aberrations. It consists of the analysis of micronuclei in two-cell human-hamster embryos. The technique used was that described by Kamiguchi et al (1991) adapted to our human-hamster interspecific fertilization system (Genescà et al., 1990).

To ascertain whether the micronuclei present in the hybrid embryos were of human or of hamster origin, we hybridized them with either human or hamster genomic DNA probes. This experiment demonstrated that close to 99% of micronuclei were of human origin.

To establish a dose-effect curve for radiation-induced micronuclei, we performed the micronucleus test in two-cell human-hamster hybrid embryos after exposure of human spermatozoa to doses of 0, 0.10, 0.25, 0.50, 1.00, 2.00 and 4.00 Gy of γ-rays. The results were then compared to those obtained when analysing chromosome breaks and fragments in human sperm chromosomes using classical metaphase spreads.
A linear relationship between the different doses of radiation and the induction of micronuclei was demonstrated (Fig. 2), although at the highest dose (4 Gy) this relationship showed a slight saturation effect.

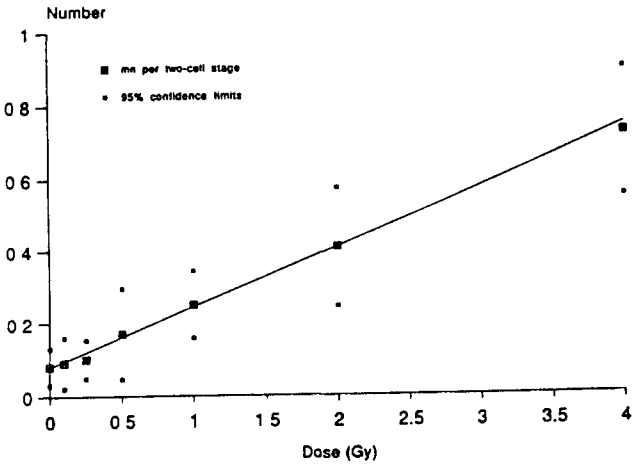

Figure 2. Dose-effect curve for the production of micronuclei (mn) by gamma-irradiation of human spermatozoa.

To determine if scoring micronuclei could be used for the quantification of chromosome damage induced in human spermatozoa, we compared the frequency of micronuclei per two-cell embryo (corrected for the estimated incidence of micronuclei of hamster origin) to the frequency of breaks and fragments in human sperm chromosome preparations, and a good coincidence was found.

Since micronuclei may contain acentric fragments (Heddle and Carrano, 1977) as well as centric fragments or whole chromosomes with damaged centromeres (Farooqi et al., 1993), and even groups of chromosomes that produce large micronuclei (Yamamoto and Kikuchi 1980), we decided to carry out a FISH study using a combination of human specific centromere probes and of unspecific telomere probes to determine the content of the micronuclei induced by the fertilization of hamster oocytes with human spermatozoa previously treated with γ-rays. In this case, human spermatozoa were irradiated under a ^{60}Co source at 2 and 4 Gy. Fluorescent in situ hybridization was carried out on fixed two-cell embryos using biotin labelled DNA probes specific for human centromeres as well as digoxygenin labelled telomere probes. Most micronuclei contain just one fragment, and the aim of the study was to determine whether the fragment was centric or acentric, and included telomeres or not either at one or both ends. Single and double FISH experiments were carried out. In this series of experiments, the frequency of micronuclei was also dose-dependent. Using double FISH, most centromere positive micronuclei were also telomere positive, indicating that they probably contained whole chromosomes; the presence of whole chromosomes in micronuclei through a lagging effect had already been demonstrated by Viaggi et al (1987) and may be related to a weak aneugenic effect of ionizing radiation. The proportion of centromere positive-telomere negative micronuclei was always under 10 %.

Induction of aneuploidy

An aneuploid individual usually arises at fertilization by the fusion of an abnormal gamete, which itself has resulted from a defect in meiosis. However, non-disjunction and the loss of mitotic chromosomes at the initial stages of embryogenesis may also result in trisomy, monosomy or chromosomal mosaicism.

Here, we describe a new assay system which has been developed by combining two techniques, the interspecific fertilization between zona-free hamster oocytes and human spermatozoa, and the fluorescent *in situ* hybridization (FISH) technique using centromere specific DNA probes. By tracing the marker chromosomes in two-cell embryos, reciprocal products of chromosome malsegregation can be easily traced. In this way, scoring of fluorescent spots in daughter nuclei and in micronuclei, gives an estimate of aneuploidy arising from meiosis, as well as the aneuploidy due to first mitotic division errors (both, non-disjunction and anaphase lag).
To determine the baseline frequency of these numerical abnormalities we have analysed 162 two-cell embryos from one normal donor with centromeric DNA probes for chromosomes 4,7 and 18.We have not taken into account those embryos showing more than one human chromosome complement because we cannot distinguish between an embryo originated by the penetration of a diploid spermatozoa from an embryo resulting from the fertilization with two normal ones. We have found a two-cell embryo with mitotic non-disjunction for chromosome 18 and some micronuclei without fluorescent signal. Therefore, accepting that all chromosomes have the same probability of being involved in these processes, the frequency of non-disjunction of the first mitotic division is 4.7%. The frequency of anaphase lag cannot be estimated until more embryos are analysed, but it seems to be lower.

This test will be used to analyse the effects of physical or chemical agents on spermatozoa during the first embryonic division.

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CHROMOSOME PAINTING IN BIOLOGICAL DOSIMETRY: SEMI-AUTOMATIC SYSTEM TO SCORE STABLE CHROMOSOME ABERRATIONS

J. M García-Sagredo[1], I.l Vallcorba[1], M.C. Sanchez-Hombre[1]. M.T. Ferro[1], A. Santos[2], N. Malpica[2], C. Ortiz[2], C. San Román Cos-Gayón[1].
[1]Department of Medical Genetics, University Hospital Ramón y Cajal, Madrid, and
[2]Grupo de Bioingeniería y Telemedicina, Universidad Politécnica de Madrid, Spain.
e-mail: jose.m.garcia@hrc.es

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ABSTRACT

From the beginning of the description of the procedure of chromosome painting by fluorescence in situ hybridization (FISH), it was thought its possible application to score induced chromosomal aberrations in radiation exposition. With chromosome painting it is possible to detect changes between chromosomes that has been validated in radiation exposition. Translocation scoring by FISH, contrarily to the unstable dicentrics, mainly detect stable chromosome aberrations that do not disappear, it allows the capability of quantify delayed acute expositions or chronic cumulative expositions.
The large number of cells that have to be analyzed for high accuracy, specially when dealing with low radiation doses, makes it almost imperative to use an automatic analysis system.
After validate translocation scoring by FISH in our, we have evaluated the ability and sensitivity to detect chromosomal aberrations by chromosome using different paint probes used, showing that any combination of paint probes can be used to score induced chromosomal aberrations.
Our group has developed a FISH analysis that is currently being adapted for translocation scoring analysis. It includes systematic error correction and internal control probes. The performance tests carried out show that 9,000 cells can be analyzed in 10 hr. using a Sparc 4/370. Although with a faster computer, a higher throughput is expected, for large population screening or very low radiation doses, this performance still has to be improved.

RESUMEN

Desde la descripción de la técnica de chromosome painting mediante hibridación in situ fluorescente (FISH), se pensó en aplicarla a la detección de anomalías cromosómicas inducidas como la exposición a radiaciones ionizantes. La técnica de chromosome painting es capaz de detectar intercambios entre cromosomas y ha sido validada en exposición a radiaciones. Esta técnica detecta, principalmente, translocaciones que son anomalías estables - al contrario de los dicéntricos usados hasta ahora en dosimetría biológica-. La estabilidad de estas aberraciones cromosómicas permite cuantificar exposiciones agudas dilatadas en el tiempo o exposiciones crónicas acumuladas.
Debido al gran número de células que hay que analizar, sobre todo si se trata de exposiciones a bajas dosis, hace imperativo el uso de sistemas automáticos de análisis.
Después de haber validado la técnica de chromosome painting, nosotros hemos evaluado el uso de diferentes librerías de sondas estableciendo que es posible usar cualquier combinación de sondas siempre que se armonicen los datos.
Nuestro grupo que ha desarrollado un sistema automático para análisis de técnicas FISH, esta adaptándole para su dedicación al análisis de translocaciones cromosómicas mediante FISH. El sistema es capaz actualmente de analizar 9.000 células en 10 h usando una Sparc 4/370. Aunque con una computadora más rápida es posible aumentar la velocidad de análisis, se necesita mejorar el sistema pensando en la necesidad de analizar grandes poblaciones o exposiciones a muy bajas dosis.

INTRODUCTION

From the second half of 60's, biological dosimetry has been prove as a useful procedure and complementary to physical procedures. This biological dosimetry has been successfully carried out by cytogenetic methodology based in dicentric scoring. Biological dosimetry by dicentric analysis is highly effective at high doses, but insensitive at low doses where biological adverse effects exists.

From the beginning of the description of the procedure of chromosome painting by fluorescence in situ hybridization (FISH), it was thought its possible application to score induced chromosomal aberrations as in radiation exposition. The first approach was based in simultaneous hybridization of centromeric probes and telomeric probes for chromosome 1 (Lucas et al, 1989). More recently, with the uses of libraries of whole chromosome probes -paint probes- (Cremer et al, 1990, Collins et al 1991), it is possible to detect changes between chromosomes, that has been validated in radiation exposition (Tucker, 93). Chromosome painting is based upon different stain of specific chromosomes using labeled DNA probes for whole chromosomes. It allows to detect color changes into the chromosomes painted that means chromosome exchanges with other chromosomes not painted. Therefore, it is an easy technique detecting chromosome translocations by visualizing color changes instead of the time consuming G-banded analysis. Furthermore, in low doses of radiation where the rate of dicentrics is under detection, the use of FISH techniques scoring chromosome translocations could be due to the easiness in scoring metaphases.

But, translocation scoring by FISH mainly detect stable chromosome aberrations that do not disappear, contrarily to the unstable chromosome aberrations as dicentrics (Gray et al, 1992; Tucker et al, 1994) that quantify acute recent expositions. The circumstance that symmetric chromosome aberrations as translocations do not disappear allows the capability of quantify delayed acute expositions or chronic cumulative expositions.

Following this hypothesis, it should be possible to analyze risk populations, as workers, not only to establish the mutagenic history of individuals, but the suitability for a specific work under risk of exposition to ionizing radiation. Confirming the hypothesis of cumulative stable aberrations, Tucker et al (1994) showed that translocations detected by chromosome painting in a control population increase with age.

After validate translocation scoring by FISH in our laboratory (Garcia-Sagredo et al, 1994) we have evaluated whether the ability and sensitivity to detect chromosomal aberrations by chromosome painting is independent or not to the specific paint probes used, showing (Garcia-Sagredo et al, 1996) that any combination of paint probes can be used to score induced chromosomal aberrations because, after data correction according to the paint probes used, the amounts of translocations are dose dependent and quite homogeneous independently of chromosomes painted.

Automation of the Analysis

The large number of cells that have to be analyzed for high accuracy (specially when dealing with low radiation doses), makes it almost imperative to use a semi- or fully automatic analysis system. However the complexity and variability of the cases that can be found has made that only in the last few years some automatic or more often semi-automatic system have been proposed.
A system for FISH translocation scoring needs the following basic steps:

- Metaphase finder
- Translocation scoring
- Manual review for increased accuracy.

Metaphase finder: For brightfield several commercial tools are available, but fluorescence metaphase finder is a more difficult problem (due to the low light intensity and bright and non-uniform background) and just recently some metaphase finder have appeared [Piper et al. 1994, Vrolijk et al. 1994]. They comprise two steps:

- ROI determination in low resolution images and background correction
- actual metaphase detection in full resolution images: segmentation and classification.

The method can also provide a quality figure for each of the metaphases located so that subsequent analysis can be restricted to the highest quality metaphases available.

FISH translocation scoring: the number (or size) of painted chromosomes in the located metaphases is determined to classify each one as normal or abnormal, without having to obtained the full karyotype (always difficult and subject to errors). In [Fantes et al 1995] a system is proposed that uses as criteria to classify the metaphases an increase in the number of painted objects or a large asymmetry in the area distribution of the expected number of painted objects.

Manual review: present analysis systems still have an undesirable proportion of cells that are classified as abnormal when they actually should be rejected (they have paint artifacts, non-specific hybridization or they have been incorrectly segmented). The analysis results are then greatly improved if the dubious cases are presented to a trained operator that visually classifies them.

Our group has developed a FISH analysis system [Santos et al 1997a, Malpica et al 1996] that is currently being adapted for translocation scoring analysis [Santos et al 1997b]. It includes systematic error correction and internal control probes. The performance tests carried out show that 9,000 cells can be analyzed in 10 hr. using a Sparc 4/370. Although with a faster computer, a higher throughput is expected, for large population screening or very low radiation doses, this performance still has to be improved.

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RADON AND RADIUM CONCENTRATIONS IN BOTTLED WATERS: AN ESTIMATE OF INGESTION DOSES

C. Dueñas[1], M.C. Fernández[1], J. Carretero[2] and E. Liger[2]
[1]Department of Applied Physiscs I. Faculty of Sciences. 29071 MÁLAGA
[2]Department of Applied Physics II. E.T.S. Informatic Engineering. 29071 MÁLAGA

ABSTRACT.- Concentration levels of Ra-226 and Rn-222 have been analysed in most of the bottled waters commercially available in Spain. Concentrations up to about 600 Bq/m^3 with a geometric mean of 12 Bq/m^3 were observed for Ra-226. For Rn-222 a geometric mean of 1200 Bq/m^3 with values ranging from 52000 to 1400 Bq/m^3 were measured. Doses resulting from the consumption of these waters were calculated. The effective dose equivalents due to the intake of Ra-226 present in these waters are expected to range from about 102 to 2 $\mu Sv \cdot y^{-1}$. Dose equivalents to the stomach due to Rn-222 intake through water consumption are estimated to reach values around 30 $\mu Sv \cdot y^{-1}$.

INTRODUCTION.- Radium and its daughter products constitute an important part of natural environmental radiation exposure [1]. Since ingestion is a major pathway, apart from inhalation of radon, for internal irradiation, the measurement of natural radioactivity in drinking water is relevant in assessing the contribution of these enviromental radiation hazards [2].

The interest of this paper lies in fact that during the last few years there has been an increase in the consumption of mineral waters, commercially bottled, partially substituing the consumption of tap water from municipal supplies. Even though the use of mineral water for therapeutic purposes has been known for a long time, at present the large scale of comsumption of bottled waters is continuosly increasing in Spain, among other factors, because of the persistent drought that many regions have been suffering over the last few years.

We have carried out a survey of Ra-226 and Rn-222 concentrations in bottled water that are commerciallised available. The aims of this programme are to draw a general picture of the natural radioactivity of bottled water in Spain and to evaluate doses to the populations resulting from their consumption. Analyses of Ra-226 and Rn-222 have therefore been performed on water samples from eighty four different sources.

MATERIAL AND METHODS.-The method used to evaluate the activities of Ra-226 consists in the radiochemical separation of Radium.This separation was carried out from 1 litre of water to which a known quanty of inactive barium as a carrier and another of lead as a contributor to the initial precipitation was added. Both the carrier and the radioisotopes precipitated as sulphates. The precipitate is purified by washing with nitric acid, disolving in alkaline EDTA, and recipritating as radium-barium sulphate after pH adjustement to 5. Finally, a precipitation of barium sulphate was obtained which permitted the calculation of the chemical of the whole process. The precipitate was transferred to a stainless steel plate ("planchet") over which was placed a detector alpha sheet, made from a piece of mylar paper coated with SZn(Ag). The diameter of the planchet is 5 cm, the same as the detector sheet. The planchet was kept in a dryer until the moment of the count. All the samples were counted for twelve hours. More details on this method can be found in [3].

The lower limit of detection (LLD) with the procedure of the sample and measuring used has been evaluated as 2 Bq/m^3.

For radon concentration, waters were hermetically sealed in plastic standard Marinelli beakers of 0.8 ℓ at time of sampling and measured with an intrinsic germanium detector, with an efficiency of 25%, a resolution of 2 kev and is surrounded by shielding material to reduce the background count. Each sample was measured at least 3h after collection, to ensure equilibrium between Rn-222 and their daughters. The Rn-222 dissolved was then determined by measuring its daughter Pb-214 and Bi-214 with each water sample being measured for several days in order to check that the Pb-214 and Bi-214 decayed with the half-life of Rn-222. The activity of Pb-214 was measured by the 295.22 kev (19.2%) emission. The activity of Bi-214 was measured by the 609.3 kev (46%) emission. The system was calibrated with solutions of known activity and prepared with the same geometry as the samples to be

Table I.- Results for Region I.

Code	^{226}Ra	^{226}Ra (He)	^{222}Rn	^{222}Rn (He)
1 - I	290 ± 20	49	25 ± 2	82
2 - I	57 ± 13	10	5 ± 1	16
3 - I	53 ± 13	9	4.6 ± 1.1	15
4 - I	110 ± 18	19	9.5 ± 1.5	31
5 - I	11 ± 5	2	2.1 ± 0.9	7
6 - I	130 ± 20	22	11 ± 2	36
7 - I	57 ± 13	10	5 ± 1	16
8 - I	110 ± 13	19	9.5 ± 1.1	31
9 - I	280 ± 13	48	24 ± 2	79
10 - I	92 ± 13	16	8 ± 1	26
11 - I	44 ± 13	8	3.8 ± 1.1	13
12 - I	53 ± 13	9	4.6 ± 1.1	15
13 - I	210 ± 30	36	18 ± 2	59
14 - I	110 ± 18	19	9.5 ± 1.5	31
15 - I	114 ± 18	19	99.0 ± 1.5	32.5
16 - I	500 ± 30	85	43 ± 3	141
17 - I	130 ± 13	22	11 ± 1	36
18 - I	75 ± 13	13	6.5 ± 1.1	21
19 - I	220 ± 20	37	19 ± 2	62
20 - I	600 ± 30	102	52 ± 3	170
21 - I	75 ± 13	13	6.5 ± 1.1	21
22 - I	26 ± 9	4	2.3 ± 0.8	8

Table II.- Results for Region II.

Code	^{226}Ra	^{226}Ra (He)	^{222}Rn	^{222}Rn (He)
1 - II	< LID	—	< LID	—
2 - II	< LID	—	< LID	—
3 - II	31 ± 13	5	2.7 ± 1.1	9
4 - II	< LID	—	< LID	—
5 - II	26 ± 13	4	2.3 ± 1.1	8
6 - II	< LID	—	< LID	—
7 - II	< LID	—	< LID	—
8 - II	35 ± 18	6	3.0 ± 1.5	10
9 - II	35 ± 13	6	3.0 ± 1.1	10
10 - II	< LID	—	< LID	—
11 - II	< LID	—	< LID	—
12 - II	35 ± 13	6	3.0 ± 1.1	10
13 - II	< LID	—	< LID	—
14 - II	< LID	—	< LID	—
15 - II	< LID	—	< LID	—
16 - II	18 ± 9	3	1.5 ± 0.8	5
17 - II	< LID	—	< LID	—
18 - II	< LID	—	< LID	—
19 - II	< LID	—	< LID	—
20 - II	< LID	—	< LID	—
21 - II	< LID	—	< LID	—
22 - II	< LID	—	< LID	—
23 - II	< LID	—	< LID	—

Table III.- Results for Region III.

Code	^{226}Ra	^{226}Ra (He)	^{222}Rn	^{222}Rn (He)
1 - III	18 ± 9	3	1.6 ± 0.8	5
2 - III	26 ± 9	4	2.2 ± 0.8	7
3 - III	< LID	—	< LID	—
4 - III	< LID	—	< LID	—
5 - III	31 ± 13	5	2.7 ± 1.1	9
6 - III	< LID	—	< LID	—
7 - III	< LID	—	< LID	—
8 - III	< LID	—	< LID	—
9 - III	< LID	—	< LID	—
10 - III	40 ± 18	7	3.4 ± 1.5	11
11 - III	< LID	—	< LID	—
12 - III	< LID	—	< LID	—
13 - III	< LID	—	< LID	—
14 - III	< LID	—	< LID	—
15 - III	40 ± 13	7	3.4 ± 1.5	11
16 - III	< LID	—	< LID	—
17 - III	< LID	—	< LID	—
18 - III	< LID	—	< LID	—
19 - III	< LID	—	< LID	—
20 - III	26 ± 13	4	2.3 ± 1.1	8
21 - III	16 ± 8	3	1.4 ± 0.7	5
22 - III	< LID	—	< LID	—
23 - III	22 ± 13	4	1.9 ± 1.1	6
24 - III	< LID	—	< LID	—
25 - III	40 ± 13	7	3.4 ± 1.1	11
26 - III	< LID	—	< LID	—
27 - III	18 ± 9	3	1.5 ± 0.8	5
28 - III	< LID	—	< LID	—
29 - III	< LID	—	< LID	—
30 - III	400 ± 26	68	34.0 ± 2.3	112
31 - III	42 ± 11	7	3.6 ± 0.9	12
32 - III	< LID	—	< LID	—
33 - III	57 ± 13	10	4.9 ± 1.1	16
34 - III	< LID	—	< LID	—
35 - III	320 ± 40	54	27 ± 3	89
36 - III	15 ± 7	3	1.3 ± 0.6	4
37 - III	< LID	—	< LID	—
38 - III	< LID	—	< LID	—
39 - III	40 ± 9	7	3.4 ± 0.8	11

measured. Under the experimental conditions used for counting time, sample geometry, background noise and correction for radioactive decay, the detection limit of the method was 225 Bq/m^3. All the results obtained are given with uncertainties as 2σ.

RESULTS.- Whenever possible, each water was analysed at least twice for each radionuclide. Fig.1 shows a map of Spain schematically divided into three main geological groups and the location of the source of bottled waters. Tables I, II and III list the Ra-226, in Bq/m^3, and Rn-222 concentrations in kBq/m^3, measured in bottled waters reported for a confidence level of 95% and grouped according to the geological distribution.

The Ra-226 and Rn-222 concentrations in the analyzed waters followed a lognormal distribution. Fig.2 shows that the assumption of a lognormal distribution is hardly justified.

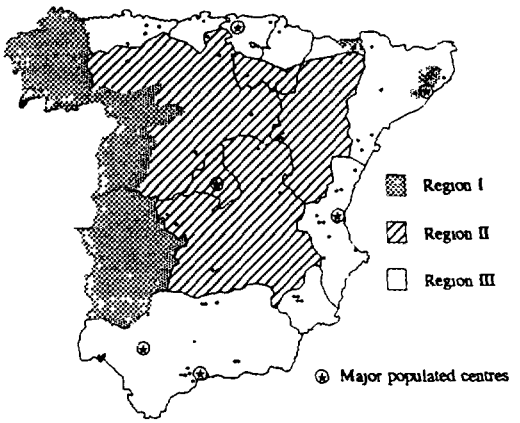

FIGURE 1.- Simplified geological distribution and location of the Spanish bottled waters tested. Region I is basically composed of granitic formations, Region II of sedimentary formations and Region III of calcareous formations.

Consumption rates depend very much on the type of water. For dose calculations we have considered a consumption rates of 1.5 ℓ per day. The annual dose equivalents per unit activity of ingested Ra-226 in the calculations in Sv·Bq^{-1} were [4]: H_{bone}= 7.1·10^{-6} and He= 3.1·10^{7} where H_{bone} is the committed effective dose equivalent to bone surface and He the committed effective dose equivalent. For the ingestion of radon, according to UNSCEAR, [5], estimates for the dose equivalent to stomach per unit activity of ingested radon were 10^{-7} Sv·Bq^{-1}. For the effective dose equivalent, a corresponding value of 6·10^{-9} Sv·Bq^{-1} was taken. The expected doses resulting from the consumption of bottled waters in μSv·y^{-1} list in tables I, II and III.

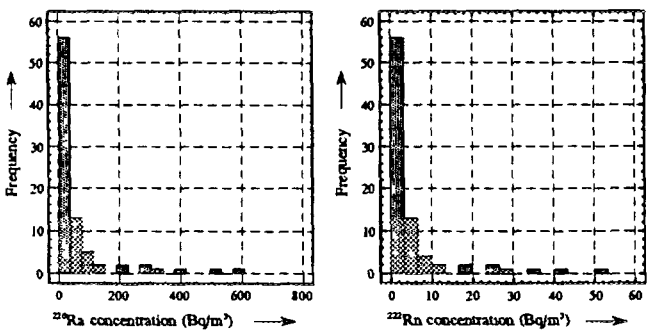

FIGURE 2.- Frequency histograms of ^{226}Ra and ^{222}Rn concentrations in Spanish bottled waters.

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Assay of new systems on *in vivo* mutagenesis for determining the effects of low doses of ionizing radiation

Cristina Bauluz, Inmaculada Sierra, Laura Martín, Almudena Real, Rosa de Vidania.
CIEMAT, Madrid, Spain *

XA9745681

ABSTRACT

Ionizing radiation reacts directly and indirectly with the genetic material in living cells and produces DNA damage. Processing of this damage by correcting enzymes may result in appearing of mutations which, in turn, may lead to carcinogenesis.

We have focused on the determination of *in vivo* mutagenesis induced after exposure to X-rays, aiming at establishing methods to evaluate the effect of low doses of radiation. *In vivo* mutagenesis has been addressed in the Muta Mouse model that carries a lacZ marker gene and provides a relatively simple assay of appearance of mutations.

Mutation frequencies were determined in the lacZ gene copies recovered from mice irradiated with 1 Gy or 4Gy of Xrays, acute or fractionated. Liver, spleen and bone marrow DNA samples were isolated at different times after irradiation, ranging from 1 day to 2 months, and evolution of mutations was studied.

Results showed different responses depending on the organ and especially on the time of analysis, suggesting that the mutagenic proccess *in vivo* is much more complex than previously deduced from *in vitro* experiments. Therefore, determination of the relationship between dose and mutagenic effect *in vivo* will require additional studies.

INTRODUCTION

Ionizing radiation is capable to interact with the living matter producing changes in intracellular molecules, both in the cytoplasm and the nucleus. Chemically reactive molecules produced by ionizing radiation in the cytoplasm may, in turn, react with the nuclear material. As a result, changes in the DNA molecular structure may arise directly or indirectly after irradiation.

Although changes can also occur in other biomolecules, it is generally believed that the biological effects observed after irradiation are mainly caused by changes in DNA structure. This is particularly true for the effects observed at long times after low-dose irradiation, especially for cancer.

In order to maintain cellular continuity, the genetic information contained in the DNA molecules must be passed on to daughters cell after cellular division. It is essential that the DNA structure and sequence are strictly preserved during the cell cycle, especially at DNA replication. In addition, since cellular functions depend upon adequate DNA

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transcription and translation into proteins, changes in DNA sequence may also disturb cell growth and survival.

Cells are provided with a series of enzymatic mechanisms devoted to correction of possible mistakes occurring during replication and/or damages induced after external injury by radiation or chemicals. Mostly, enzymatic repair of damaged DNA occurs correctly, in the sense that both DNA structure and coding sequence are restored. However, removal of certain types of damage or at certain points during cell cycle may be particularly difficult and the repair proceeds with error. In this case, the original sequence of DNA is changed and it is said to have mutations.

Mutations may be classified as *point mutations* (affecting to single base pairs in the DNA sequence), *insertions and deletions* (affecting to one or more consecutive bases which are added or lost, respectively, with respect to the original sequence). The type of mutation is highly dependent on the type of damage induced by a particular agent. In the case of ionizing radiation all types of mutations have been found to occur, although large deletions appear to be the most important.

The biological effects derived from changes in the DNA sequence depend on the relevance of the protein affected by mutations and even on the relative importance of the mutated region with regard to protein functionality. In other words, similar mutations may range from unimportant to crucial, depending on the region of the gene(s) affected. Normally, large deletions will compromise the function of one or several proteins and will appear more deleterious than point mutations, but certain point mutations are known to be sufficient to produce a strong effect.

Radiation-induced cancer is supposed to be due to mutations occurring on critical genes coding for proteins involved in the control of cellular growth and differentiation. The higher the dose, the higher the probability of those critical genes being affected.
Most of the knowledge on the mechanisms for induction of mutations after irradiation comes from experiments in which cells, cultured *in vitro*, had been irradiated at high doses of X or γ rays. However, isolated cells do not behave as cells within a tissue and it is possible that the results obtained do not reflect the actual mutagenic changes that would lead to a carcinogenic process in a living organism. More recently, mutations at particular genes have been studied after *in vivo* irradiation. These experiments usually involved *in vitro* culture of cells during several cell generations, in the presence of a selecting medium. Apart from the limitations due to cell type and possible artefacts due to selection, these methods provide valuable results. There is the problem, however, that results appear highly variable depending on the gene studied and on the experimental conditions used, and there are not yet clear conclusions regarding the mutation frequency induced by a given dose of radiation.

In the last years, transgenic animals have played an important role on the elucidation of the molecular mechanisms involved in carcinogenesis and other pathological processes.
In this regard, animal models for the evaluation of *in vivo* mutagenesis have been designed and are being used to study the mutagenic properties of many chemicals. These models appear to be useful also to determine the mutation frequency induced by ionizing radiation under different conditions of *in vivo* exposure, thus giving a better approach to the knowledge of the mutagenic mechanisms operating *in vivo* and allowing for

determination of the number and type of mutations remaining after various times after irradiation.

OBJECTIVES AND EXPERIMENTAL APPROACH.

Within a collaborative project CIEMAT-CSN, we focused on the study of the mutagenic process induced *in vivo* by ionizing radiation with particular interest on determining the effect of low doses of X rays.

Aiming at this, we decided to use the transgenic model "Muta Mouse" consisting of an otherwise normal mouse, carrying the bacterial gene LacZ integrated in both copies of chromosome number 3. This gene serves as a molecular marker in which it is relatively simple to determine the frequency of mutations appearing after irradiation of the whole animal; therefore, this mouse model gives the potential to determine induced mutation frequencies in any tissue, under any irradiation conditions.

Female Muta Mice (10-week old) were subjected to irradiation with X rays from a Phillips equipment (MG324). Mice were introduced into a metacrylate chamber designed to this purpose and situated onto a rotating platform to ensure uniform irradiation. Within this system, we were able to vary either dose (varying time of irradiation) or dose rate (varying distance).

In order to first establish conditions for mutation analysis, two moderate doses of X rays (1Gy and 4 Gy) were assayed in these experiments. Future experiments will address the effect of lower doses. Doses were given either acute or fractionated in five consecutive days. Mice were sacrificed at different times after irradiation, ranging from 1 day to two months. Relevant organs were extracted, deep frozen and stored at -70°C until analysis.

Mutation frequencies in the lacZ genes isolated from tissues of irradiated mice were determined as follows :

Genomic DNA was isolated from the tissue of interest by incubation at 50°C in lysis buffer (containing SDS, proteinase K and RNAse), phenol extraction and alcohol precipitation. About 6 to 10 μgs of genomic DNA were incubated with Muta Plax extracts (Epicentre) at 32 °C to package fragments containing the lacZ marker gene into infective lambda phages. Packaged mixtures were used to infect an engineered strain of E. coli ($lacz^{-}galE^{-}$) unable to grow in the presence of galactose. Plating was performed in the presence of P-gal, a product which is metabolized to toxic galactose when a functional copy of the lacZ gene is present in E. coli. In this assay, phages carrying intact lacZ genes are unable to form plaques, whereas phages carrying mutant copies of the lacZ gene do not transform the P-gal and, therefore, are able to survive and form plaques. Thus, only mutant copies of the marker gene are detected in this way. Plating was also performed, in parallel, in the absence of P-gal to allow for total packaged phages to be scored. Mutation frequency in a given sample was determined as the relation between mutant and total phages scored for that sample.

RESULTS AND DISCUSSION.

Mutation frequencies were determined in the lacZ gene of DNA samples isolated from liver, spleen and bone marrow of mice irradiated with either one single dose of 1 Gy or 4 Gy, or with 5 doses (consecutive days) of 0.2 Gy or 0.8 Gy. Thus, comparisons can be made between organs from the same animals and between doses, both acute and fractionated. Control animals (non irradiated) were also analyzed in order to determine the background mutation frequency in the lac Z gene of the three selected tissues.

Available results showed that the mutation frequency increases up to about 5-fold in liver and spleen after acute irradiation of 4 Gy ; values not significantly higher than the background mutation frequency were found after 1 Gy of X-rays. On the contrary, preliminary results obtained in bone marrow showed an increase in the mutation frequency at 1 Gy, indicating the possibility of strong differences in "sensitivity" to mutagenic effects between organs. Most probably, this accounts for differences in growth rates of different cell populations *in vivo*, rather than for different sensitivities to damage by radiation. Since it is the total mutagenic effect what may be relevant for carcinogenesis, confirmation of these results would be in good agreement with the observed high frequency of hemopoietic cancers induced by radiation.

Differences were also observed between organs with regard to the kinetics of the mutation frequency. Liver and spleen showed a detectable increase of mutations after a few days, which lasted until about 20 days after irradiation; after that time, the mutation frequencies returned to background values. In the bone marrow, the mutation frequencies appeared to increase at later times but remained higher for longer times. The reason of the decay of the mutation frequencies might be related to elimination of cells with high number of mutations, perhaps through an apoptotic phenomenon, but confirmation of this hypothesis would require complementary experiments.

It is interesting to remark that the results shown here, although not yet conclusive, indicate that mutagenesis occurring in an organ *in vivo* is a complex process that varies very much with time after irradiation and may display a different pattern within different organs. Variation with time should be taken into account when comparing the effect due to different irradiation conditions such as dose rate or fractionated doses, since maximal mutation rates may appear at different times. Similarly, comparisons between organs should consider differences in their kinetics for the accumulation of mutations; otherwise, it would be possible that organs with a delayed increase in the mutation frequency were regarded as less sensitive for this effect.

Finally, we would like to stress that the mutagenic process *in vivo* appears to be much more complex than what is deduced from older *in vitro* experiments and it does not seem likely that a simple relationship between dose and mutation frequency will apply to all cases. Therefore, much work has to be done to gain further knowledge on this process, and especially to relate it to tumor appearance, in order to be able to use mutation frequency as an early indicator of carcinogenic risk after radiation injury.

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PROPOSAL OF A PROBABILISTIC DOSE-RESPONSE MODEL

M Barrachina *

Abstract *A biologically updated dose-response model is presented as an alternative to the linear-quadratic model currently in use for cancer risk assessment The new model is based on the probability functions for misrepair and/or unrepair of DNA lesions in terms of the radiation damage production-rate in the cell (supposedly a stem cell) and its repair-rate constant The model makes use interpreting it on the basis of misrepair probabilities, of the "dose and dose-rate effectiveness factor" of ICRP and provides the way for a continuous extrapolation between the high and low dose and dose-rate regions, ratifying the "linear non-threshold hypothesis" as the main option Anyhow the model throws some doubts about the additive property of the dose*

1. INTRODUCTION

Induction of long term effects (such as cancer) by low level ionizing radiation exposure remains a highly controversial question, that cannot be answered at present time with any degree of certainty or scientific consensus [1]

The reasons for such a disappointing situation may be the scarcity, heterogeneity, and poor quality of the data on human carcinogenic effects of radiation, most of them collected from the atomic bomb survivors of Hiroshima and Nagasaki (H & N), after long term follow up studies of their excess leukemia and solid cancers (still in course), together with the best possible reconstruction of their dosimetric histories [2] Obviously, the precarious accuracy and completeness of the data will become a source of uncertainty of the lifetime cancer risk estimates [3]

Furthermore, the use of the linear-quadratic (LQ) model for risk assessment may have even worsened the uncertainty problem, as far as the LQ model only "aims to describe the observed data mathematically, as simply and with as much fidelity as possible, but without necessarily subscribing to an underlying biological model" [4], or "incorporating few, if any, of the advances in molecular biology of the past decade or so" [5] And, what is more astonishing is the fact that the H & N response curves for leukemia and solid cancers hardly fit into the LQ model, because their upwards curvatures are not clear at all [6]

Then we may ask why the LQ model stands up as the reference model for risk assessment The answer may be simple "because it justifies, at low doses, the well-known paradigm of the linear non-threshold hypothesis" (LNTH), on which the official radiation protection (RP) is built up all over the world

Finally, we should notice that the use of a single dose response curve, instead of different curves for different exposure regimes, is somewhat suspicious of paying an excessive tribute to the Paracelsus' aphorism "dosis sola facit venenum" In fact, we believe that the dose rate may be as important in RP as it is dose itself

We will see, later on, that facts and questions related to response curves may be looked at in quite a different manner, if we introduce in the response model the recent advances in cell biology

2. DAMAGE AND REPAIR

2.1 Damage

Oncogenesis arises from damage to a single cell This damage (mutation) is a change (at a locus) in the genomic code, that has to fulfill two subtle conditions first, not to be detectable by the damage surveillance system of the cell, and, second, not to prevent the viability of its mitotic reproduction

* Ex-Technical Adviser of the Spanish Nuclear Safety Council
Private address La Rinconada 12 28023 - Madrid Spain

This "fixed", subtle and viable damage is the consequence, in turn, of a primary DNA damage (or lesion) originated by the passage of ionizing radiation (or the action of other carcinogenic agents) This primary DNA damage may consist of DNA single strand breaks (ssb), double strand breaks (dsb), loss of bases, gene deletions, etc The spectrum of these lesions depends on the linear energy transfer (LET) of radiation, and a good picture of it can be obtained by computerizing the radition's energy deposition "tracks" The main conclusion being, however, that the quantitative production of primary damage Δ (= k D) is linear with dose D, up to many tens of gray [7] (or sievert, as numerically equivalent, for low LET radiation)

2.2 Repair

Since Muller's seminal discovery (1927), the primary damage has been considered to be something "static", in the sense that lesions remained "alive" over the time, and that neighboring lesions could cooperatively contribute to lethal damage formation This "static" concept has been at the origin of the multi-hit theories of radiation action, that have provided the foundations for the LQ model Nowadays, however, the concept of primary damage is much more "dynamic", as far as three short-term outset pathways are foreseen

- repair, the cell recovers normality Notwithstanding, it is claimed that repair is not hundred percent efficient, and a fraction of the damage is misrepaired (with introduction of random errors)
- unrepair, the cell cannot repair the lesions because of unavailability of the repair system, either by saturation or by genetic deficiencies The unrepaired cells may probably die by apoptosis, except those subtle lesions that overcoming the surveillance system may remain unrepaired
- apoptosis, the cells with non-repairable lesions are condemned, by enzymatic means, to follow the death pathway

Therefore, repair, when successful (i e , correct repair), together wit apoptosis, are the only two ways to prevent the cancer initiation step, and the appropriate mechanisms used by the cell can be seen elsewhere[8] [9] [10] [11] [12] [13] [14] [15] [16] Thus, it seems very likely that minor DNA lesions may have unexpectedly high biological effects (like cancer), due to their inefficient removal by DNA repair, and it is quite obvious that these "minor lesions" can be identified with the residual damage left by the repair system, either through its own error introduction (misrepair) or because its repair capacity is overwhelmed by excessive damage (unrepair)

Actually, we do not know how to assess the probability attributable each to misrepair, or unrepair, in the cancer initiation step, but we should notice that unrepair is the consequence of the limited capacity of the repair system of the cell to cope with the damage production in it Nevertheless, under stationary exposure conditions (D' = constant, being D' the dose rate), we can see that the repair probability, p, of one lesion is fairly predicted by an exponential function of the type

$$p = \exp(-\lambda \cdot D') \qquad \{E\ 1\}$$

where λ , the repair rate constant of the cell, is

$$\lambda = \ln 2 / {}_0D', \qquad \{E\ 2\}$$

being ${}_0D'$ the dose rate whose 50 percent damage production is repairable by the cell This function also predicts that at high dose rates ($D' >> {}_0D'$) no lesion will be repaired, and that at low dose rates ($D' << {}_0D'$) no lesion will be left unrepaired

Now, if we take into account the claim that repair is not hundred percent effective, we can predict the probabilities of cancer induction by misrepair (p_m), or unrepair (p_u), and the cancer prevention by correct repair (p_c), as it is stated by the functions {E 3} to {E 6}, shown in Table I, where α is the cancer risk (10^{-1} Sv $^{-1}$) recommended by ICRP (1991) for the high region (high doses and high dose rates), and α_0 / α is the fraction of cancers induced by misrepair in the low region The conversion of primary damage Δ (= k D lesions) to final effect E (= α D lifetime cancers) can be accomplished by taking as a reference the high region of H & N, where no correct repair seems to be possible ($p_c = 0$, or w = 1) and α lifetime cancers have been estimated per unit dose, what leads to the equivalence of k / α

primary lesions per cancer Likewise, in the low region, the lesions left misrepaired will contribute the fraction α_0 / α to cancer induction

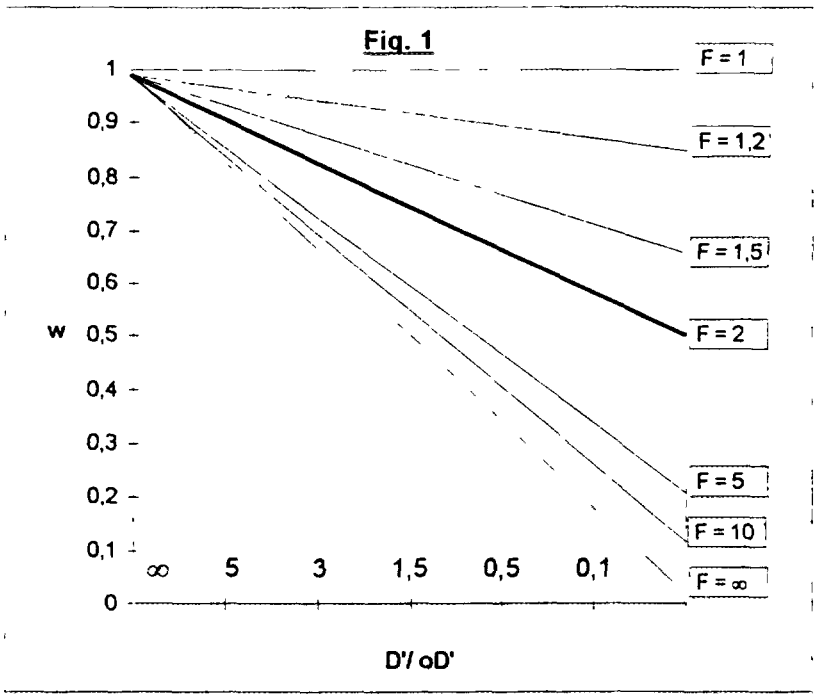


Fig 1.- Probability of Misrepair and Unrepair, w, for several values of DDREF (briefly, F).

We should notice, on the other hand, that $(\alpha_0 / \alpha)^{-1}$ is the "dose and dose rate effectiveness factor" (DDREF) introduced by ICRP, and that $w = p_m + p_u$ is the function that provides the way for the continuous extrapolation from the high region to the low region. In fig. 1, the w function is represented, {E·6}, for several DDREF values; among them, the value 2 selected by ICRP, that may be interpreted as the misrepair at low doses of as much as 50% of the lesions produced.

Table 1. - Attributable probabilities of cancer induction by misrepair, or unrepair; and of cancer prevention by correct repair.

Probability Functions	Limit	Values	
	$D' >> {}_0D'$	$D' << {}_0D'$	
$p_m = (\alpha_0 / \alpha) \cdot \exp(-\lambda \cdot D')$	0	α_0 / α	{E·3}
$p_u = 1 - \exp(-\lambda \cdot D')$	1	0	{E·4}
$p_c = (1 - \alpha_0 / \alpha) \cdot \exp(-\lambda \cdot D')$	0	$1 - \alpha_0 / \alpha$	{E·5}
$w = p_m + p_u = 1 - (1 - \alpha_0 / \alpha) \cdot \exp(-\lambda \cdot D')$	1	α_0 / α	{E·6}

Finally, with respect to the existence of a threshold in the cancer induction step, such a threshold should not exist for positive values of α_0, but it could exist for $\alpha_0 = 0$, or $\alpha_0 < 0$. In this case, of negative values of α_0, not only the threshold exists, but, furthermore, it indicates that low doses stimulate unknown biological mechanisms that prevent the cancer initiation step of other carcinogenic agents (hormesis).

3. CAPACITY OF THE CELLULAR REPAIR SYSTEM

The cornerstone of the response model proposed is the assumption that the cells - particularly, the stem cells - have a certain repair-rate capacity for any type of lesion, either of internal origin (by endogenous oxidative free-radicals) or external origin (by environmental toxicants, background radiation, etc.).
The number of spontaneous (internal and external) lesions repaired - per cell, per hour - amounts to several thousands of ssb, adducts, and so forth, [17] , what sums up a much greater quantity than the total lesions produced, per cell, by a dose irradiation of 1 Gy of low LET radiation [18] . Does it mean that cells are able to cope with the damage of dose rates in the order of 1 Gy · hr $^{-1}$? The answer is not at all straightforward, because the damage spectrum may be different in either case (metabolic versus radiation damage).
So, short of proof, let us assume that the cells, according to the definition of their repair rate constant {E·2}, are able to repair 50 percent of the lesions produced by a dose rate of 0,2 Gy · hr $^{-1}$, what is equivalent to making the assignment of this value to oD'. With this provision at hand, the probability functions of Table 1 become operative to explore the response curves of stationary irradiation regimes.

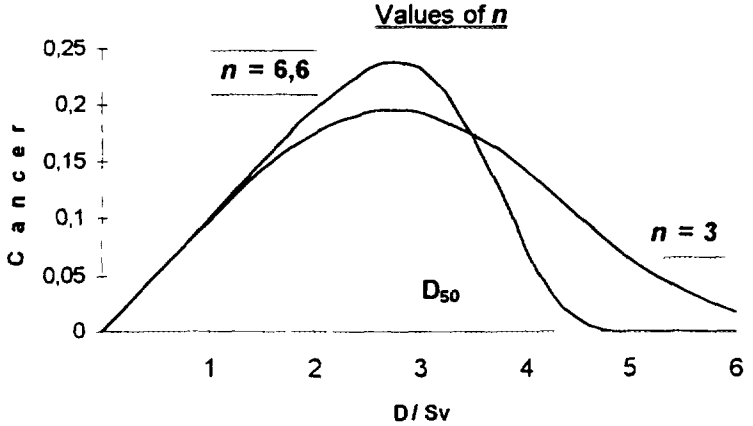
4. COMMENT ON "CELL KILLING"

It is well known that in the high region, the H & N cancer curves show a decline in slope, or even downward curvature, for doses over 2,5 Gy, what is usually seen as the competing effect of "cell killing" against cancer induction. This is quite true if cancer risk is referred to the survivors, as it is the case for the studies of H & N, but it should not be so, in absolute terms, with respect to the population "at the time of the bombings" (or population "at risk"), that it is that which really matters from the predictive point of view.
Taking this into account, the term "cell killing" should be changed to "individual survival", what would reduce dramatically the cancer risk in absolute terms, as far as an individual receiving 3,5 Gy (if this is the lethal dose 50 percent,D_{50}) has a 50 percent probability of dying from acute radiation syndrome, without having the possibility of expressing any cancer at all. We have followed this criterion by using the survival probability function :

$$s = \exp\left(-\ln 2 \cdot (D / D_{50})^{n}\right), \qquad \{E\cdot 7\}$$

that is a kind of Weibull's function adapted to nuclear power plant accidents, with n as a parameter of shape depending on medical treatment. In this context, the dose response in the high region (over 1 Sv) is shown in Fig. 2 (with preferred value $n=3$, over the recommended 6.6 [19]).

Fig 2 .- Response Curves in the High Dose Region for Two Values of *n*



5. THE PROBABILISTIC DOSE- RESPONSE MODEL

The construction of a model to deal with the complexities of radiation cancer responses, under different exposure regimes, forcefully has to make use of same framework of simplifying assumptions, that, in our case, is as follows:

- 1st, Linearity; the number of primary lesions per cell, Δ, produced by dose D, is
$$\Delta = k \cdot D \qquad \{E\cdot 8\}$$
- 2nd, Clonality ; a cancer arises from a single cell with a primary misrepaired (or unrepaired) lesion, that takes genetic advantage in its progress to a fatal tumor.
- 3rd, Reparability; primary lesions may be correctly repaired; the probability w, {E·6}, for one lesion to be left misrepaired (or unrepaired) is assessable in terms of the dose rate (D') of primary lesion production-rate, and the repair rate constant λ of the cell {E·2}.
- 4th, Survivorship; for an individual dying from radiation cancer, its survival probability s, {E·7}, should be taken into account for acute irradiation (as in H & N).
- 5th, Correlativeness; the misrepaired (or unrepaired) lesions are correlated to the carcinogenic effect E,
$$E = \alpha \cdot D \qquad \{E\cdot 9\}$$
by assuming that α takes the value 10^{-1} Sv^{-1} (as does ICRP) in the high region of H & N, where the probabilities w and s are supposed to be 1.

Under this framework of assumptions, the carcinogenic risk effect E is
$$E = \alpha \cdot D \cdot w \cdot s \qquad \{E\cdot 10\}$$
or, in its explicit form,
$$E = \alpha \cdot D \cdot [\,1 - (1 - \alpha_o/\alpha) \cdot \exp(-\lambda \cdot D')] \cdot [\exp(-\ln 2 \cdot (D / D_{50})^{n})] \qquad \{E\cdot 11\}$$
where, α_o / α is the cancer's fraction attributable to misrepair in the low dose region; and, its inverse $(\alpha_o/\alpha)^{-1}$, the DDREF factor.

λ, The repair rate constant of the cell, supposed to be 3,47 $hr \cdot Sv^{-1}$.

D_{50}, the human lethal dose 50 percent (3,5 Sv).

n, a shape parameter of the survival curve (taken here as n = 3).

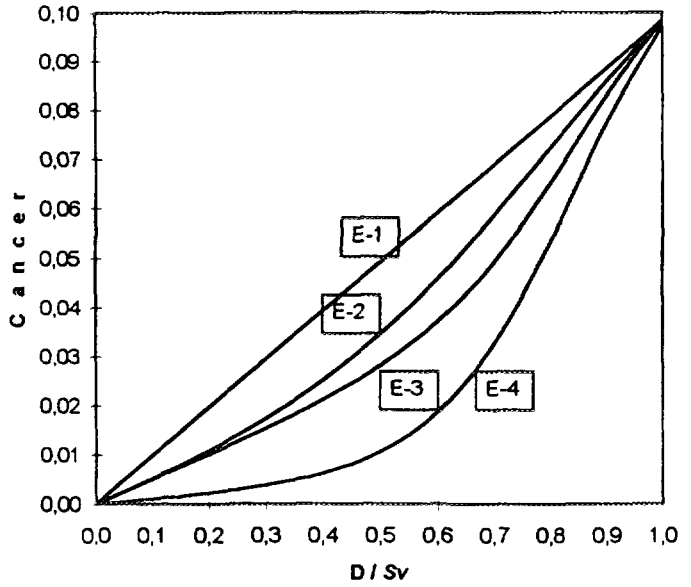
By the very nature of the model, the response curves can be split in three regions (and so can RP), as follows:

- The low region (D < 0.1 Sv; D' < 0.1 Sv ·hr^{-1}), for which equation {E·11} becomes
$$E_L = \alpha_o \cdot D \qquad \{E\cdot 12\}$$
where α_o, the "nominal cancer risk probability factor", takes the value $5 \cdot 10^{-2}$ Sv^{-1} [7] according to ICRP (but smaller values are possible).
- The intermediate region (0,1 Sv < D < 1 Sv; D' > 0.1 Sv ·hr^{-1}), for which equation {E·11} becomes
$$E_I = \alpha \cdot D \cdot [\,1 - (1 - \alpha_o/\alpha) \cdot \exp(-\lambda \cdot D')] \qquad \{E\cdot 13\}$$
- The high region (D > 1 Sv; D' > 1 Sv ·hr^{-1}), for which equation {E·11} becomes
$$E_H = \alpha \cdot D \cdot [\exp(-\ln 2 \cdot (D / D_{50})^{3}] \qquad \{E\cdot 14\}$$

6. INFLUENCE OF THE DOSE-RATE INTHE RESPONSE CURVES

The dose-rate effect is clearly manifested in the intermediate and low dose regions, in which equation {E.13} reduces to {E.12}, for low values of D·/0D·. In Fig.3, four theoretical dose response curves are shown, corresponding to the data of dose (D/*Sv*). dose-rate (D·/ *Sv/hr*), and exposure time (t/*hr*) given in Table II.

Fig. 3 - Influence of the Dose Rate in the Response Curve



The values of the parameters for E-1, E-2, E-3 are $\alpha = 0,1$; $\alpha_o = 0,05$ and $\lambda = 3,46$ hr Sv^{-1}, and for E-4, α_o changes to 0,01.

Table II. Data for three series of ten dose-points, obtained as specified in E-1, E-2, and E-3

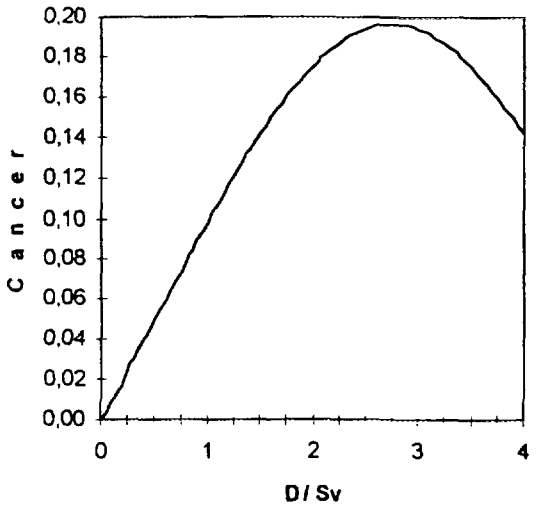
	D	0,1	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1
E-1	t-1	0,1	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1
	D'-1	1	1	1	1	1	1	1	1	1	1
E-2	t-2	10	7,743	5,995	4,642	3,594	2,783	2,155	1,669	1,292	1,000
	D'-2	0,001	0,026	0,050	0,086	0,139	0,216	0,325	0,479	0,697	1,000
E-3	t-3	100	59,948	35,938	21,544	12,916	7,743	4,642	2,783	1,668	1,000
	D'-3	0,001	0,003	0,008	0,019	0,039	0,077	0,151	0,288	0,540	1,000

The main conclusions drawn from Fig. 3 are :

a) for constant dose-rate irradiation, E-1, the response curve is linear; this has been recently confirmed for dsb in human fibroblasts [20]
b) for variable dose-rate, in correspondence to a geometrical irradiation time distribution in the interval (10-1) hr, curve E-2; or (100-1) hr, curve E-3, the dose-response curves are different.
c) for variable dose-rate in curve E-4, identical to E-3, the response is most sensitive to the value of α_o, in this case equivalent to DDREF = 10 , while the previous curves where for DDREF =2, as recommended by ICRP.

Finally, there are other important exposure regimes in which the dose rate will be time-dependent, D'(t), during irradiation. The most outstanding case is that of H & N, with a very short time of exposure (30 seconds) and dose rate extremely variable, according to position. We do not know the repair kinetics under these conditions, but, if we suppose a repair time of 24 hrs., we would roughly approach the cancer effect by supposing that the $D' \approx 5 \cdot D$ (in Sv hr^{-1}), what would give the dose-response of Fig. 4. Despite the uncertainty of this curve, it is clear that we do not need the quadratic term of the dose to obtain the response curves observed for leukemia and solid cancers in H & N.

Fig. 4 - Rough Simulation of H & N Cancer Effect, for the value 2 of DDREF



$\alpha = 0,1$
$\alpha_o = 0,05$
$\lambda = 3,46$ hr Sv^{-1}
$D_{50} = 3,5$ Sv

... .

The author wishes to acknowledge the help received from S. Ballarín.

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CELLULAR RESPONSE AFTER IRRADIATION: CELL CYCLE CONTROL AND APOPTOSIS

E Siles, MT Valenzuela, MI Núñez, R Guerrero, M Villalobos, JM Ruiz de Almodóvar
LABORATORIO DE INVESTIGACIONES MÉDICAS Y BIOLOGÍA TUMORAL,
Hospital Clínico, Facultad de Medicina, Universidad de Granada
GRANADA, SPAIN

XA9745683

Abstract

The importance of apoptotic death was assessed in a set of experiments, involving eight human tumour cell lines (breast cancer, bladder carcinoma, medulloblastoma). Various aspects of the quantitative study of apoptosis and methods based on the detection of DNA fragmentation (*in situ* tailing and comet assay) are described and discussed. Data obtained support the hypothesis that apoptosis is not crucial for cellular radiosensitivity and that the relationship between p53 functionality or clonogenic survival and apoptosis may bee cell type specific.

Passage of mammalian cells through the cell cycle is controlled by a number of key control point. Information from these checkpoint control is integrated through the regulated activity of a family of cell cycle-regulated kinases and their catalitic partners, cyclins (positive regulators) and CDK inhibitors, which can block cell cycle progresion at various points. In mammalian cells, the regulatory environment is complicated by the presence of different types of cyclin-dependent kinases that may participate in G_1/S and G_2/M checkpoints, a set of positive regualtors of these CDKs and several inhibitors.

Cell homeostasis is regulated by a balance between proliferation, growth arrest and cell death. Until recently, studies on oncogenesis have focused on the regulation of cell proliferation (Stanbridge and Nowell, 1990), however emerging evidence suggests that the current paradigm of neoplasia should be revised with proliferation taking a subsidary place to the primary regulation of growth arrest and cell death (Hall y Lane, 1994).

Two different forms of cell death have been described: apoptosis and necrosis, which can be distinguished by the distinctive changes that take place within the affected cells. Necrosis is a pathologic form of cell death usually caused by an acute cellular injury, it is typified by irregular clumping of chromatin without radical change in its distribution, rapid cell swelling and lysis. In contrast in apoptosis the cell plays an active role, this process is characterized by the early activation of endogenous proteases leading to cytoskeletal disruption, cell shrinkage and membrane blebbing and by the degradation of the DNA into fragments of size of oligonucleosomes. Although both modalities can be induced by the cytotoxic stress there are several cellular factors which determine the nature of growth arrest and the type of cellular death in response to ionizing radiation. Among them the tumour suppressor gene, p53, is known to take part in the apoptotic process and its protein product can act to block the progression or the survival of cells that have sustained genetic damage being a direct sensor of DNA damage and promoting either its repair or the lethal events leading to cellular death. These events promoted by the p53 pathway avoid the rise of pools of aberrant surviving cells and seem to be essential for a good therapeutic response to radiation or chemotherapeutic drugs.

In previous studies (Siles et al., 1996; Valenzuela et al., 1997) we have examinated the cell cycle distribution after γ-irradiation and heat treatment; the cell lines were divided into 2 groups depending on the effects seen. To extend these results we have assessed the importance of apoptotic death in a panel of eight human tumour cell lines after treatment with 6 Gy of ionizing radiation.

MATERIALS AND METHODS

Cell culture and radiation treatment

Eight human tumour cell lines have been studied in this work. They all have been described previously (Siles *et al.*, 1996). Six of them were derived from human breast cancer (MCF-7 clones BB, BUS

and GS, T47D, EVSA-T, MDA-MB-231), RT-112 from a human bladder carcinoma and D283MED is a human medulloblastoma cell line. This set of cells has been divided into two groups depending on the p53 protein and RT112, MDA MB 231, MCF-7 BB, EVSA-T y T47D with non-functional p53 protein. Four of the cell lines were used to performe time course experiments: MCF-7 BUS, D283MED both of them with functional p53, RT112 and MDA MB 231 both of them with non-functional p53. In the rest of the cells lines only one experimental point, 48 hours after cell treatment, was analyzed.

Cell lines were grown in 10% fetal bovine serum-supplemented Dulbecco's modified Eagle's medium (FBS-DMEM) (PAA-Laboratories, Linz, Austria) with penicillin (100 units/ml) and streptomycin (0.1 mg/ml). Cells were incubated at 37°C in a humidified atmosphere of 5% CO_2/95% air. Freedom from mycoplasma contamination was checked regularly by testing with Hoechst 33528 dye (Sigma, St. Louis, MO, U.S.A.).

Cells in the exponential growth phase were irradiated using a ^{60}Co source at a dose rate of 1.67 Gy/min. For apoptosis time-course experiments after cellular irradiation, a single 6 Gy dose was delivered.

RESULTS

Lost of cellular adherence

The quantification of the cells floating in the medium at different times after irradiation with a single dose has been used as indicative of the cellular death by apoptosis (Ling et al., 1994). This parameter has been included in this work even though its inespecificity, as it can give us information about the reproducibility of the different experiments and about the comparability of the deattached cells measured in the comet or end-labelling experiments. Actually, the fraction of floating cells must be similar whatever method is used to assess apoptosis after treatment.

The relationship between the percentage of deattached cells found in both groups of expemeriments (x-axis:*in situ* tailing; y-axis: comet assay) has been studied. The statistical analysis shows that points coming from different experiments fit closely to a straight line which parameters ($r = 0.949$, $p < 0.001$) are demostrative of the equal effect produced by irradiation.

We have studied the kinetic of the lost of adherence in the different cell lines studied. All of them, except D283MED, show a progressive increase in the floating population with the time after treatment. The experimental points plotted draw a linear relationship between the deattached cell number and the time after radiation exposure (slope = 0.127±0.01, $r = 0.991$ and $p = 0.001$).

On the other hand, D283MED shows a different pattern of lost of cellular adherence, with higher values which cannot be fitted to a straight line.

Analysis by *in situ* tailing of the apoptic death induced after γ-irradiation

Using *in situ* tailing we have measured the percentage of apoptotic cells 12, 24, 36 or 48 hours after irradiation. Experiments were performed at least three times with each cell line and each experimental point was compared with the corresponding control, non irradiated cells, to establish whether apoptosis occured or not spontaneously. Having into account all the experiments performed, the fraction of cells in control flasks in which the *in situ* tailing was positive was in no case over 1%. On the other hand, joining together the results obtained we have calculated the mean values corresponding to the fraction of stained cells at 24 (0.31%±0.29%) and 48 hours (0.42%±0.32%) and we have found no significative statistical difference between these two points. That means that the cell culture conditions were kept invariable in control flasks through the whole experimental time and that apoptosis is not an important factor in control cultures.

In the treated flasks floating and adherent cells were analyzed independently to quantify the fraction of apoptotic cell in both populations and to clarify if the dead population was coincident with those cells

which lose the adherence to the monolayer. No significative incidence of apoptosis could be detected in the adherent cells, however in the floating population the percentages found differed widely among the different cell lines. Focusing on the four cell lines in which the time-course of apoptosis was studied, the main differences were found between D283MED in which the apoptosis increases continously reaching 66.5% 48 hours after irradiation and MDA MB 231 in which hardly no apoptosis can be detected. The cells RT112 show values that increase slowly with the time and MCF-7 BUS has intermediate percentages of apoptosis reaching a maximum, 31%, 36 hours after irradiation.

Among the other four cell lines in which only one experimental point was analyzed, MCF-7 GS shows clearly the most important value as nearly all the floating population was positive when the end-labelling technique was applied.

We have represented the time-course of the total percentage of apoptosis obtained by considering the two populations, floating and adherent cells together. D283MED turned out to be the most apoptotic cell line although the maximun value, 48 hours after irradiation, was only 14.06±0.51. MCF-7 BUS shows slightly higher values than the other two cell lines, RT112 and MDA MB 231.

Analysis by comet assay of the apoptotic death induced after γ-irradiation.

We proceeded in the same way described previously to quantify the apoptosis induced after γ-irradiation by the comet assay. Experiments were performed three times and the controls, non irradiated cells, were also analyzed to establish the incidence of spontaneous apoptosis. Again no differences were found among control cells with the time, and the values obtained were in all cases non significative from a quantitative point of view, although the assesment of apoptosis by comet assay in controls were slighly higher than the results obtained by the *in situ* tailing method (range of values from 0.5 to 5%).

In treated flasks the fraction of cells measured by comet assay showing changes compatible with apoptosis has been quantified in the adherent population where the proportion of apoptotic cells reaches maximun values 12 hours after irradiation in MCF-7 BUS and MDA MB 231, or 36 hours after irradiation in D283MED and RT112 and decreases with the time. In the other four cell lines studied, the values are again higher than those obtained by the end- labelling method specially in EVSA-T.

The apoptosis in the floating population is also much higher than the one detected by *in situ* tailing. Considering firstly the four cell lines in which a time-course experiement was performed, RT112 cells show the maximum values as all the non-adherent cells showed the typical "apoptotic comet". D283MED cell line does also have an increasing and considerable percentage of apoptosis which reaches 84% 48 hours after treatment. MCF-7 BUS decreases with the time and MDA MB 231 cells have a low percentage of "apoptotic comets" in the floating population. In MCF-7 BB, MCF-7 GS, EVSA-T and T47D-B8 the apoptotic comet shape is also significative.

Finally,we have also represented the time course of the total apoptosis quantified by considering the two populations, floating and adherent cells together. MCF-7 BUS and MDA MB 231 show decreasing values, on the contrary in D283MED and RT112 the apoptosis is induced progresively reaching a maximum 48 and 36 hours after irradiation respectively.

DISCUSSION

Apoptosis represents a physiological mechanism of cell death involved in the regulation of cell proliferation and differentiation. Its critical role in the control of cell number is of obvious relevance to an understanding of different disease states such as cancer. Besides an increasing body of evidence suggests that anticancer agents (e.g. ionizing radiation) act to induce apoptosis, which means that factors increasing the propensity for apoptosis may have a critical role in therapy (Lowe et al., 1993). According to this view,

in this paper we have analyzed by using different methodologies the apoptotic response to ionizing radiation in a panel of different human tumour cell lines which had been previously studied according to its p53 functionality (Siles et al., 1996).

The quantitative study of apoptosis is not easy, specially as apoptosis is a dynamic process in which the cell plays an active role that finishes with cell removal. A first approach used by some authors has been the measurement of the floating population after different treatments e.g. ionizing radiation, TGF β-1 or overexpression of v-mos oncogene (Ling et al., 1994; Busch et al., 1994; Soldatenkov et al., 1995), in those reports the cells that lose the adherence to the monolayer are shown to be apoptotic by DNA. We have also used the measurement of the floating population with two different objectives: a) As indicative of the reproducibility of the different experiments performed in the same cell line and b) As a possible indicator of cell death, the analysis of apoptotis has been carried out independently in the floating and adherent cells. After γ-irradiation the deattached cells increase slowly (0.12% per hour) continously during 48 hours in all the cell lines used except in D283MED, previously described as apoptotic after ionizing radiation treatment in which the proportion of these cells increases significantly, 19.95% ± 2.05% at 24 hours after irradiation to keep aproximately constant until the end of the experiment. So the response to the same stimulus seems to be cell type dependent, in fact a high proportion of the deattached cells in MDA MB 231were healthy mitotic cells in which the deep morphology change made them lose the adherence to the monolayer.

Different methods based on the detection of DNA fragmentation have been recently developed. In this work we have applied two of them, *in situ* tailing and comet assay. The first one identifies apoptotic cells by direct fluorescence detection of labeled DNA, it has been previously described (Gold et al., 1994) as a sensitive method with an almost complete correlation with the typical morphology of apoptosis. The advantages of using the enzyme TdT, which catalyzes a template independent addition of deoxyribonucleotide triphosphate to the 3'-OH ends of double-or single-stranded DNA, can be summarized in three main points: a) The intensitiy of labelling of apoptotic cells which means more sensitivity b) The kinetic of addition of deoxynucleotides to the broken DNA is very quick c) Necrotic cells keep unstained. The second one is a simple, rapid and inexpensive method for DNA strand break detection in individual cells. Its use has increased significantly in the past few years. Since apoptosis is characterized by extensive DNA cleavage, this assay has been proved useful in detecting apoptotic cells as those ones in which only a small amount of DNA stays in the original position of the nucleus (Roselli et al., 1995). According to previous reports, performing the comet assay using either alkali or neutral lysis method produced similar results. In this work we have used the neutral method to identify apoptotic comets. Both methods were applied independently to the floating and adherent populations and the comparison of the results obtained led us to conclude that they are not detecting the same event, as it has not been possible to make any statistical significative correlation between them. In fact if we consider the cell line RT112 all the deattached cells showed apoptotic features according to the comet assay while no more than 12% were considered possitive by *in situ* tailing, on the contrary MCF-7 GS cells showed 95% of apoptosis by *in situ* tailing and 57.3% by comet assay. Besides, in the adherent population no apoptotic cells were identified by *in situ* tailing, which is in agreement with the results reported by other authors (Soldatenkov et al, 1995; Bush et al, 1994), however higher percentages of apoptosis were detected by the comet assay, specially in MCF-7 BUS at the beginning of the experiment. These two methods are based on the detection of DNA strand breaks which take place in the oligonucleosomal links by the activation of endogenous endonucleases. Another qualitative method based in this same principle is the detection of "ladders" on DNA gel electrophoresis. This analysis was previously used by us (Siles et al., 1996) in this panel of cell lines and allow us to compare the quantitative results obtained by both methodologies and the qualitative stimation of electrophoresis to determine which method is the most accurate to study apoptosis. This comparison has led us to conclude that the comet assay does not correlate with the biochemical results, in fact the highest values of total apoptosis obtained correspond to the group identified as ±, while the + and - ones have similar averages of apoptosis. Nevertheless there was a better correlation with the apoptosis quatitified by *in situ* tailing, in this case the percentage of apoptosis increases as the "ladder" gets more intense. The results reported here, raise the possibility that the comet assay, at least in the cell lines analyzed, does not measure specifically apoptosis but maybe cell death independently of the form, apoptosis or necrosis, in which it takes place.

The induction of apoptosis after DNA damage has been described by different authors to be wild-type p53 dependent. We have previously reported a close relationship between cellular radiosensitivity and p53 functionality, determined by the constitutive p53 levels, the G_1 arrest after irradiation or the p53 protein response to radiation. This would presumibly led us to think that in cells with functional p53 this protein allows more time for DNA repair to be completed, preventing the occurence of genetic alterations or to exit by apoptosis in the case of too severe damage. Our results do not however indicate a link between the quantitative incidence of apoptosis in the cells lines studied and either p53 functionality or SF2. The independence between p53 and the incidence of apoptosis have also been published by other authors. Although the most radiosensitive cell line, D283MED turned out to be the most apoptotic, its apoptotic index is not big enough to account for its low SF2 (0.18). In fact it has been suggested previously that it may be incorrect to make predictions about radiosensitivity or chemosensintivity of cells based only on knowledge of their mode of cell death. Thus our data support the hypothesis that apoptosis is not crucial for cellular radiosensitivity and that the relationship between p53 functionality or clonogenic survival and apoptosis may be cell type specific.

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DOSIMETRIA BIOLOGICA DE DOSIS BAJAS (0.05 - 0.4 Gy) CON DICENTRICOS MICRONUCLEOS Y FRAGMENTOS CROMOSOMICOS

L. RODRIGUEZ*; E. SANCHEZ*; C. LINARES*; A. SILVA+L. BARRIOS♦; J. NAVLET*
* Dpto de CC Morfológicas y Cirugía. Universidad de Alcalá de Henares.
+ Dpto de CC Sanitarias y Medicosociales. Universidad de Alcalá de Henares.
♦ Centro Técnico de informática. Consejo Superior de Investigaciones Científicas.

Este trabajo se realizó en el marco de un acuerdo entre el Consejo de Seguridad Nuclear y la Universidad de Alcalá de Henares, y con la colaboración del Servicio de Radiopatología y Radioprotección del Hospital General "Gregorio Marañón" de Madrid, en el que se hicieron las irradiaciones.

Resumen

Se han irradiado muestras de sangre de 4 individuos con 6 dosis de rayos γ entre 0.05Gy y 0.40 Gy, dejando una alícuota como dosis 0 Gy. Se hicieron cultivos de linfocitos para el estudio de cromosomas dicéntricos (DC) y fragmentos cromosómicos (fr), parando la primera mitosis postirradiación con colcemid. También se hicieron cultivos para el estudio de micronúcleos (MN) en células binucleadas, parando la primera citocinesis postirradiación con citocalasina B.
Después de los correspondientes estudios al microscopio óptico se hizo el análisis estadístico de los datos observados en DC, fr y MN. Hemos realizado el análisis de regresión lineal múltiple de los datos de los 4 individuos. Hemos obtenido la media de los 4 individuos para cada variable y dosis y hemos hecho el análisis de varianzas.

En las condiciones de nuestro estudio, ni los DC ni los MN son dosímetros válidos para dosis inferiores a 0.4 Gy. Sin embargo hay indicios de que los fragmentos están correlacionados con la dosis a estos niveles.
Aumentando tanto los puntos de dosis como el número de metafases estudiados, pensamos que se podría hacer una curva dosis-respuesta que permitiera estimar la dosis recibida por una muestra irradiada con un grado de confianza razonable.

1. INTRODUCCION

La comunicación que se presenta forma parte del trabajo desarrollado para el Consejo de Seguridad Nuclear que consistía en la realización de curvas dosis-respuesta con dicéntricos y con micronúcleos para Rayos X y Rayos γ, así como la utilización de la de la citometría de flujo en el recuento de MN y estudios de dosimetría biológica en irradiaciones parciales y en dosis bajas, del que presentamos parte de los resultados

2. DATOS OBSERVADOS

Para obtener las muestras, se irradiaron alícuotas de sangre periférica de los cuatro donantes a distintas dosis de rayos γ en una unidad de cobaltoterapia "Teratron 80", con una tasa de dosis de 0.03 Gy/min. Las dosis a las que se irradiaron las distintas alícuotas fueron 0.05, 0.1, 0.15, 0.2, 0.3 y 0.4 Gy para cada individuo, se dejó una alícuota en cada caso sin irradiar como dosis 0 Gy.

Los datos obtenidos tras el estudio microscópico se muestran en las tablas I y II en las que se recogen los individuos a los que corresponden la muestras, las dosis de irradiación en Gy, el número de metafases analizado (N° CEL), la frecuencia de DC (Y2),el número de fragmentos cromosómicos acéntricos (N° fr) y su frecuencia (FR). En la tabla II se muestra, además de la frecuencia de MN por célula, el número de células con 0, 1 , 2 y 3 MN.

Tabla I. Datos del estudio de DC y fragmentos

INDIVIDUO	DOSIS (GY)	N° CEL	N° DC	Y2	0 DC	N° fr	FR
1	0	500	0	0	500	0	0
2	0	500	0	0	500	0	0
3	0	500	1	0 002	499	1	0 002
4	0	500	0	0	500	0	0
1	0 05	500	4	0 008	496	1	0 002
2	0 05	500	2	0 004	498	2	0 004
3	0 05	500	10	0 02	490	4	0 008
4	0 05	500	2	0 004	498	1	0 002
1	0 1	500	2	0 004	498	2	0 004
2	0 1	500	3	0 006	497	3	0 006
3	0 1	500	7	0 14	493	4	0 008
4	0 1	500	2	0 004	498	0	0
1	0 15	500	1	0 002	499	2	0 004
2	0 15	500	5	0 01	495	2	0 004
3	0 15	500	4	0 008	496	3	0 006
4	0 15	500	5	0 01	495	2	0 004
1	0 2	350	0	0	350	2	0 00571
2	0 2	350	4	0 0114	346	2	0 00571
3	0 2	350	9	0 0257	341	3	0 008571
4	0 2	350	3	0 00857	347	1	0 00285
1	0 3	350	3	0 00857	347	4	0 01142
2	0 3	350	2	0 00571	348	3	0 00857
3	0 3	350	2	0 00571	348	4	0 01142
4	0 3	350	2	0 00571	348	1	0 00285
2	0 4	350	3	0 00857	347	2	0 00571
3	0 4	350	5	0 01428	345	6	0 01714
4	0 4	350	5	0 01428	345	4	0 01142

Tabla II Datos del estudio de MN

INDIVIDUO	DOSIS(GY)	N° CEL	N° MN	Y4	0 MN	1 MN	2 MN	3 MN
1	0	500	14	0 028	486	14	0	0
2	0	500	14	0 028	487	12	1	0
3	0	500	11	0 022	490	9	1	0
4	0	500	14	0 028	489	8	3	0
1	0 05	500	10	0 02	491	8	1	0
2	0 05	500	15	0 03	486	13	1	0
3	0 05	500	14	0 028	486	14	0	0
4	0 05	500	11	0 022	490	9	1	0
1	0 1	500	16	0 032	488	8	4	0
2	0 1	500	10	0 02	492	7	0	1
3	0 1	500	15	0 03	486	13	1	0
4	0 1	500	5	0 01	495	5	0	0
1	0 15	500	8	0 016	493	6	1	0
2	0 15	500	11	0 022	491	7	2	0
3	0 15	500	15	0 03	487	12	0	1
4	0 15	500	6	0 012	494	6	0	0
1	0 2	500	7	0 014	493	7	0	0
2	0 2	500	17	0 034	483	17	0	0
3	0 2	500	16	0 032	486	12	2	0
4	0 2	500	5	0 01	495	5	0	0
1	0 3	500	27	0 054	474	25	1	0
2	0 3	500	19	0 038	483	15	2	0
3	0 3	500	14	0 028	486	14	0	0
4	0 3	500	9	0 018	493	5	2	0
1	0 4	-	-	-	-	-	-	-
2	0 4	500	21	0 042	485	11	2	2
3	0 4	500	24	0 048	481	14	5	0
4	0 4	500	10	0 02	490	10	0	0

3. ESTUDIOS DE DC, MN Y FR POR REGRESIÓN

Se ha hecho una regresión lineal múltiple, poniendo Y2 en función de la dosis y del cuadrado de la dosis, de forma:

$$Y2 = a + bD + cD2$$

Se siguió el mismo procedimiento con los MN (Y4) y con los fr (FR)

Los resultados de estas regresiones se muestran en las tablas III, IV y V, en las que se recogen los valores de:

R: Coeficiente de correlación múltiple directo.

a, b, y **c**: Coeficientes de las ecuaciones

P: Probabilidad de que a, b, y c sean nulos.

Tabla III. Resultado del ajuste de Y2 a una ecuación lineal-cuadrática.

R	Coef. De las ecuaciones (10^{-2})	P
0.4196	a = 0.304 b = 4.390 c = 6.54	- 0.16 0.38

Tabla IV. Resultado del ajuste de Y4 a una ecuación lineal-cuadrática.

R	Coef. De las ecuaciones (10^{-2})	P
0.4759	a = 2.61 b = -5.42 c = 21.82	- 0.30 0.10

Tabla V. Resultado del ajuste de FR a una ecuación lineal-cuadrática.

R	Coef. De las ecuaciones (10^{-2})	P
07328	a = 0.154 b = 2.270 c = 0.340	- 0.15 0.93

Como se puede observar en las tablas III y IV, el ajuste de Y2 e Y4 a la función propuesta no es buena ya que sus coeficientes de correlación múltiple (R) tiene valores muy bajos, no existiendo correlación aparente entre Y2 eY4 y la dosis recibida por la muestra.

Sin embargo, como se puede ver en el análisis de regresión de los fr (tabla V), el coeficiente de correlación múltiple R es indicativo de que las dos variables estudiadas están bien correlacionadas, de hecho este es el mejor resultado de regresión, mejor que los DC y que los MN.

Parece que los fragmentos son la mejor variable para explicar la dosis. Evidentemente la ecuación obtenida no nos permite predecir la dosis a partir de el número de fragmentos encontrados, pero esto puede ser debido al escaso número de aberraciones encontradas de manera que si se aumentase el número de metafases estudiadas es probable que el ajuste de los datos mejorase.

4. ESTUDIO DE LAS MEDIAS

En cada dosis se han calculado las medias de Y2 (Y2m) Y4 (Y4m) y FR (FRm)de los cuatro individuos.

Para saber si estas varían al aumentar la dosis se ha realizado un análisis de la varianza de estas medias respecto a la dosis para determinar si hay diferencias estadísticas entre ellas, proponiendo como hipótesis nula la igualdad de las medias. Además, se ha aplicado el test de Tukey para determinar en que dosis el valor de la variable Y2, Y4 y FR se distinguen estadísticamente del valor de la tasa basal (dosis 0), para determinar si una pequeña dosis de radiación puede ser detectada mediante este sistema de dosimetría. En las tablas VI, VII y VIII se muestran los resultados, donde se recoge en la primera columna el valor de la probabilidad de que las medias sean iguales entre sí, y, en la segunda columna, las dosis que son estadísticamente distintas de 0 según el test de Tukey.

Tabla VI. Análisis de la varianza de las medias de Y2 y test de Tukey.

Análisis Varianza de medias. (p dosis)	Dosis ≠ 0, según test de Tukey
0.1490	Ninguna

Según estos resultados, los valores de las medias de Y2 no difieren significativamente unas de otras. Al aplicar el test de Tukey, las diferencias con 0 Gy no son estadísticamente significativas como está recogido en la segunda columna de la tabla V.
Los resultados obtenidos por análisis de la varianza de la medias confirman el hecho de que entre 0 y 0.4 Gy no existe correlación entre Y2 y la dosis.

Tabla VII. Análisis de la varianza de las medias de Y4 y test de Tukey.

Análisis Varianza de medias. (p dosis)	Dosis ≠ 0, según test de Tukey
0.2977	Ninguna

Según estos resultados, los valores de Y4 m no presentan diferencias estadísticamente significativas al aumentar la dosis. Por otra parte, según el test de Tukey en ninguna dosis de las estudiadas Y4m se distingue de el valor de Y4 m obtenido en el control.

Tabla VIII. Análisis de la varianza de las medias y test de Tukey.

Análisis Varianza de medias. (p dosis)	Dosis ≠ 0, según test de Tukey
0.0052	0.3 Gy

Según estos resultados asumimos que las medias presentan diferencias estadísticamente significativas, y además la primera dosis que se distingue de 0 Gy con un 95 % de confianza según el test de Tukey es 0.3 Gy. Este resultado mejora el obtenido con Y2 y con MN. Estos resultados vuelven a confirmar los obtenidos por regresión en el sentido de que FR es la variable que mejor correlacionada está con la dosis.

5. CONCLUSIONES

En las condiciones de nuestro estudio ni los cromosomas dicéntricos ni los micronúcleos son dosímetros válidos para dosis bajas, inferiores a 0.4 Gy. Sin embargo parece que los fragmentos acéntricos merecen nuestra atención ya que hay indicios de que están correlacionados con la dosis a estos niveles. Aumentando tanto los puntos de dosis como el número de metafases estudiados, pensamos que se podría hacer una curva dosis-respuesta que permitiera estimar una dosis inferior a 0.4 Gy recibida por una muestra irradiada con un grado de confianza razonable.

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Estudio *in vivo* de los mecanismos de oncogénesis hematológica tras exposición a radiación ionizante utilizando un modelo de ratones deficientes en p53.

José Antonio Casado, Cristina Bauluz, Rosa de Vidania, Almudena Real. CIEMAT[§]. Madrid. Spain.

([§] Proyecto cofinanciado por el Consejo de Seguridad Nuclear).

Resumen.

El desarrollo de un sistema de protección radiológica adecuado, se basa en el conocimiento de los efectos sobre la salud producidos fundamentalmente a dosis moderadas y bajas de radiación. El conocimiento de éstos efectos sigue siendo actualmente insuficiente para determinar con exactitud el riesgo para la salud derivado de dichas exposiciones. Los estudios epidemiológicos tienen serias limitaciones para abordar esta problemática. Mediante estudios con nuevos modelos experimentales se puede obtener información de interés al respecto y en concreto sobre los mecanismos de oncogénesis de radiación.

En este trabajo, se utiliza un modelo de ratones deficientes en p53, para estudiar la incidencia de cánceres hematológicos tras irradiación. Con objeto de caracterizar las poblaciones potencialmente implicadas en el desarrollo carcinogénico, se han realizado análisis de morfología celular, expresión de marcadores de superficie y contenido de DNA en células hematopoyéticas.

Los ratones con p53 alterado desarrollan fundamentalmente linfomas tras la irradiación. También se observó desarrollo de leucemias, si bien el número de ratones analizados es bajo. La metodología propuesta muestra gran potencialidad para el estudio de alteraciones celulares y moleculares implicadas en el desarrollo carcinogénico radioinducido.

Introducción.

El conocimiento de los riesgos para la salud derivados de la exposición a radiación es necesario para poder proteger al hombre de los efectos nocivos de ésta. El desarrollo de cáncer es el principal efecto de la exposición a dosis moderadas y bajas de radiación ionizante. A pesar de que en las últimas décadas se ha producido un gran avance en el conocimiento de la carcinogénesis y del papel de la radiación en este proceso, en la actualidad siguen existiendo incertidumbres sobre el nivel de riesgo carcinogénico derivado de la exposición a dosis bajas, en gran parte debido al reducido número de resultados concluyentes de estudios epidemiológicos para estas dosis.

Una dificultad para estimar la incidencia de cáncer radioinducido tras exposición a dosis bajas, reside en la baja probabilidad de que éstos se desarrollen y los largos períodos de latencia asociados. Asimismo, los tumores inducidos por radiación no son diferentes a los desarrollados de forma espontánea en la población.

Se han realizado multitud de estudios experimentales con objeto de aportar información de utilidad sobre los riesgos derivados de exposición a dosis bajas de radiación. Hay que tener en cuenta, sin embargo, que la diferente radiosensibilidad entre especies de mamíferos hace que la información cuantitativa acerca del riesgo de cáncer en humanos no pueda basarse únicamente en estudios realizados con animales. En contrapartida, los modelos experimentales permiten estudiar los mecanismos de oncogénesis de radiación, así como la forma de la curva dosis-respuesta y la influencia de diversos factores físicos y biológicos sobre la respuesta biológica a dosis bajas de radiación, aspectos difíciles de abordar en estudios epidemiológicos [1] [2].

En los últimos años, el desarrollo de nuevas técnicas de biología molecular y celular ha permitido diseñar modelos experimentales de ratones transgénicos y deficientes para genes relevantes en el control de la proliferación y diferenciación celular, que ofrecen diversas ventajas frente a las aproximaciones tradicionales para el estudio de los mecanismos de oncogénesis de radiación. Este es el caso de los ratones deficientes en el gen supresor de tumores p53, los cuales muestran una elevada sensibilidad al desarrollo de cánceres radioinducidos, principalmente hematopoyéticos [3] [4]. El gen p53 se encarga del control del ciclo celular e interviene en la regulación de procesos tan importantes como la apoptosis o muerte celular programada.

Objetivo.

Utilizando el modelo experimental de ratones deficientes en p53, se estudia la inducción de alteraciones celulares y moleculares en las poblaciones hematopoyéticas de sangre periférica, médula ósea, timo y bazo, como consecuencia de la exposición a rayos-X. Se analiza la correlación entre dichas alteraciones y la aparición de cánceres hematológicos, con objeto de conocer los mecanismos de oncogénesis de radiación y caracterizar indicadores tempranos del proceso carcinogénico.

Materiales y Métodos

Ratones hembras F1(C57BL/6xDBA) de 13 semanas, normales para p53 (p53+/+) o deficientes para el gen (heterozigotos p53+/- y homozigotos p53-/-), se irradiaron con una dosis aguda de 1 ó 4Gy de rayos-X (tasa de dosis de 1,04 Gy/min).

A distintos tiempos post-irradiación, se extrajo sangre periférica de la vena lateral de la cola de los animales de cada uno de los grupos y de ratones no irradiados, para realizar un análisis hematológico individualizado. Para ello, se utilizó un analizador hematológico Technicon H-1E de Bayer, que determina entre otros parámetros, el contenido de leucocitos, eritrocitos y plaquetas, fórmula leucocitaria, contenido de peroxidasa y contenido de hemoglobina. La técnica utilizada para extraer sangre, no requiere que el animal sea sacrificado, permitiendo hacer un seguimiento durante el período de tiempo que dura el experimento y correlacionar posibles alteraciones detectadas en sangre periférica con aparición de tumores de origen hematopoyético.

Diariamente se revisó el estado general de los animales con objeto de controlar la posible aparición de tumores, o algún síntoma de enfermedad. En estos casos los animales fueron sacrificados, extrayéndoles los órganos hematopoyéticos (médula ósea, bazo, timo y sangre periférica) para su análisis. En cada uno de los órganos del ratón con tumor y de un ratón control, se realizaron los siguientes análisis, utilizando un citómetro de flujo Epics Elite ESP de Coulter: (1) Morfología de las poblaciones celulares, basándose en su tamaño y complejidad. (2) Expresión de moléculas de superficie en las células, mediante marcaje específico con anticuerpos, para caracterizar el fenotipo de las células potencialmente implicadas en el desarrollo del tumor. (3) Contenido de DNA, mediante la técnica de ioduro de propidio, determinando que proporción de células está en cada una de las etapas del ciclo celular y su ploidía (indicador de inestabilidad genética).

Resultados.

Ninguno de los ratones p53 +/+ irradiados o controles han desarrollado tumor alguno hasta el momento (10 meses). En contraste, todos los ratones p53 -/-, tanto irradiados como control, desarrollaron linfoma de timo durante los dos primeros meses de estudio. Está descrito en la bibliografía que estos ratones desarrollan tumor desde los 3 meses de edad, lo que explicaría nuestros resultados, ya que los ratones p53-/- tenían 13 semanas de edad al inicio del experimento [3].

En los ratones p53+/- se observó una correlación entre la incidencia de tumores y la dosis de radiación administrada. Así, un 20% de los ratones irradiados con 1 Gy desarrollaron tumor, frente a un 80% en los expuestos a 4 Gy. Los tumores observados eran fundamentalmente linfomas de timo, si bien en algunos ratones irradiados con 4 Gy se detectaron síntomas leucémicos. Ningún ratón p53+/- sin irradiar ha desarrollado tumor hasta el momento (10 meses).

Ratones que desarrollaron linfoma de timo

Los ratones p53+/- y p53-/- que desarrollaron linfoma de timo, no mostraron alteraciones significativas en ninguno de los parámetros hematológicos de sangre analizados. Sin embargo, los análisis morfológicos de tamaño y complejidad celular, mostraron la presencia de una población anómala (mayor tamaño y

complejidad), además de la población normal observada en sangre control. En timo también se observó una población celular anómala, de mayor complejidad pero sin variación de tamaño. En médula ósea y bazo de ratones con tumor, las poblaciones celulares eran equivalentes a las observadas en los órganos control.

Con objeto de caracterizar la población morfológicamente anómala observada en sangre periférica y timo, se realizaron análisis con marcadores de superficie específicos. Los marcadores analizados fueron Thy-1 (linfocitos-T) y B220 (linfocitos B) (Tabla I).

Tabla I: Proporción de linfocitos T y linfocitos B en sangre y timo de un ratón con linfoma de timo y un ratón control (% de células totales).

Órgano	Linf- T (Thy1+)		Linf- B (B220+)	
	Control	Tumor	Control	Tumor
Sangre	35	19	43	37
Timo	99	99	0	0,1

En sangre de ratones con tumor había un descenso en el contenido de linfocitos T respecto al valor control (19% y 35% respectivamente). Este descenso podría ser debido a una alteración en la funcionalidad del timo, al localizarse allí las células cancerosas, ya que se trataba de un linfoma de timo avanzado.

Los análisis de contenido de DNA en el timo de ratones con linfoma, mostraron que un 2% de las células se encontraban en fase G0/G1 del ciclo celular (83% en el timo control) y cerca del 40% en fase G2/M (11% en el timo control), lo que indicaría bien que las células están proliferando activamente, o que son células tetraploides quiescentes. En médula ósea y bazo no se observaron diferencias respecto al control.

Ratones con síntomas de leucemia

Alrededor de 150 días post-irradiación, se observó en dos ratones p53+/- irradiados con 4 Gy, al hacer el análisis hematológico rutinario, un contenido anormalmente alto de leucocitos en sangre y una alteración en la fórmula leucocitaria (% de neutrófilos muy alto y de linfocitos muy bajo respecto al control). Estos datos sugerían la existencia de un estado leucémico. Uno de los animales murió poco después de detectar estas alteraciones, no pudiendo ser analizado. El otro animal fue sacrificado, extrayéndole la médula ósea, sangre y bazo, en los que se analizó morfología celular (tamaño y complejidad), expresión de los marcadores de superficie Thy-1, B220 y GR-1 (específico de células mieloides) y contenido de DNA celular.

En sangre, médula ósea y bazo del ratón con síntomas de leucemia, se detectó una población celular anómala en tamaño y complejidad, respecto a las poblaciones del ratón control. Es interesante resaltar que en ratones con linfoma de timo, únicamente se detectaron poblaciones morfológicamente anómalas en sangre, mientras que la médula y el bazo no mostraban diferencias respecto a las poblaciones control.

Los resultados obtenidos en el análisis de marcadores de superficie se muestran en la Tabla II. En los tres órganos analizados del ratón con síntomas de leucemia, se observó un descenso en el % de linfocitos B respecto a los valores control. El % de células que expresan el marcador GR-1, específico de células mieloides maduras y en proceso de maduración estaba muy aumentado en los órganos hematopoyéticos del ratón con síntomas de leucemia, sugiriendo su origen mieloide. El contenido de linfocitos T estaba disminuido en la sangre y el bazo de los ratones con síntomas de leucemia, no observándose diferencias significativas respecto al control en la médula ósea.

Tabla II: Proporción de distintos tipos celulares en sangre, médula ósea y bazo de un ratón con síntomas de leucemia y un ratón control (% de células totales).

Órgano	Linf-T (Thy-1+)		Linf-B (B220+)		Mieloide (GR-1+)	
	Control	Tumor	Control	Tumor	Control	Tumor
Sangre	31	10	45	0,8	8	95
Médula ósea	5	8	9	0,1	51	93
Bazo	31	3	44	0,2	11	85

Los análisis de contenido de DNA en los órganos hematopoyéticos con síntomas de leucemia mostraron que en médula ósea y bazo había una mayor proporción de células en proliferación respecto a órganos control, mientras que en sangre periférica no se observaron diferencias significativas respecto al control en cuanto al contenido de DNA.

Conclusiones.

A pesar de que el número de ratones analizados hasta el momento es bajo, los resultados obtenidos parecen indicar que los ratones con p53 alterado son un buen modelo experimental para el estudio de cánceres hematológicos radioinducido, ya que la incidencia observada tras irradiación es alta, no siendo los períodos de latencia extremadamente largos.

El análisis rutinario de parámetros hematológico en sangre, se presenta como una técnica con ventajas para detectar posibles estadíos pre-leucémicos. El estudio citométrico de marcadores de superficie específicos de linaje celular presenta una gran potencialidad tanto para caracterizar las poblaciones celulares (linaje y estadío de maduración) implicadas en el desarrollo del tumor una vez que éste es manifiesto, como para analizar indicadores tempranos de malignidad antes de que el tumor esté en estadío avanzado de desarrollo.

En la actualidad se están realizando estudios dirigidos a profundizar en la caracterización celular de las poblaciones hematopoyéticas implicadas en el desarrollo carcinogénico tras exposición a radiación, así como alteraciones moleculares que puedan estar implicadas en dicho proceso, mediante análisis de expresión génica por Northern Blot. Se han iniciado en nuestro laboratorio estudios equivalentes a los descritos en este trabajo, pero con protocolos de irradiación fraccionada con objeto de reproducir las condiciones de irradiación crónica a dosis bajas, de interés en el contexto de protección radiológica.

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NIVELES DE RADÓN EN CASAS Y PUESTOS DE TRABAJO EN UNA REGIÓN URANÍFERA DE ESPAÑA

L. S. Quindós Poncela*, P. L. Fernández Navarro*, J. Gómez Arozamena*, A. López Romero**

* Cátedra de Física Médica. Facultad de Medicina de la Universidad de Cantabria. Cantabria. España.

** Empresa Nacional del Uranio, S.A. (ENUSA). Madrid.España.

RESUMEN

Se presentan los resultados de un estudio relativo a la evaluación de las dosis por inhalación de radón a la población de una región uranífera española, comparándose éstas con las recibidas por los trabajadores de unas explotaciones mineras ubicadas en dicha zona.

1. INTRODUCCIÓN

De acuerdo con las recomendaciones de la ICRP [1], el estudio de la exposición al radón en áreas con niveles de radiación potencialmente elevados debe permitir caracterizar las dosis recibidas por las personas, tanto en sus casas como en sus puestos de trabajo. Estas áreas suelen presentar unas concentraciones de radionucleidos naturales en sus suelos, en particular los de la serie del uranio, significativamente superiores a la media, lo cual supone un incremento notable de la dosis por irradiación externa y, al mismo tiempo, debido a los elevados valores de la exhalación de radón del suelo, una acumulación de éste en las casas con el consiguiente aumento de la dosis por inhalación del mismo.

Las medidas realizadas por nuestro equipo durante los últimos años han puesto de manifiesto que las áreas españolas de mayor riesgo potencial al radón se corresponden con las Comunidades de Galicia y Extremadura, la Sierra de Guadarrama en Madrid y algunas zonas de las provincias de Zamora y Salamanca [2]. De todas ellas, presenta un especial interés la región de los Arribes del Duero (Salamanca) donde se encuentran ubicadas las principales reservas de uranio de España, algunas de ellas en fase de explotación como es el caso de las instalaciones mineras de ENUSA en Saelices el Chico (Salamanca).

El presente trabajo muestra los resultados de las medidas de la concentración de radón realizadas tanto en puestos de trabajo de dicha empresa como en viviendas localizadas en pueblos situados en un entorno de 15 km. de la instalación, evaluándose a partir de los mismos las dosis recibidas por los trabajadores y la población en general.

2. MÉTODO, RESULTADOS Y CONCLUSIONES

La medida integrada de la concentración de radón se ha llevado a cabo mediante detectores de trazas de la firma Tech/Ops Landauer, Inc., USA, empleando tiempos de exposición de un año. El estudio realizado a lo largo del período 1993-1996, abarca un total de 52 medidas en diferentes puestos de trabajo de las instalaciones y más de 100 en viviendas de los pueblos seleccionados en el entorno de la misma.

Tabla 1.- Concentraciones de radionucleidos naturales y tasa de exposición en las zonas estudiadas.

	Ac. ^{226}Ra (Bq Kg^{-1})		Ac. ^{232}Th (Bq Kg^{-1})		Ac. ^{40}K (Bq Kg^{-1})		TASA DE EXPOSICION (nGyh^{-1})	
	MEDIA	RANGO	MEDIA	RANGO	MEDIA	RANGO	MEDIA	RANGO
MINA	431,0	100-17000	38,0	15,0-65,5	1010	650-1191	130,2	60-8175
PUEBLOS	82,0	40-300	40,0	14,0-74,0	1260	680-1900	76,0	40-160

de los pueblos, así como de la tasa de exposición debida a la radiación gamma externa de origen terrestre en ambos casos. Por su parte, la exhalación de radón del suelo presenta valores que oscilan entre 40 y 900 $Bq.m^{-2}.h^{-1}$ en los distintos pueblos seleccionados, lo que unido a las características propias de la edificación de las viviendas, construidas a base de materiales autóctonos, da lugar a que el 40% de las mismas presenten niveles de radón superiores a los 150 Bq. m^{-3}. Todo ello justifica que las zonas estudiadas sean calificadas, razonablemente como de alto nivel de radiación.

La Tabla 2 refleja las concentraciones de radón medidas en los puntos designados, pudiéndose apreciar en la misma el amplio intervalo de variación que presentan las referidas a los pueblos, así como, el hecho de que en el caso de las instalaciones no se encuentran, en ningún caso, concentraciones superiores a los límites recientemente recomendados por la Unión Europea [3]. En este sentido, son de destacar los elevados valores correspondientes al pueblo de Villar de la Yegua, situado a unos 10 Km. de las instalaciones, directamente relacionados con las altas concentraciones de radionucléidos de origen natural correspondientes a una zona mineralizada en la que no se ha llevado a cabo labores de explotación minera [4].

A partir de los valores recogidos en la Tabla 2, y empleando los factores de conversión a dosis referidos a trabajadores y población en general [5], se han evaluado las correspondientes dosis por inhalación de radón para un tiempo de exposición de 2000 h, encontrándose para los puestos de trabajo un valor medio de 1.25 mSv, con un intervalo de variación de 0.20 a 3.75 mSv, mientras que para la población el valor medio resultante es de 0.59 mSv y el rango de variación de 0. 18 a 9.87 mSv.

A la vista de estos resultados, parece evidente concluir que, además de estudiar la influencia que las condiciones de trabajo pueden tener en la dosis recibida por los trabajadores, lo que sin duda conllevaría la necesidad de tener que medir en dichas zonas factores de equilibrio y fracción libre, es necesario, igualmente, si se quiere disponer de un historial dosimétrico completo de aquellos, llevar a cabo medidas en viviendas que hagan posible disponer de información relativa a las dosis por inhalación de radón recibidas en las mismas, ya que éstas, como se muestra en el presente trabajo, resultan ser del mismo orden o incluso, a veces, superiores a las medidas en los puestos de trabajo. En este sentido, en la actualidad nuestro equipo está desarrollando un proyecto de investigación cuyo objetivo es tratar de resolver en un futuro próximo las cuestiones planteadas anteriormente.

Tabla 2.- Concentraciones de radon en $Bq.m^{-3}$ en los puestos de trabajo de viviendas analizadas.

LUGAR	1993	1994	1995	1996	V. MEDIO	DESVIACION STANDARD
Sageras del Rio	92,5	88,8	125,8	96,2	100,8	17,0
Majuelos	77,7	88,8	107,3	111,0	96,2	15,7
Gallegos de Argañán	48,1	70,3	96,2	81,4	74,0	20,3
Saelices el Chico	59,2	62,9	85,1	162,8	92,5	48,2
Ciudad Rodrigo	18,5	25,9	33,3	33,3	27,7	7,1
Villar de la Yegua	1607,0	1590,2	1210,0	1800,0	1551,7	247,0
C. Martin Viejo	121,2	141,2	101,2	111,2	118,7	17,1
Villar de Argañán	140,4	160,2	125,3	130,2	139,0	15,4
LUGARES DE TRABAJO						
Precipitación Elefante	122,1	111,0	136,9	155,4	131,4	19,2
Oficinas Exploración	107,3	111,0	-	107,3	108,5	2,1
Lab. Preparación Muestras	144,3	159,1	85,1	44,4	108,2	53,2
Taller de Mina	122,1	122,1	136,9	148,0	132,3	12,6
Extracción Elefante	373,7	551,3	-	447,7	457,6	89,2
Oficinas Quercus	59,0	59,2	59,2	59,2	59,2	0,1
Precipitación Quercus	18,5	-	33,3	25,9	25,9	7,4
Cabina Trituración	236,8	-	240,5	233,1	236,8	3,7
Laboratorio (CuartoPR)	92,5	96,2	107,3	92,5	97,1	7,0
Sala Trituración	410,7	477,3	414,4	584,6	471,8	81,2
Sala Control Principal.	22,2	40,7	33,3	29,6	31,4	7,7
Secado Quercus	25,9	33,3	81,4	33,3	43,5	25,5
Cabina de Perforadora	96,2	181,3	-	-	138,8	60,2

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CHROMATID INTERCHANGES AT INTRACHROMOSOMAL TELOMERIC DNA SEQUENCES

José Luís Fernández[1], Fernando Vázquez-Gundín[1], Aurora Bilbao[2], Jaime Gosálvez[3], Vicente Goyanes[4].

1.- Centro Oncológico de Galicia. Avda. de Montserrat s/n. 15009 La Coruña.Spain
2.- Departamento de Ciencias Morfológicas, Universidad del País Vasco. Spain
3.- Unidad de Genética, Departamento de Biología, Universidad Autónoma de Madrid. Spain
4.- Unidad de Genética, Hospital "Teresa Herrerra". La Coruña.Spain

ABSTRACT

Chinese hamster Don cells were exposed to X-rays, mitomycin C and teniposide (VM-26) to induce chromatid exchanges (quadriradials and triradials). After fluorescence in situ hybridization (FISH) of telomere sequences it was found that interstitial telomere-like DNA sequence arrays presented around five times more breakage-rearrangements than the genome overall. This high recombinogenic capacity was independent of the clastogen, suggesting that this susceptibility is not related to the initial mechanisms of DNA damage.

INTRODUCTION

Telomeres are differentiated structures that constitute the physical end of chromosomes. In vertebrate chromosomes, the functional telomeric DNA sequences are $(TTAGGG)_n$ repeats [1]. These repeats are organized with specific proteins constituting structures that prevent chromosome fusion and exonucleolytic degradation.

Besides classical $(TTAGGG)_n$ terminal sequences, a wide variety of vertebrates show interstitial $(TTAGGG)_n$ sequences in their chromosomes. These areas have been considered as sites of preferential chromosome breakage, fragility and recombination [2]. Chinese hamster Don cells present a remarkable centromeric block of interstitial telomeric-like DNA sequences in most of their chromosomes, which is easily delineated by FISH [3]. We have analysed the presence or absence of intrachromosomal telomeric blocks at breakage-rearrangements sites of chromatid-type interchanges induced by three clastogens of different mechanism of DNA damage induction.

MATERIALS AND METHODS

Chinese hamster Don cells were grown in monolayer, in RPMI medium. Twelve hours before harvesting, mitomycin C (0.5µg/ml) or Teniposide (VM-26) (0.05µg/ml) was added. Some cultures were exposed to X-rays, 55kVp, from a Philips RT-100 machine. The administered dose was 3Gy, 3h before harvesting. Colchicine (0.5µg/ml) was added for the last 2h of cultures.

After cytogenetic processing, chromosomes in slides were denatured and incubated with a telomeric probe biotin-labelled. Slides were washed and the bound probe detected by avidin-FITC (yellow-green fluorescence) with a round of signal amplification. Chromosomes were counterstained with propidium iodide (PI) (red fluorescence).

Chromatid interchanges such as quadriradials and triradials were randomly scored, since these lesions were easy to detect under the PI filter set the microscope. Furthermore, these exchanges maintain strict pairing of sister chromatids, so breakage-rearrangement sites can be accurately located. The FITC filter set allowed visualization of the position of telomere-like sequences in the rearrangement.

RESULTS AND DISCUSSION

Figure 1a shows the chromosomes of a Chinese hamster Don cell after FISH with a telomeric probe. It is clearly visualized the FITC signal at centromeric areas of most of the chromosomes, revealing the presence of intrachromosomal telomeric sequence arrays. Figure 1b and 1c present a quadriradial and a triradial respectively, where an interstitial telomere block is associated with a breakage-rearrangement site (arrows).

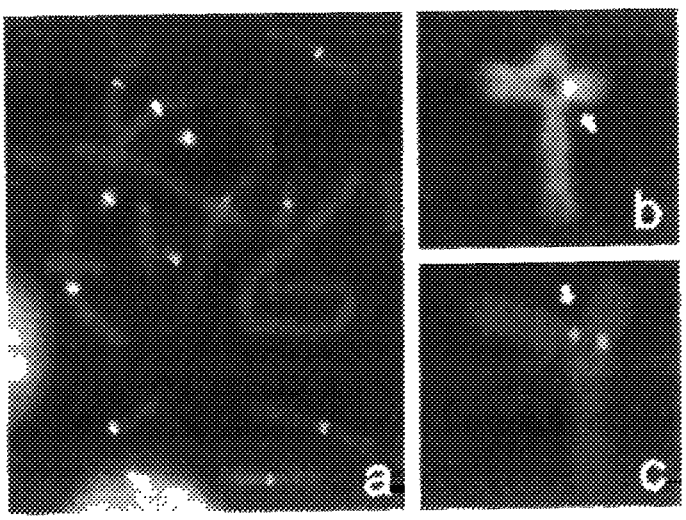

Figure 1. Chinese hamster Don chromosomes showing hybridization signals of telomeric DNA sequences at centromeric location of most of chromosomes. (a) Normal mitosis. Quadriradial (b) and triradial (c) with a block of intrachromosomal telomeric sequences involved in a breakage-rearrangement site (arrows).

Around 40% of the chromatid interchanges induced by each of the three clastogens showed a breakage-rearrangement site related to a block of telomere-like DNA sequence arrays (Table I)[4]. Using image analysis software it was found that these arrays constitute the 8.13 $\pm$ 0.62% of the genome. Therefore, the frequency of interchanges at interstitial telomeric sites was around five times that expected if assuming induction at random (Table I). This was a similar result to that referred by Alvarez et al. (1993)[5] in Chinese hamster cells exposed to gamma-rays, analysing chromosome damage. Moreover, Balajee et al. (1994) [6] also reported that around 22%-39% of chromosome aberrations induced by several restriction endonucleases involved internal telomeric repeat sequences.

Table I: Frequencies of chromatid exchanges induced by clastogens in Chinese hamster Don chromosomes.

Agent	Dose	Scored triradials and quadriradials			
		Total	Expected in telomeric-like DNA sequences (%)	Observed in telomeric-like DNA sequences (%)	Obs/Exp
X-rays	3Gy	63	8.13	42.86	5.27
Mitomycin C	0.5μg/ml	59	8.13	44.07	5.42
Teniposide (VM-26)	0.05μg/ml	148	8.13	37.84	4.65

These data support that telomere-like sequence arrays could promote breakage and recombination in themselves or the neighbouring chromatin once DNA damage has been locally induced. This increased susceptibility may be related to a specific organization of chromatin in this areas. In fact, evidence exists of a differential structuration of telomeric sequences either on terminal or on interstitial localizations [7]. Furthermore, telomerase activity could also play an important role in sensitivity to radiation-induced chromosomal breakage [8]. This sensitivity has possibly practical consequences, since an interstitial telomere array is present at a murine chromosome 2 fragile site, which could be involved in leukaemogenesis [9].

The mechanism of DNA damage produced by the three agents employed in our study was different among them. Ionizing radiation induces a broad spectrum of DNA lesions, including strand breaks, in clusters of interaction of the incident tracks. Teniposide (VM-26) is an inhibitor of DNA topoisomerase II. Finally, mitomycin C produces monoadducts and crosslinks in DNA. Since the sensitivity of interstitial telomere like sequences was similar, independently of the agent employed (Table I), our results suggest that this sensitivity is not related to the initial mechanisms of DNA damage. Furthermore, analysis of aberrations at this specific sequence areas can not reveal the feature of a characteristic aetiological agent.

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VALORACIÓN DE LAS DOSIS RECIBIDAS POR EL PERSONAL PROFESIONALMENTE EXPUESTO FRENTE A LOS LÍMITES ESTABLECIDOS EN LA DIRECTIVA 96/26 EURATOM. RECLASIFICACIÓN DEL PERSONAL

Prieto C., España M.L., Pérez L., Tomasi L., López Franco P.

Servicio de Protección Radiológica. Hospital Universitario de la Princesa.
C/Diego de León, 62. 28006, Madrid.

Resumen

Las recomendaciones de ICRP-60 de 1990 dieron base a la Directiva 96/26/Euratom en la que se establecen nuevos límites de dosis para los trabajadores profesionalmente expuestos. Estos nuevos límites de dosis suponen reducciones importantes respecto a los anteriores (todavía vigentes en España) y podrían suponer la reclasificación de algunos de estos trabajadores. En el presente trabajo se pone de manifiesto que la mayoría de los trabajadores profesionalmente expuestos de las áreas bajo nuestra responsabilidad podría clasificarse como de Categoría B.

INTRODUCCIÓN

La reciente aprobación por parte de la Unión Europea, el 13 de mayo de 1996, de la directiva 96/29/Euratom[1], "por la que se establecen las normas básicas relativas a la protección sanitaria de los trabajadores y de la población contra los riesgos que resultan de las radiaciones ionizantes", supone una drástica reducción de las dosis efectivas para trabajadores y miembros del público, siendo esta reducción especialmente significativa para la protección del feto.

El límite anual de dosis efectiva para las personas profesionalmente expuestas, que recomienda Comisión Internacional de Protección Radiológica a través de la ICRP-60[2] de 1990 es de 20 mSv/año promediada a lo largo de períodos de 5 años definidos por el organismo regulador, siempre y cuando no se superen los 50 mSv en un año cualquiera, estableciéndose restricciones adicionales para el caso de mujeres gestantes. Queda implícito en estos límites de dosis recomendados que "la restricción de dosis para la optimización no debería superar los 20 mSv en un año cualquiera"[2].

OBJETIVO

El objetivo de este trabajo es valorar el grado de cumplimiento de estos nuevos límites en los seis centros principales de las áreas sanitarias asignadas al Servicio de Protección Radiológica del H.U. de la Princesa, y evaluar en qué medida se ha ido consiguiendo no sólo el cumplimiento delos mismos, sino una optimización de las dosis recibidas. El objetivo final es la reclasificación, si fuera necesario, de los profesionales en categoría A o B.

MATERIAL Y MÉTODO

La determinación de las dosis ha sido realizada mensualmente mediante dosimetría personal con dosímetros de termoluminiscencia de LiF (en el centro de referencia durante todo el periodo evaluado. En los otros 5 centros se utilizaron dosímetros de $CaSO_4$ hasta junio de 1995, y partir de esa fecha de LiF.

En este estudio se han agrupado las dosis recibidas por aproximadamente 400 trabajadores profesionalmente expuestos, en los siguientes intervalos:

• (0-2) mSv/año.	
• [2-6] mSv/año.	**Categoría B**
• (6-20) mSv/año.	**Categoría A**
• > 20 mSv/año.	

RESULTADOS

En las tablas I a IV se presenta, por centros, el porcentaje de trabajadores profesionalmente expuestos clasificados en cada uno de los intervalos de dosis efectiva seleccionados.

CENTRO I				
Año	<2 mSv	2-6 mSv	6-20 mSv	>20 mSv
91	100%	0%	0%	0%
92	98.2%	1.8%	0%	0%
93	98.3%	1.7%	0%	0%
94	100%	0%	0%	0%
95	98.6%	1.4%	0%	0%
96	97.7%	2.3%	0%	0%

CENTRO II				
Año	<2 mSv	2-6 mSv	6-20 mSv	>20 mSv
91	100%	0%	0%	0%
92	100%	0%	0%	0%
93	100%	0%	0%	0%
94	100%	0%	0%	0%
95	100%	0%	0%	0%
96	100%	0%	0%	0%

CENTRO III				
Año	<2 mSv	2-6 mSv	6-20 mSv	>20 mSv
91	76%	18%	6%	0%
92	95%	5%	0%	0%
93	95%	5%	0%	0%
94	100%	0%	0%	0%
95	100%	0%	0%	0%
96	100%	0%	0%	0%

CENTRO IV				
Año	<2 mSv	2-6 mSv	6-20 mSv	>20 mSv
91	100%	0%	0%	0%
92	100%	0%	0%	0%
93	100%	0%	0%	0%
94	100%	0%	0%	0%
95	100%	0%	0%	0%
96	100%	0%	0%	0%

CENTRO V				
Año	<2 mSv	2-6 mSv	6-20 mSv	>20 mSv
91	100%	0%	0%	0%
92	98%	0%	2%	0%
93	100%	0%	0%	0%
94	100%	0%	0%	0%
95	100%	0%	0%	0%
96	100%	0%	0%	0%

CENTRO VI				
Año	<2 mSv	2-6 mSv	6-20 mSv	>20 mSv
91	100%	0%	0%	0%
92	100%	0%	0%	0%
93	100%	0%	0%	0%
94	100%	0%	0%	0%
95	100%	0%	0%	0%
96	100%	0%	0%	0%

CONCLUSIONES

1. Ninguno de los trabajadores profesionalmente expuestos de los centros sanitarios estudiados ha recibido dosis efectivas superiores a los límites establecidos en la Directiva 96/29/Euratom. Esto es cierto, no solamente en los 6 últimos años, sino también en los últimos 17 años, tal y como se demostró en un trabajo presentado en el IV Congreso Nacional de la Sociedad Española de Protección Radiológica de 1991[4].
2. La inmensa mayoría de los trabajadores profesionalmente expuestos en los centros bajo nuestra responsabilidad recibe dosis inferiores a 1/10 de los límites recomendados. En 3 de los 6 centros estudiados el 100% del personal profesional expuesto ha recibido menos de 2 mSv/año.
3. Basándonos en las dosis efectivas recibidas en los últimos 6 años podemos afirmar que la casi totalidad del personal profesionalmente expuesto, en las zonas estudiadas, podría clasificarse como de categoría B. Los dos únicos casos de dosis efectiva superior a 6 mSv/año son debidos posiblemente a un mal uso de los dosímetros, pues estos mismos trabajadores recibieron dosis inferiores a 2 mSv/año durante el resto de los años que abarca el presente estudio, y no tuvieron cambios significativos en su actividad profesional.
4. Merece destacar, que algunos de los profesionales que trabajan en radiología intervencionista, recibieron en alguno de los periodos objeto de este estudio, dosis equivalente en cristalino y muñeca superiores a 3/10 del límite anual de dosis, razón por la cual estos trabajadores deberán clasificarse de categoría A.
5. La disminución progresiva de la dosis recibida por el personal profesionalmente expuesto fue especialmente importante en el periodo 1980-1990[4], siguiendo ahora una época de mantenimiento en cotas realmente mínimas de dosis. El mantenimiento de estos niveles mínimos de dosis supone un trabajo activo y continuado en el área de formación e información del personal profesionalmente expuesto, asi como la actuación en el campo del control de calidad,

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RECOMENDACIONES DE ICRP-60 PARA MUJERES GESTANTES, OCUPACIONALMENTE EXPUESTAS. VALORACIÓN DE SU CUMPLIMIENTO EN SEIS CENTROS SANITARIOS

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ESPAÑA M.L., PRIETO C., PÉREZ L., TOMASI L., LÓPEZ FRANCO P.

Servicio de Protección Radiológica. Hospital Universitario de la Princesa.
C/ Diego de León, 62. 28006 Madrid. España

RESUMEN

La disminución en el límite de dosis equivalente a la entrada del abdomen aplicable a mujeres gestantes , ocupacionalmente expuestas, recomendado por ICRP -60, conlleva la necesidad de valorar dosimetricamente los distintos puestos de trabajo dentro de los diferentes Servicios existentes en un centro sanitario, para garantizar que sea sumamente improbable la superación de dicho límite, y por tanto la eficacia del sistema de protección para el feto. Los resultados obtenidos en este trabajo, relativos exclusivamente a la dosis de radiación externa, muestran la adecuación del sistema de protección actual en la mayoría de los puestos de trabajo valorados, aunque para algunos se deben establecer criterios mas estrictos para las trabajadoras gestantes, con el fin de lograr una mayor optimización de la dosis. En el caso de las operadoras gestantes de Medicina Nuclear se debe realizar un esfuerzo adicional, con el fin de garantizar que sea muy improbable la superación del límite considerado.

INTRODUCCIÓN

ICRP en su Publicación nº 60 [1], recomienda un límite de dosis equivalente para las trabajadoras gestantes, ocupacionalmente expuestas, de 2 mSv en la superficie del abdomen, y 1/20 del Límite de Incorporación Anual para la incorporación de radionúclidos, desde la declaración del embarazo hasta el final del mismo, garantizando de esta forma la protección del feto. En este sentido ICRP subraya que " su sistema de protección, y en particular el establecimiento de restricciones de dosis relacionadas con la fuente, garantizará el cumplimiento con el límite establecido, sin necesidad de aplicar restricciones específicas sobre el empleo a mujeres embarazadas, recomendando que las autoridades reguladoras deberían definir aquellos trabajos de los que las trabajadoras gestantes deberían estar excluidas ". Algunos países han establecido un valor superior a 2 mSv [2], y la Directiva 96/29/ Euratom [3], establece que las condiciones de trabajo de la mujer embarazada serán tales que sea improbable que la dosis equivalente al feto exceda 1 mSv, lo que supone una drástica reducción sobre el límite establecido en la legislación española vigente [4], que es de 10 mSv, desde la declaración del embarazo hasta el final del mismo. La trasposición al ordenamiento jurídico español de la Directiva 96/29 supone una revisión de los condicionantes que, en materia de protección radiológica, deben establecerse para que las mujeres gestantes puedan desarrollar su trabajo como personal profesionalmente expuesto a radiaciones ionizantes .

OBJETIVOS

El presente estudio tiene como objetivos: valorar los puestos de trabajo del personal sanitario ocupacionalmente expuesto, desde el punto de vista de su adecuación para ser ocupados por mujeres gestantes, según las nuevas recomendaciones de ICRP, teniendo sólo en cuenta las dosis recibidas por radiación externa, el establecimiento de restricciones de dosis relacionadas con la fuente, y la posible modificación de las normas de seguridad de la instalación si así se requiere. Posteriormente este estudio se completará realizando una estimación de las dosis recibidas por incorporación de radionúclidos en los casos en que sea necesario

MATERIAL Y METODOS

El estudio se ha realizado en ocho Servicios de un hospital de referencia: Radiodiagnóstico, Hemodinámica, Quirófanos, Medicina Nuclear, Oncología Radioterápica, Análisis Clínicos, Endoscopias, e Inmunología, así como en los Servicios de Radiodiagnóstico de cinco centros sanitarios. El estudio dosimétrico abarca las dosis recibidas, por radiación externa, por los profesionales ocupacionalmente expuestos a radiaciones ionizantes, durante periódos de nueve meses consecutivos , durante los tres últimos años, en los que no ha habido cambios significativos en las distintas instalaciones, lo que ha supuesto el seguimiento de 222 profesionales, distribuidos en cinco categorías profesionales: Facultativos, ATS (Ayudante técnico sanitario), Auxiliares de enfermería, Técnicos, y Celadores.

La estimación de la dosis a la entrada del abdomen se ha realizado a partir de la dosimetría personal de los trabajadores. Se han utilizado dosímetros TLD de FLi, estimándose un error máximo del 10 % en condiciones de laboratorio. En aquellos casos en que se ha superado el límite de 2 mSv en un mes, se ha procedido a un estudio posterior para valorar si la frecuencia de que esto ocurra es significativa.

RESULTADOS

En los Servicios de radiodiagnóstico, de los cinco Centros sanitarios, los resultados obtenidos muestran que el 100% de los profesionales han recibido dosis menores a 1,5 mSv en los periodos establecidos.

Los resultados obtenidos en los distintos Servicios del Hospital de referencia se presentan en las siguientes Tablas , indicando en cada caso el tamaño de la muestra (n) . En cuatro de los nueve Servicios, Tablas I,II,III,IV, el 100% del personal ha recibido ,en los periodos estudiados, dosis inferiores o iguales a 1,5 mSv, siendo en algunos casos menores o iguales a 1mSv. En las Tablas V,VI,VII,VIII, se presentan los resultados de cuatro Servicios en los que el personal ha superado, solamente en uno de los periodos estudiados, el límite considerado no superándose salvo en uno de los Servicios (Tabla VIII) el valor de 2,5 mSv . En el Servicio de Hemodinámica (Tabla VII), el límite se ha superado debido a la dosis recibida en un sólo mes, por lo que se realizó un estudio posterior teniendo en cuenta las dosimetrías de los últimos seis años, siendo la frecuencia de que esto suceda del 0,4%. Por ultimo en la Tabla IX, se presentan los resultados correspondientes al Servicio de Medicina Nuclear, donde la operadora ha superado el límite establecido en todos los periodos estudiados, aunque nunca ha superado el valor de 2,5 mSv en 9 meses.

SERVICIO DE INMUNOLOGIA				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativos (n=10)	80%	20%		
Técnicos (n=3)	67%	33%		

TABLA I

SERVICIO DE ANALISIS CLINICOS				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativo (n=1)	100%			
Técnicos (n=2)	100%			

TABLA II

SERVICIO DE ENDOSCOPIAS				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativos (n= 2)				
ATS (n=3)	100%			
Auxiliares (n=4)	75%	25%		

TABLA III

SERVICIO DE ONCOLOGIA RADIOTERAPICA				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativos Físicos (n=2)	100%			
Facultativos Médicos (n=6)	100%			
Técnicos/ ATS (n=4)	25%	75%		
Auxiliares (n=1)		100%		
Celadores (n=1)		100%		

TABLA IV

SERVICIO DE RADIODIAGNOSTICO				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativos (n=19)	44%	45%		11%
ATS (n=7)	16%	84%		
Técnicos (n=18)	74%	26%		
Auxiliares (n=6)	83%	17%		
Celadores (n=1)	100%			

TABLA V

SERVICIO DE QUIRÓFANOS				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Traumatólogos (n=10)	22%	52%		26%
Neurocirujanos (n=4)	50%		50%	
ATS (n=1)	100%			
Celadores (n=1)	100%			

TABLA VI

SERVICIO DE HEMODINAMICA				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativos (n=3)	33%	34%		33%
ATS (n=1)	100%			
Auxiliares (n=1)		100%		
Celadores (n=1)				100%

TABLA VII

SERVICIO DE RADIODIAGNOSTICO (Radiología Intervencionista)				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤4 mSv
Facultativos (n=2)		50%		50%
ATS (n=1)		100%		
Auxiliares (n=1)	100%			

TABLA VIII

SERVICIO DE MEDICINA NUCLEAR				
	D≤1 mSv	1<D≤1.5 mSv	1.5<D≤2 mSv	2<D≤2.5 mSv
Facultativo (n=2)		100%		
ATS/TER (n=1)				100%

TABLA IX

CONCLUSIONES

La valoración de los puestos de trabajo para ser ocupados por trabajadoras gestantes, ocupacionalmente expuestas, no puede ser genérica, sino que debe realizarse específicamente en cada Centro sanitario, dada la variedad de equipamiento, técnicas utilizadas, fuentes a las que se encuentran expuestas, así como las barreras estructurales existentes.

En la actualidad el programa de optimización de dosis, basado en formación continuada, diseño de la instalación, y cumplimiento del reglamento de funcionamiento, es correcto, ya que la dosis equivalente que puede recibir el feto durante el periodo de gestación es muy inferiores al límite vigente en la legislación española .

En ocho de los nueve Servicios controlados en el Hospital de referencia, se podría establecer con las condiciones actuales de trabajo una optimización de la dosis equivalente en la superficie del abdomen de 1,5 mSv, para las trabajadoras gestantes, ya que el porcentaje del personal que lo supera muestra que es realista el establecimiento de dicho valor, pues sólo se ha superado en uno de los periodos estudiados . Sin embargo en algunos de los puestos de trabajo de los Servicios de Radiología intervencionista y en quirófanos, creemos es necesario establecer normas de seguridad mas estrictas para las trabajadoras gestantes.

El Servicio de Medicina Nuclear representa un caso especial ya que el personal no facultativo superaría el nuevo límite en todos los periodos estudiados, aunque el valor máximo obtenido sugiere que, en este caso, con el establecimiento de un sistema de protección adicional para las trabajadoras gestantes , se conseguiría la optimización la dosis debida a radiación externa a valores inferiores al límite recomendado por ICRP-60

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ADAPTIVE RESPONSE INDUCED BY OCCUPATIONAL EXPOSURES TO IONIZING RADIATION

J.F.Barquinero[a], L.Barrios[b], P. Murtra[b], M.R.Caballín[a], R.Miró[c], M.Ribas[d] and J.Egozcue[b]

a.- Unitat d'Antropologia, Dpt. Biologia Animal, Biologia Vegetal i Ecologia, Fac. Ciències.

b.- Unitat de Biologia Cel.lular, Dpt. Biologia Cel.lular i Fisiologia, Fac. Ciències.

c.- Unitat de Biologia, Dpt. Biologia Cel.lular i Fisiologia, Fac. Medicina.

Universitat Autònoma de Barcelona, 08193 Bellaterra. Spain

d.- Servei d'Oncologia, Hospital de la Santa Creu i Sant Pau de Barcelona.

Abstract

We have found a significant decreased sensitivity to the cytogenetic effects of ionizing radiation (IR) and bleomycin (BLM) in lymphocytes from individuals occupationally exposed to IR when compared with a control population. These results suggest that occupational exposures to IR can induce adaptive response that can be detected by a subsequent treatment by IR or by BLM. However, no correlation between the results obtained with both treatments was observed. A great heterogeneity in the frequencies of chromatid aberrations induced by BLM was observed. The study of the influence of different harvesting times showed that there was no correlation with the frequencies of chromatid breaks. Our results indicate that the use of BLM to detect adaptive response has several difficulties at the individual level.

Introduction

In vitro pretreatments with tritiated thymidine or with low doses of X-rays make phytohemagglutinin stimulated human lymphocytes less susceptible to cytogenetic damage by subsequent high acute doses of X-rays [1,2]. This phenomenon has been called

Adaptive Response (AR). The ability to respond to small doses of X-rays has only been detected when the adaptive dose is done on phytohemagglutinin stimulated human lymphocytes [3,4]. On the other hand, Wolff et al [5] reported that human blood lymphocytes adapted by *in vitro* exposure to low doses of ionizing radiation (IR) showed a decrease in the frequency of chromatid and isochromatid lesions induced by a subsequent treatment with bleomycin (BLM). Moreover, individuals exposed to IR accidentally also showed a decreased sensitivity of their lymphocytes to a challenge dose of BLM [6]. Pretreatment with low concentrations of BLM can also induce AR [7].

Wojcik and Streffer [8] showed that the fixation time could influence the frequency of chromosomal abnormalities induced by IR.

The aim of the present study was to compare the effect of the challenge doses of IR and BLM on lymphocytes of an occupationally exposed population and if there is any relationship between the time of fixation and the level of chromosome aberrations observed after *in vitro* treatment of human lymphocytes with BLM.

Materials and Methods

Peripheral blood samples from 12 occupationally exposed individuals to X and/or gamma-rays, that work in radiotherapy and radiodiagnostic services, were used. For comparisons peripheral blood samples from non-exposed individuals were used.

Blood samples were irradiated with a challenge dose of 2 Gy using a cobalt source. Dose rates varied from 96.12 to 91.95 cGy/min. In order to emulate *in vivo* conditions, IAEA recommendations were followed [9]. After irradiation blood samples were cultured for 48h. The chromosomal aberrations considered were dicentrics (dic).

In the study of the effect of BLM, a challenge dose of 0.03U/ml was added 5 hours before harvesting.

In the study of the influence of harvesting time performed in three individuals, a total of 24 cultures were made for each individual. Eight cultures were harvested at 48h, eight at 50h

and the remaining eight at 52h. For each time of harvesting, the eight cultures were treated as follows: two (C) were used as control, two (A) received only the adaptive dose of BLM (0.03mU/ml) 24h after the culture start, two (CH) received only the challenge dose of BLM (0.03U/ml) 5h before harvesting and the other two (T) received both the adaptive and the challenge treatment with BLM.

For BLM sudies, chromatid breaks (ctb) were considered.

In all cases, to select first division metaphases, 12 μg/ml of BrdU was added since the set up of the cultures.

Results and Discussion

Adaptive response for the challenge dose of 2 Gy of γ-rays

In the control study, the frequency of dic did not shows significant differences between the exposed and the non-exposed population, although the frequency of acentric chromosomes was significantly higher in the exposed population ($p<0.001$). Increased frequencies of structural chromosome abnormalities in populations exposed to IR have been described by several authors [10-17].

Table I.- Cytogenetic results after IR and BLM treatments.

	2 Gy of gamma-rays		0.03U/ml of BLM	
	Non exposed	Occupationally exposed	Non exposed	Occupationally exposed
Number of subjects	8	12	11	12
Cells analyzed	2504	4742	2138	2502
ctb/cell (rank)			0.4 (0.21 to 0.66)	0.29 ()0.18 to 0.43
dic/cell (rank)	0.31 (0.26 to 0.37)	0.26 (0.21 to 0.31)		

After 2 Gy irradiation, the frequency of dic was significantly lower in the exposed population when compared with the non-exposed one ($p<0.001$) (table I). These results indicate that occupational exposures to very low doses of IR make human lymphocytes less susceptible to subsequent *in vitro* irradiation at high doses. The individual frequencies of dic ranged from 0.263 to 0.375 in the non-occupationally exposed population and from 0.214 to 0.307 in the occupationally exposed one. In both cases the Pearson's chi-squared test showed homogeneity in the frequencies of dic per cell. A significant negative correlation was observed between the frequency of dic and the doses occupationally received during the last year ($p<0.025$) and the mean dose of the last three years ($p<0.05$). These results could indicate that the differences in the response to subsequent high doses of IR could be related mainly to the occupationally doses received recently [18].

It is interesting to note that these results could have some implications in biological dosimetry. The estimated dose after 2 Gy irradiation was, in general, lower in the occupationally exposed individuals (mean= 1.86 Gy) than in the non-exposed ones (mean= 2.05 Gy). In three occupationally exposed individuals, the 95% confidence interval of the estimated dose did not include the challenge dose of 2 Gy [18].

Adaptive response for the challenge dose of BLM

In the control study the frequencies of ctb were higher in the occupationally exposed population but the difference was not significant. After BLM treatment, the occupationally exposed population showed significantly lower frequencies of ctb than the non-exposed one ($p<0.025$) (table I). This result could indicate that an AR induced by occupational exposures to IR can also be detected after BLM treatment of peripheral blood cultures [19]. This is in agreement with the idea that an AR induced by a low dose of a mutagenic agent can be detected after a challenge dose of the same or similar DNA damaging agent [5,7]. Both, IR and BLM induce double-strand breaks in DNA.

When the individual frequencies of ctb were considered, Pearson's chi-squared test showed heterogeneity in both populations (occupationally exposed $p<0.0005$; non-exposed $p<0.005$). The ctb frequencies ranged from 0.21 to 0.66 in the non-exposed

population and from 0.18 to 0.43 in the occupationally exposed one. It is interesting to note that there is a considerable overlaping between the distribution of the individual frequencies of ctb between both populations. Similar heterogeneity was observed by Tedeschi et al [20] after BLM treatment of blood cultures from children contaminated as a consequence of the Chernobyl accident.

When the IR and BLM results were considered, no correlation was observed between the effect of IR and BLM in both populations. The homogeneity in the frequencies of dic observed after 2 Gy treatment could be due to the irradiation of cells at the G_0 stage. However, the heterogeneity observed after BLM treatment 5h before harvesting could be due to the clastogenic effect on a cell population growing asynchronically.

Influence of different harvesting times on the study of the AR to BLM

Variability for the induction of AR has been suggested to be due to differences in cell cycle kinetics [8]. However other studies suggested that adaptation is not caused by changes in the rate of cell progression to mitosis after a challenge dose, indicating that cell stage sensitivity could not be an important factor in AR [21,22].

In the present study, no correlation was observed between the time of harvesting and the frequencies of ctb induced either on T or CH+A-C cultures. Moreover, the frequencies of ctb per cell in the three individuals studied were, in general, lower in the T cultures than in

Table II.- Frequencies of ctb/cell induced by BLM treatment in the T and CH+A-C cultures of three individuals.

	Individual 1			Individual 2			Individual 3		
Harvesting time	48h	50h	52h	48h	50h	52h	48h	50h	52h
ctb/cell T culture	1.21	0.72	0.87	0.64	0.70	0.52	1.08	0.93	1.23
ctb/cell CH+A-C cultures	0.89	0.98	1.18	0.80	1.03	0.69	1.27	0.98	0.70

T= Adaptive and challenge dose; CH=Challenge dose; A=Adaptive dose; C=Control

the CH+A-C cultures for any time of harvesting although, the differences were not significant (table II). On the contrary, only for individual 3 the frequency of ctb per cell in the T/52h culture (1.23) was significantly increased when compared with the frequency of CH+A-C/52h cultures (0.7)($t=2.003$; $p<0.025$ one-sided test).

The great interindividual variability observed to the sensitivity to BLM, indicate that the use of BLM to detect AR has several difficulties at the individual level and the results obtained must be considered carefully.

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OPTIMIZACIÓN DE LA PROTECCIÓN RADIOLÓGICA A PARTIR DEL HALLAZGO DE LESIONES RADIOINDUCIDAS EN CARDIOLOGÍA INTERVENCIONISTA

[1]E Vañó, [2]L Arranz, [2]JM Sastre y [2]N Ferrer

[1]Cátedra de Física Médica. Departamento de Radiología. Hospital Universitario San Carlos. Universidad Complutense. 28040 Madrid. España.
[2]Servicio de Protección Radiológica. Hospital Ramón y Cajal. 28034 Madrid. España.

ABSTRACT- RESUMEN

RADIOLOGICAL PROTECTION OPTIMIZATION DERIVED FROM RADIATION INDUCED LESIONS IN INTERVENTIONAL CARDIOLOGY FINDING

Interventional Cardiology is one of the specialities in which patients are submitted to the greatest radiation doses with x ray systems used for diagnostic purposes and then, it is also a speciality of high occupational radiation risk. In the last years, several cases of radiation induced lesions produced on patients derived of new complex interventional procedures have been described. As consequence, different rules for avoiding this kind of incidents have been recommended by international Organisations and regulatory Bodies. Nevertheless it has been devoted relatively few attention to the evaluation of the occupational risks that inevitably are also high in these facilities. In this work, some cases of radioinduced skin lesions produced on patients submitted to cardiac ablation procedures are described. Radiological protection considerations of interest for the regulatory Bodies are made, that permit to minimize the probability of these incidents, in what to the X-rays equipment is referred as well as to the operation procedures and level of radiation protection training of the medical specialists.

OPTIMIZACIÓN DE LA PROTECCIÓN RADIOLÓGICA A PARTIR DEL HALLAZGO DE LESIONES RADIOINDUCIDAS EN CARDIOLOGÍA INTERVENCIONISTA

La Cardiología Intervencionista es una de las especialidades que utiliza equipos de rayos X para diagnóstico en la que se imparten mayores dosis de radiación a los pacientes y en consecuencia, en la que los especialistas médicos están sometidos a mayores riesgos ocupacionales de irradiación. En los últimos años se han descrito varios casos de lesiones por radiación en pacientes, consecuencia de nuevos procedimientos intervencionistas complejos, lo que ha llevado a que diversas organizaciones internacionales se ocupen del tema y a que algunos organismos reguladores dicten normas que tiendan a evitar estos incidentes. No obstante se ha dedicado relativamente poca atención a la evaluación de los riesgos ocupacionales que inevitablemente son también elevados en estas instalaciones. En este trabajo se describen algunos casos de lesiones radioinducidas producidas en la piel de pacientes sometidos a procedimientos de ablación cardíaca. Se hacen las consideraciones de protección radiológica de interés para los Organismos reguladores, que permiten minimizar la probabilidad de estos incidentes, tanto en lo que al equipo de rayos X se refiere como a los procedimientos de operación, así como al nivel de entrenamiento en protección radiológica de los especialistas médicos.

1. Introducción

La Cardiología Intervencionista (CI) es una de las modernas especialidades en la que se imparten las mayores dosis de radiación a los pacientes con equipos de rayos X utilizados con fines diagnósticos y en consecuencia es también una especialidad de alto riesgo ocupacional por radiación. Se acepta que el riesgo radiológico al que se somete a estos pacientes, aunque puede ser elevado, está en general, suficientemente justificado y siempre será menor que los otros riesgos presentes en las intervenciones. No obstante, en algunos procedimientos complejos, las dosis en la piel de los pacientes pueden llegar a superar los umbrales de efectos deterministas (1) produciendo lesiones que deben ser consideradas (y evitadas en lo posible) en la planificación de los procedimientos intervencionistas.

Uno de los primeros países en llamar la atención sobre los riesgos de lesiones en piel debidas al uso de la fluoroscopia fue Estados Unidos. La Food and Drug Administration (FDA), publicó en 1994 una recomendación alertando a los especialistas en Radiología Intervencionista (RI) y CI sobre las precauciones a tomar (2), promulgando posteriormente una norma en la que se limita la tasa de dosis que pueden emitir los equipos de fluoroscopia que se instalen en ese país (3). En 1995, la Organización Mundial de la Salud (OMS) conjuntamente con el Instituto Alemán de Higiene de las Radiaciones y la Comisión Europea (CE), organizaron un "Workshop" en Munich (4) para estudiar los diferentes aspectos de seguridad en RI (la publicación de las conclusiones la realizará próximamente la OMS). También durante los últimos tres años, un grupo de trabajo de la Comisión Electrotécnica Internacional (CEI) ha elaborado una norma sobre aspectos de seguridad en los equipos de RI (5) que está en fase de consulta en los diferentes países miembros de la CEI y que previsiblemente se publicará a finales de 1998.

Que el riesgo radiológico no sea el más importante en este tipo de procedimientos no debe impedir que se le preste la debida atención para tratar de minimizarlo en lo posible, y especialmente cuando existe la posibilidad de lesiones por radiación.

La relación entre las dosis a los pacientes y el nivel de riesgo ocupacional no se puede establecer con facilidad (6) debido al gran número de factores que intervienen: características del equipo de rayos X (si se trata de un arco en C o de un equipo de geometría fija, filtración del haz, etc), protocolo del procedimiento intervencionista (tamaño del campo, orientaciones del haz de rayos X, etc), distancia del paciente a la que trabaje el especialista, utilización de dispositivos de protección (como las mamparas articuladas, protectores de tiroides, guantes, etc). Vañó y col. (resultados pendientes de publicación y (7)) han obtenido experimentalmente factores que relacionan el producto dosis-área en salas de CI con las dosis en hombro que recibiría un cardiólogo que no utilizara mampara de protección. Estos factores, diferentes en función del equipo y del protocolo utilizados, son del orden de los 100 μGy/1000 cGy.cm^2.

Desgraciadamente no todos los equipos actualmente en uso en las instalaciones de CI son idóneos para los procedimientos cada vez más complejos que se vienen realizando y en algunas ocasiones los especialistas médicos se ven obligados a trabajar con niveles de riesgo radiológico para ellos y para los pacientes, mayores de lo que sería deseable. También a veces la formación en protección radiológica de estos especialistas no es suficiente, y ello puede contribuir a que no sean conscientes de los elevados niveles de dosis que se pueden estar poniendo en juego en determinadas ocasiones.

En los casos en los que se llegan a producir lesiones por radiación en los pacientes, se deben investigar las causas y corregir los protocolos utilizados. En general, las causas podrán ser múltiples: procedimientos intervencionistas muy complejos, con tiempos de fluoroscopia muy largos, equipos de rayos X no del todo adecuados, protocolo técnico no optimizado (tubo de rayos X muy cerca de la piel del paciente, intensificador de imagen alejado del paciente, campo de radiación no colimado, etc), formación insuficiente en protección radiológica de los especialistas médicos, etc. A todo ello hay que añadir la posibilidad de que los cardiólogos no utilicen regularmente los dispositivos de protección disponibles en la sala (especialmente las mamparas articuladas suspendidas del techo), con lo que sus dosis ocupacionales podrán ser elevadas.

Los dispositivos de medida de dosis a los pacientes (cámaras de transmisión u otros) que ya incorporan algunos equipos modernos, o técnicas de medida de dosis piel como la desarrollada por el Grupo de Física Médica de la Universidad Complutense (8) no es habitual que se utilicen de forma rutinaria por lo que las estimaciones de dosis, cuando son necesarias, se deben realizar "a posteriori" lo que supone una gran incertidumbre en los resultados.

2. Evaluaciones dosimétricas y consideraciones de protección radiológica

En marzo de 1997, la Unidad de Arritmias de un gran centro hospitalario de Madrid, informó al Servicio de Protección Radiológica que había detectado en 4 pacientes, lesiones eritomatosas, probablemente de origen radioinducido. Las lesiones se presentaban siempre en la zona lateral derecha de los pacientes, coincidiendo con la zona de entrada del haz de rayos X del tubo horizontal de un equipo

biplano. Los procedimientos intervencionistas fueron en todos los casos ablaciones cardíacas por catéter con radiofrecuencia.

Tres de los pacientes eran de corta edad (7, 12 y 17 años) por lo que además de los efectos deterministas producidos, el incremento de probabilidad de efectos estocásticos en este tipo de procedimientos debe ser tenido en cuenta en las estrategias de optimización. No se registraron los tiempos de fluoroscopia aunque según estimación de los propios cardiólogos implicados, podían ser del orden de 90-120 minutos. Hasta que no se produjo el diagnóstico de la radiodermitis del cuarto paciente, el Servicio de Cardiología no sospechó que las lesiones pudieran deberse a la radiación, por lo que no se advirtió de las mismas al Servicio de Protección Radiológica. A partir de esta confirmación, se suspendió el uso del equipo de rayos X utilizado para esos procedimientos y se procedió a un análisis detallado de los hechos y a una evaluación dosimétrica.

El equipo de rayos X utilizado fue un General Electric (GE) biplano, instalado en 1977, con generador MSI 1250 y dos tubos MS-100, montados con sus respectivos intensificadores. La geometría del sistema permitía el uso de dos haces de rayos X sin posibilidad de cambio en la orientación, uno en dirección vertical y otro en dirección horizontal. El tubo de rayos X del haz vertical está debajo de la camilla, con el intensificador sobre el paciente, y el horizontal se puede situar de forma que su conjunto colimador esté prácticamente en contacto con el brazo derecho del paciente. La Unidad de Arritmias del Hospital en el que se produjeron los incidentes, venía solicitando desde hacía varios años, una sustitución del equipo de rayos X por su deficiente calidad de imagen.

Dado que en todos los casos los informes del Servicio de Cardiología indicaban que las lesiones "han aparecido en el punto de contacto de la piel con el tubo lateral", se procedió a evaluar con detalle el subsistema tubo-intensificador del haz horizontal y se comprobó que cuando el colimador de este tubo se pone en contacto físico con el brazo o costado derecho del paciente, la piel queda a una distancia aproximada del foco de unos 30 cm.

En base a la estimación realizada con posterioridad a los incidentes conjuntamente con los últimos informes de control de calidad del equipo (el tubo de rayos X del haz horizontal ya estaba fuera de uso), la tasa de dosis promedio en el tubo del haz horizontal podría haber sido de unos 32 mGy/min a 60 cm. Con el conjunto colimador del tubo puesto en contacto con la piel del paciente, la tasa de dosis sería de unos 128 mGy/min, si no se utiliza la magnificación. Con 90-120 minutos de escopia en el haz de rayos X horizontal, la dosis acumulada en la piel de los pacientes ha podido ser de unos 11-15 Gy. Hay no obstante una gran cantidad de factores que han quedado sin definir y que afectan mucho a los valores de dosis estimados. Si en algunos casos se hubiera trabajado con el intensificador más alejado del paciente que los 10 cm habituales, el control automático de brillo hace que las tasas de dosis en la piel puedan ser significativamente mayores. Pasar de 90 cm de distancia foco-intensificador, a 120 cm, puede significar aumentar la tasa de dosis en piel en un factor 1,8. No hay tampoco constancia de que el conjunto colimador del tubo horizontal haya estado en contacto con la piel del paciente durante todo el procedimiento. Las dimensiones y peso del paciente también representan un factor importante de variación de la dosis a la entrada: pacientes de mayor envergadura y proyecciones laterales, requieren más dosis a la entrada si se quiere mantener la calidad de imagen con niveles de contraste y resolución similares.

Aunque en los casos descritos nuestra estimación razonable es que las dosis piel estén cerca de los 11-15 Gy, no se pueden descartar valores mayores (o menores) en alguno de los pacientes, sólo la evolución de las lesiones será el indicador real de las dosis recibidas.

El riesgo ocupacional ha podido ser también bastante elevado. Considerando el tamaño del intensificador utilizado (23 cm), y las distancias foco-paciente y foco-intensificador, el campo de radiación a la entrada del paciente ha podido ser del orden de 50 cm^2, y con las dosis estimadas de 11-15 Gy a la entrada del paciente, el producto dosis-área sería de unos 55.000-75.000 $cGy.cm^2$, lo que llevaría a un valor de dosis en hombro del cardiólogo (utilizando el factor antes citado (7) de 100 μGy/ 1000 $cGy.cm^2$), del orden de 5,5-7,5 mGy por procedimiento, por lo que resulta imprescindible la utilización de medios de protección (delantales, protectores de tiroides, gafas plomadas, pantallas suspendidas del techo, etc). El valor real puede ser mayor o menor que esta cifra dependiendo también de un gran número

de factores: sobre todo la distancia entre el cardiólogo y el paciente y su posición con respecto al tubo de rayos X, cuando se utilizaba el haz horizontal. Es evidente que el riesgo potencial ocupacional puede ser también alto para este tipo de procedimientos, especialmente para el cristalino de los cardiólogos si no utilizan los dispositivos de protección adecuados.

3. Conclusiones

Se han detectado lesiones en la piel de algunos pacientes sometidos a procedimientos complejos de cardiología intervencionista (ablaciones endocárdicas por catéter de radiofrecuencia) y se ha estimado que las dosis ocupacionales pueden ser también altas. En consecuencia se ha procedido a proponer criterios de interés para los especialistas y para los Organismos reguladores, con el fin de optimizar los procedimientos de protección radiológica.

Debería plantearse "a priori" en los diferentes centros que practiquen este tipo de procedimientos, si los equipos de rayos X que se están utilizando son compatibles con los requerimientos de seguridad exigibles actualmente y recomendados internacionalmente. Debería ser prioritario un mejor entrenamiento en temas de protección radiológica para los especialistas en cardiología.

En los procedimientos complejos de CI, las medidas de dosis a los pacientes y las dosis ocupacionales en varias localizaciones anatómicas de los cardiólogos, o el registro de parámetros que permita su estimación realista "a posteriori", deberían formar parte del protocolo rutinario de los procedimientos.

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ANALYSIS OF OCCUPATIONAL DOSES IN INTERVENTIONAL RADIOLOGY AND CARDIOLOGY INSTALLATIONS

E. Vañó (1,2), L. González (1), J.I Ten (1), J.M Fernández (2) and E Guibelalde (1)

(1) Medical Physics Group. Department of Radiology. Complutense University. 28040 Madrid
(2) Medical Physics Service. San Carlos University Hospital 28040 Madrid.

ABSTRACT

The relationship between patient dose (PD) and occupational dose (OD) is not easily predictable in interventional radiology installations due to a large number of factors which can modify the occupational risk (OR) In the present work an analysis is made of the four main aspects which influence OR, namely, x-ray beam used, radiation protection (RP) tools available (aprons, thyroid protectors, gloves, screens, etc) and their regular use, type and number of procedures performed (diagnostic or therapeutic, complexity level, etc), and RP training level of the specialists

High filtration x-ray beams can entail a decrease of 20% in OD A regular use of ceiling mounted faceplates can involve dose savings up to 65% Mean values of dose per procedure for interventional radiologists are something greater (about 15%) than those recorded for cardiologists, except for the dosimeters placed on left forearm and shoulder. The ratio between OD and PD range around 100 μSv/1,000 cGy cm^2 The influence of the staff RP training level on OD is difficult to assess In the IC Service from the Madrid San Carlos University Hospital (SCUH), PD have been reduced in above 30% and OD in a factor of 3, after running some training programmes

1 INTRODUCTION

OD values for interventional radiology (IR) and interventional cardiology (IC) specialists may increase significantly unless suitable RP tools (aprons, thyroid protectors, glasses, gloves and ceiling articulated screens) are used on a regular basis [1-5] Even when using them regularly, the large workload undergone by some staff give rise to noticeable doses. Some authors have suggested than dose to lenses could be the key factor to restrict the activity of these specialists, so that OD values keep below OD limits established by the regulatory bodies [2].

A correct estimation of effective doses (ED) to this staff requires dose measurements on at least two locations, under and outside the leaded apron. Mateya et al. [6] have published recently results from a simulation carried out on a phantom, using x-ray beams of 76 and 104 kVp, showing that ED estimates made from the under apron dosimeter readings undervalue notably its actual value

Manufacturers of x-ray systems for IR and IC are including features (as beam high filtration with some tenths of mm of copper) which allow to reduce PD and OD level provided the correct operation and proper use of the equipment [7, 8] Safety aspects convey an outstanding relevance, therefore the International Electrotechnical Committee has created a working group to develop a rule [9] (now in draft version) which will regulate in the future the construction of this equipment

The relationship between PD and OD is not easily predictable in IR installations, given the large number of factors which influence the OR Great changes can be expected from variations in x-ray machine types and working protocols Sometimes, neglecting the use of the ceiling suspended screen reduces the intervention time, as comfort improves the working rate, but it entails an increase in OD, while PD can be reduced Conversely, the use of protective gloves helps to decrease OD, but PD may raise, since hand tactile perception is decreased and the procedure may become enlarged in time [10]

Another key aspect to take into account is the RP training. Different international bodies have insisted on the importance of training and the World Health Organization, in a recent workshop held in Munich [11], has suggested to settle a second level of RP training, specific for IR specialists

It is advisable to study OR estimators independent on some clinical protocol features (use of different arc orientations, use of articulated screen, etc) to obtain information about dose changes between specialists performing a given intervention type. In this scope, the Medical Physics Group from the Madrid Complutense University is developing a research project, with support of the Nuclear Safety Council, in which OD are being studied, using results from personal dosimetry and environmental dose data, together with the number and type of procedures performed in various installations.

2. MATERIALS AND METHODS

Several IC and IR laboratories, equipped with different x-ray systems and protective elements have been searched throughout our study, appraising the four aspects on which OR level depends, that is, x-ray beam used, RP available tools and their use, type and number of procedures carried out, and RP training level.

OR level has been determined from thermoluminiscent dosimetry (TLD), by placing individually calibrated TLD-100 chips from Harshaw/Bicron/NE-Technology (BICRON-NE, Solon, OH, 44139 USA) at different locations on the specialist. TLD readings were obtained for every single procedure, together with the dose-area product measured to assess PD. To this aim and to relate PD and OD values, transmission ion chambers type DIAMENTOR from PTW (PTW, Freiburg, Germany) were used.

Records from one or more direct reading electronic dosimeters located in different sites on the C-arm x ray system have been another valuable dosimetric indicator. Their readings after each intervention, virtually independent on both beam incidence angles and use made of protective elements (articulated screen, particularly), allowed to estimate the maximum OR levels in the various IR facilities with a sensitivity in the μSv range. Some different electronic devices were used, though the results presented here are arisen from dosimeters SIEMENS - NRPB EPD1 (Siemens, Erlangen, Germany).

3. RESULTS

3.1) Influence of the x-ray beam

The IC service from the SCUH has two Philips equipment, an Integris system equipped with the "spectrabeam" feature [7] (enabling to place in the beam different copper filters between 0.1 and 0.4 mm thick, plus 1.5 mm aluminum) and other conventional system (Optimus M200), used by the same staff and for similar procedures, what has allowed a comparison between both systems in routine clinical use conditions. An analysis of 1,700 procedures leads to obtain mean values of dose, at a distance of 1 m from the scatterer volume, of 0.41 ± 0.05 mSv/intervention for the Optimus and of 0.33 ± 0.05 mSv/intervention for the Integris, that is, a dose saving of 20% for this last system [10]. Similarly, dose-area product mean values for coronariography were 4772 cGy.cm^2 in the Optimus system and a 14% below [12, 13] (4127 cGy.cm^2) in the Integris.

3.2) Available RP tools and their use level.

Proper use of the ceiling articulated faceplate is not possible in the most suitable position throughout all the procedure, even being available in IR theatres. Our data of dose per procedure to left shoulder of the specialist (outside the leaded apron) from TLD on a sample of 83 procedures in six different rooms supply averaged values of 382 μSv (without regular use of the screen) and 136 μSv (a practical decrease of 65%). However, these values are very affected by x-ray equipment type, procedure and specialist skillness.

3.3) Type and number of procedures performed.

OD distributions due to scatter radiation, measured by TLD at nine different sites on the specialist have resulted more homogeneous in IR than in IC. Cardiologists become more irradiated on their left hand side, while radiologists use to work at a lower distance to the patient and in variable positions. Except for the dosimeters located at left shoulder and forearm, averaged doses per procedure are something larger for radiologists than for cardiologists (around 15%). Doses to hands have reached until 2.2 mSv/procedure in IC and 3.0 mSv/procedure in IR.

TABLE I: Annual Effective Dose (derived from under-apron dosimetry) in the Interventional Cardiology Service of the San Carlos University Hospital (Medical Staff values)								
Year	**1988**	**1989**	**1991**	**1992**	**1993 RP TRAINING**	**1994 RP TRAINING**	**1995**	**1996**
Number of Cardiologists	4	6	8	11	7	12	10	13
Range (mSv/year)	0.8 - 17.5	1.1 - 27.8	1.9 - 26.5	0.9 - 24.2	1.0 - 4.40	0.6 - 13.0	0.7 - 4.10	0.4 - 5.80
Mean ± Std (mSv/year)	8.0 ± 7.1	9.1 ± 9.2	9.0 ± 9.3	7.4 ± 8.3	1.9 ± 1.0	3.0 ± 3.3	1.8 ± 1.2	1.5 ± 1.6
Median (mSv/year)	6.80	5.85	5.05	3.70	1.55	1.60	1.30	0.90

Ratios between OD and PD have furnished values between 84 and 120 μSv/1,000 cGy.cm^2 to shoulder of the specialist when no articulated screen is used. A professional using a x-ray equipment specifically designed for IR, which performs 3 procedures a day with a mean value of 8,000 cGy.cm^2/procedure may receive 50 mSv/month to shoulder (and something lower to eyelens). These results should be used carefully, keeping in mind their dependence on x-ray facility type, procedure and specialist skillness. For example, performing an intracoronary ecography in IC increases both PD and OD of 30% [14].

3.4) Specialist RP training level.

This is one of the most difficult aspects to assess, since it requires an inspection time interval long enough and available detailed dose data before and after running RP training programmes directed to staff [15, 16]. However, it is recognized as the most important item in RP optimization programmes [11, 15]. It can be worth to quote data from the SCUH. Its IC service meets variable number of specialists (around eight staff usually) which received a specific training during 1993 and 1994. Before the programme several cases of exceeding OD limits had been observed, and protective screen were seldom used. In the last dosimetric assessments, PD values have decreased of above 30% and median values of OD are about 1/3 of the previous ones, and no occupational overexposure incident has been observed ever since. Protective screens and other RP tools are now regularly used in the service. Table I shows OD values measured since 1988 in the IC laboratories of the SCUH.

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STRAPIR, AN EUROPEAN INITIATIVE FOR OPTIMIZING RADIATION PROTECTION IN INTERVENTIONAL RADIOLOGY

[1]E. Vañó, [1]L. González, [2]R. Van Loon, [3]R. Padovani, [4]C. Maccia and [5]G. Eggermont

[1]Medical Physics Group. Radiology Department. Complutense University. 28040 Madrid. Spain.
[2]Department of Fundamental Electricity and Instrumentation. Vrije Universiteit Brussel and Federal Agency of Nuclear Control. B-1050. Brussels. Belgium.
[3]Istituto di Fisica Sanitaria. Ospedale S. Maria della Misericordia, Udine, Italy.
[4]C.A.A.T.S. 43, Bd Maréchal Joffre. 92340 Bourg-la-Reine. France.
[5]Department of Radiation Protection. Vrije Universiteit Brussel. B-1050. Brussels. Belgium.

ABSTRACT

In 1995, an European initiative for optimizing radiation protection in interventional radiology was proposed by 8 research groups. The project acronym was STRAPIR (Staff Radiation Protection in Interventional Radiology). Interventional Radiology involves an important number of specialists and their risk level is not well known, since dosimetric records exhibit important discrepancies. Many professionals using these techniques are not radiologists and the basic rules of radiation protection, known by radiologists, are not always correctly and completely followed, hence the use of protection devices is not as regular as desirable. Additionally, x-ray systems not specifically designed for interventional procedures are still used in many hospitals, what entails a significant occupational risk increase to the specialists. Some relevant questions for regulatory bodies are presented, namely, reliability of the actual data banks for occupational dosimetry, use of two personal dosimeters for assessing effective dose, actions to strengthen the systematic use of personal dosimeters and protection tools, proposals for specific training in radiation protection and use of x-ray systems specifically designed for interventional procedures, publication of reports about accidents and incidents, are also discussed.

1. INTRODUCTION

In April 1995, an European initiative for promoting the study of the occupational doses in Interventional Radiology (IR) installations and optimizing Radiation Protection (RP) was taken by the Complutense University of Madrid and the Vrije Universiteit of Brussels. Other groups joined this project in a second phase, namely:

1. Department ELEC and the Radiological department of the Vrije Universiteit Brussel. Belgium. Prof. R. Van Loon.
2. Medical Physics Group. Radiology Department. Complutense University of Madrid. Profs. E. Vañó and L. González.
3. Department of Clinical Physics - Leeuwarden. Holland. Dr Hummel, Engineer from the University of Delft.
4. Radiodiagnostics St Radboud - University Nijmegen. Holland.
5. Istituto di Fisica Sanitaria - Ospedale S. Maria della Misericordia, Udine. Italy. Dr. R. Padovani.
6. Radiologie Cardiovasculaire - Hospital Broussais Paris. France. Head Prof. J-C Gaux. and Dr. C. Maccia. CAATS.
7. Radiological Clinic - Semmelweiss Medical University. Budapest. Dr. Karlinger MD.
8. Radiation Hygiene Laboratory. Bucharest.

The acronym assigned to the project was STRAPIR (Staff Radiation Protection in Interventional Radiology) and it was submitted for partial funding to the European Commission (EC) services. The scientific evaluation of the proposal was good but not enough priority to this topic was assigned. Notwithstanding, some of the partners decided to continue their work in this important field at national level, looking for a future opportunity for EC coordination and funding.

The STRAPIR project deal with regulatory aspects related with "control measures for practices causing exposure".

IR is a technique during which the "intervention" of the medical staff on the patient is made mainly under fluoroscopic control. This practice usually conveys rather important exposure of professional as well as of the patient. The situation for the medical staff in these cases is different from other radiological techniques, since they should remain close to the patient while the X-ray source is in use and in most cases for long period of time. Beside those medical specialists, a number of other workers need to be present in the room, therefore the risk is enlarged substantially to the auxiliary staff. So IR is one of the medical specialities that present great occupational radiation risk for the specialists practising it. In this sense, the International Commission of Radiological Protection (ICRP) has shown interest and concern in the topic, in its last published recommendations on occupational protection in medical exposures (1). Also the World Health Organization (WHO) is interested in this topic, and recently has sponsored a Workshop in Munich, Germany, about safety aspects of IR (2).

Although this branch of radiology involves an important number of specialists, their risk level is not well known, since dosimetric records exhibit important discrepancies. One should keep in mind that an important number of the professionals using these techniques are not radiologists (e.g. those accomplishing cardiac catheterisation). Therefore the basic rules of radiation protection, known by radiologists, are not always correctly and completely followed. As in conventional radiology, protection devices such as mobile screens, lead aprons, thyroid protectors, gloves, etc., represent an important loss of comfort for the specialist. The use of these devices therefore is not as intensive as it would be. This deficient practice introduces a variable whose evaluation is of major importance.

New imaging technologies, as those incorporating digital images, have improved the quality of the images substantially and lowered the risk for the patient by demanding lower concentrations of contrast medium. On the other hand the impact of these new technologies on the dose received by workers and patients is not yet clearly investigated.

It is necessary to perform measurements to quantify doses received by workers on modern equipment because the distribution of dose can differ largely from that found in conventional radiology. with C-arm systems the position of the X-ray tube and the direction of the beam can differ widely depending on the type of intervention and the skill of the professional.

This topic fits in undoubtedly the interest of regulatory Bodies under the heading of optimisation of radiological protection in complex exposure situations: Development of practical methods aiming to optimize procedures to situations where reduction of exposure is possible, through the identification of factors affecting occupational doses, development of tools to simulate typical scenarios in IR and calculate occupational exposures, and development of training schemes for staff, are the main items in STRAPIR project.

Additionally, x-ray systems not specially designed for IR with overtable x-ray tube, are still frequently used, with a very high risk for staff. In these cases the system of radiation protection should be applied as an "intervention" philosophy (3) where the benefit of possible RP measures would be greater than the inconveniences for the clinical work.

The fact that IR techniques provide large benefits from the medical point of view means a noticeable increase in the number of facilities and professionals practising it (4) with an increasing workload of both equipment and workers. Therefore special attention has to be paid in monitoring occupational doses. A very prudent

attitude must be adopted in the application of the radiological protection measures, since a very forceful performance in the case of overdose of these specialists seems to lead to neglecting the use of dosimeters, instead of a more cautious use of radiation (5).

2. OBJECTIVES

This co-operative multidisciplinary research project can be summarised as it follows:

- Evaluation of the doses received by medical specialists and auxiliary staff in whole body (effective dose), hands, arms, eye lenses and thyroid as a function of type and number of interventions performed in selected intervention samples (taking into account the type of equipment and the technical protocol used). Revision of the algorithms for effective dose evaluation.

- Establishment of both individual and area dosimetry protocols within the facilities and estimation of advantages of using different protection devices.

- Strategies for optimisation of medical and technical protocols for the selected interventions, with reference to the optimal dose-image quality relationship, total number of images and fluoroscopy time required (6,7,8, 9).

- Design of training activities in radiation protection as well as strategies to spread specific criteria of operational radiation protection having the greatest impact at this type of facilities. This fits also in the scope of the recently revised patient Directive (Medical Exposures Directive) (10) prepared by the Commission, requiring training in a common curriculum and mandatory refresher courses, especially in areas requiring special attention such as IR (11).

3.- CONCLUSIONS AND QUESTIONS TO BE SOLVED BY THIS RESEARCH PROJECT

Besides a part of these objectives will be covered by the European Concerted Action DIMOND (12), some important questions would be considered in multinational research projects in the future. Regulatory Bodies would be also directly implied in some of the issues of the project:

1. Reliability of the actual data banks for occupational dosimetry in IR.
2. Convenience for advising the systematic use of a minimum of two personal dosimeters for IR specialists (under and over the leaded apron).
3. Actions for promoting the systematic use of personal dosimeters and equilibrium with the sanctioning capacity of the Regulatory Bodies.
4. Actions for promoting the systematic use of RP tools (screens, tyroid protectors, glasses, etc).
5. Convenience for advising a second specific level of training in RP for specialists in IR.
6. Actions for promoting the exclusive use of x ray systems specifically designed for IR procedures.
7. The publication of reports about accidents and incidents in IR, with relevant dosimetric and operational data, should be published encouraged. A national reporting systems are recommended (ERPET recommendation (11)).
8. IR procedures must be performed only by physicians with special training (including radiation protection training) and experience. Radiographers, nurses and involved staff must receive radiation protection training appropriate to their role. All staff should be familiar with the particular operating characteristics of their equipment (ERPET recommendation (11)). Guidelines and objectives of training courses should be defined.
9. Techniques for improving image quality and reducing patient and staff doses, without impairing clinical efficacy, should be more widely disseminated than at present. Manufacturers have a key role in this process and should be encouraged to participate in training courses for IR professionals (ERPET recommendation (11)).

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MAPA DE RADIACION GAMMA NATURAL DE ESPAÑA
CARACTERIZACIÓN RADIOMÉTRICA DE DIFERENTES TIPOS DE SUPERFICIES

Autores: Enrique Suárez Mahou (CSN), José Angel Fernández Amigot (ENUSA), Joaquín Botas Medina (ENUSA).

Resumen

La radiactividad gamma procedente del suelo y rocas es debida a la presencia en los mismos de los elementos Uranio, Torio y Potasio-40. La forma de caracterizar radiométricamente una superficie es una función del objetivo perseguido. Se puede realizar sobre grandes superficies (decenas o centenas de miles de kilómetros cuadrados para su utilización en estudios a escala nacional), superficies medias (50 a 1000 Km2 para su uso por ejemplo: en estudios epidemiológicos o biológicos sobre áreas con un fondo radiométrico determinado) y pequeñas superficies inferiores a cinco kilómetros cuadrados (emplazamientos industriales, estudios preoperacionales, etc.)

En este artículo se consideran aspectos de la caracterización radiométrica de superficies de interés y se expone la contribución del Proyecto MARNA (Mapa de Radiación Natural Provisional de España) a la elección y caracterización radiométrica de las mismas.

1. FUENTES NATURALES DE RADIACION GAMMA

En la naturaleza, la radiación gamma emitida por las rocas es debida debido a la presencia en las mismas de los elementos: potasio, torio y uranio. Existen también otros elementos radiactivos naturales pero que se encuentran en tan pequeña proporción que su contribución a la radiación gamma total es despreciable. Los picos de energía significativos del espectro gamma que se emplean en la medida de radioelementos naturales son: 1,46 MeV., correspondiente al potasio 40, que se utiliza para determinar el contenido en potasio natural, los de 1,1204 y 1,764 MeV., correspondientes al bismuto 214, descendiente del uranio natural, que se utilizan para estimar el contenido en uranio y el de 2,62 MeV, correspondiente al talio 208, descendiente del torio natural, que se emplea para determinar el contenido en torio natural.

El agua del mar presenta un contenido medio de uranio de 0,002 ppm; las aguas subterráneas 0,0002 ppm, y el petróleo 0,1 ppm.

El potasio natural contiene un 0,0119% de potasio 40.

En cuanto a la contribución media terrestre de cada uno de ellos a la radiación gamma natural un 45% proviene del potasio, un 45% proviene del torio y un 10% proviene del uranio natural.

Una concentración de 1% de potasio produce una tasa de exposición de 1,05 μR/h, mientras que 1 ppm de torio daría lugar a 0,310 μR/h, y por último 1 ppm de uranio a 0,625 μR/h.

El contenido medio de uranio de las rocas superficiales oscila entre 1 y 3 ppm. Mucho más abundante es el torio que puede alcanzar proporciones 3 y 4 veces superiores a las del uranio. Tanto el torio como el uranio se encuentran en la naturaleza en estado tetravalente, pero mientras el ión U+4 en ambiente oxidante pasa facilmente a hexavalente, el torio no cambia de valencia por lo que es mas dificilmente movilizable. En condiciones de oxidación, el uranio hexavalente forma el ión uranilo (UO2++) que puede dar origen a numerosos minerales.

2. METODOLOGIA PARA LA ESTIMACION

Para la caracterización radiométrica de una gran superficie o pequeño emplazamiento , se debe definir:

- Su radiometría media con un límite de confianza predeterminado (en unidades físicas).

- Su variabilidad radiométrica que en el caso del proyecto Marna está fuertemente condicionada por las características geológicas del medio natural en el que se efectuan las medidas.

Ambos parámetros son estadísticos y condicionan la metodología y la magnitud del desmuestre radiométrico a realizar.

Una caracterización radiométrica adecuada del emplazamiento permitirá comparar la variación introducida en el mismo por fuentes externas de naturaleza radiactiva similar.

La definición de las bases de la caracterización radiométrica puede hacerse mediante un desmuestre sistemático o aleatorio. En cualquier caso los resultados se transmitirán despues a un mapa de isorradas y se definirán los parámetros de la población estadística. Para calcular los límites de confianza se puede aplicar la T de Student y después cerrar progresivamente las mallas de desmuestre cuando los citados límites sobrepasen los que se deseen alcanzar.

También debe de ser evaluado el limite de confianza del propio sistema de medidas hasta reducirlo a las cifras que se deseen alcanzar (corrección de las fluctuaciones estadísticas, constantes de tiempo; errores de desmuestre, análisis, varianzas de extensión y de estimación, etc.).

3. RESULTADOS. PROYECTO "MARNA" (Mapa de Radiación Gamma Natural de España a escala 1:1 000 000)

Los datos que integran el proyecto Marna son los siguientes:

- Los generados mediante prospecciones radiométricas aéreas, autoportadas y a pié durante más de treinta años de investigaciones realizadas por la Junta de Energía Nuclear y ENUSA a lo largo de sucesivos planes nacionales de exploración e investigación de Uranio, PNEIU.

- Los generados durante la vigencia de los Convenios CSN-ENUSA para la realización del Proyecto MARNA.

En resumen, se dispone en el momento actual de unos 220.000 datos radiométricos a escala nacional, que han sido reducidos a unos 16.000 para la elaboración a escala 1:1.000.000 del citado Mapa de Radiación Gamma Natural. (Fig. 1). Además pueden obtenerse mapas mucho mas detallados sobre las zonas cubiertas por los proyectos Marna y Marna 2, un ejemplo de ellos se presenta en los mapas que figuran al final de este artículo.

4. APLICACION DEL PROYECTO "MARNA" A LA ESTIMACION DE LA EXPOSICION A FUENTES NATURALES DE RADIACION GAMMA PROCEDENTE DEL SUELO

Corte Radiométrico

Si en el mapa de la Fig. 1 realizamos un corte radiométrico para el intervalo $\geq$ 10 μR/h, obtenemos el mapa de la Fig. 2, igualmente podríamos conseguir la representación gráfica de otros intervalos.

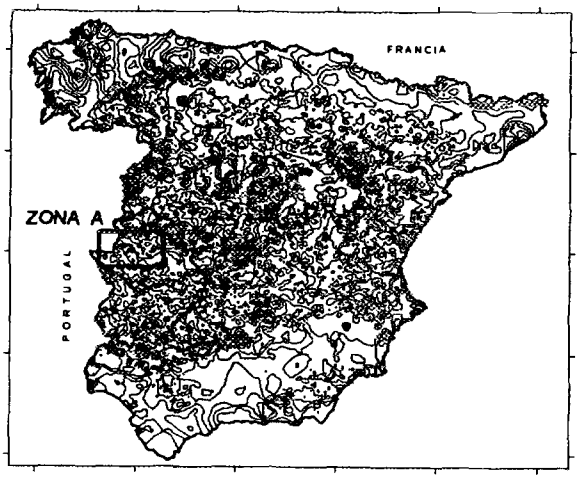

Fig. 1. Mapa de Radiación Gamma Natural Provisional de España

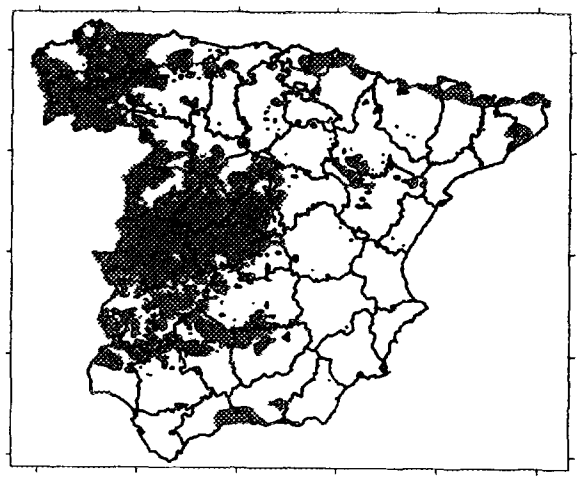

Fig. 2. Corte Radiométrico del Mapa de Radiación Gamma Natural Provisional de España. Intervalo igual o mayor que10 μR/h

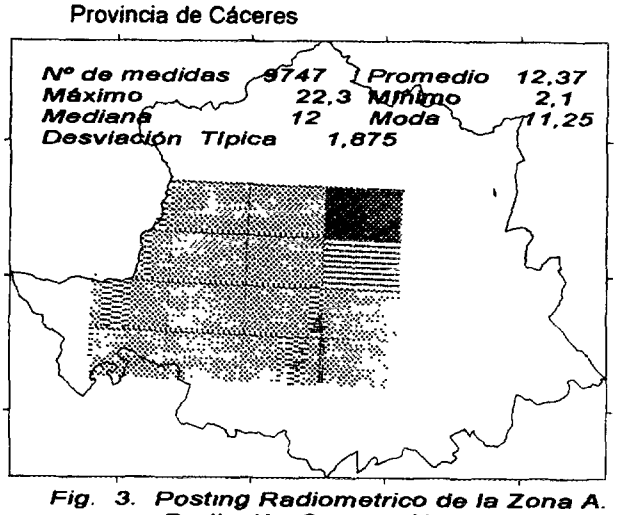

Fig. 3. Posting Radiometrico de la Zona A. Radiación Gamma Natural

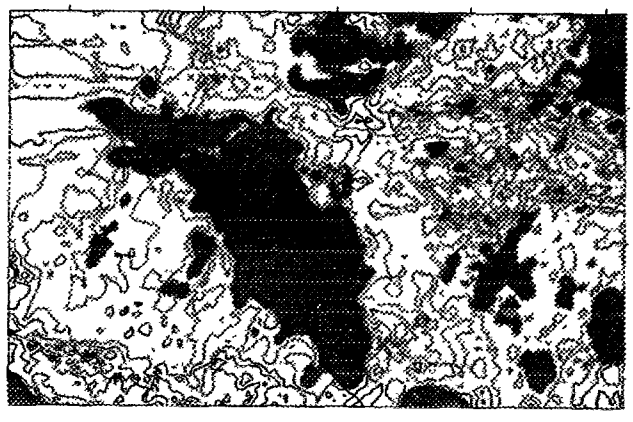

Fig. 4. Mapa Radiométrico de la Zona A. Radiación Gamma Natural

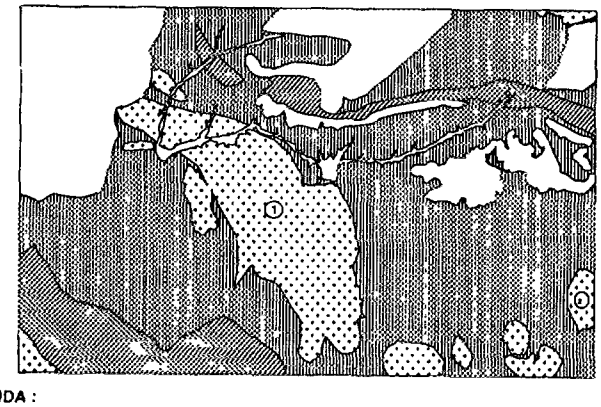

Fig. 5. Esquema Geológico de la Zona A.

Efecto Zoom

Si elegimos una determinada Zona (A en la Fig. 1) se puede obtener la posición de los puntos de medida o datos radiométricos de la misma (Fig. 3) y su caracterización radiométrica estadística al estado de conocimiento actual.

Control geológico

Una combinación de estudios geológicos y radiométricos resulta muy sugerente, si comparamos los mapas geológicos y radiométricos de la zona objeto de estudio (Figs. 4 y 5).

Realización de mapas de potencial de emisión de radón

Se realizan teniendo en cuenta las características geológicas de las zonas consideradas y la radiometría asociada a las mismas.

Realización de mapas dosimétricos

Las estimaciones de dosis debidas a la radiación gamma ambiental se realizan a apartir de los mapas de radiación gamma natural mediante la aplicación de factores correctores admitidos por la comunidad internacional.

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DOSIS EFECTIVA A PACIENTES EN PROCEDIMIENTOS DE RADIOLOGÍA VASCULAR INTERVENCIONISTA EN MÁLAGA Y TENERIFE (ESPAÑA)

[1]Rafael Ruiz Cruces, MD, PhD; [2]José Hernández Armas, PhD; [1]Manuel Pérez Martínez, PhD; [2]Juan García-Granados, BSc; [2]Francisco J. Díaz Romero, MD, PhD; [1]Antonio Díez de los Ríos Delgado, PhD.

[1]Grupo de Investigación en Protección Radiológica. Dpto. de Radiología y M.Física. Facultad de Medicina. Universidad de Málaga.
[2]Grupo de Investigación en Protección Radiológica. Dpto. de Radiología y M.Física. Universidad de La Laguna. Tenerife.

Resumen

Este trabajo de investigación tiene como objetivo estimar la dosis efectiva que reciben los pacientes en procedimientos de radiología vascular intervencionista con sistema digital. La dosis efectiva (E) es el mejor evaluador del riesgo radiológico. Para su estimación se ha partido de una cámara de ionización plana, mediante la cual se obtuvieron los valores del producto de dosis-área ($Gy.cm^2$). Mediante el método descrito en el report NRPB R-262 se han seleccionados proyecciones que se ajustan al campo irradiado en cada uno de los procedimientos analizados. Los valores del producto de la dosis-área y dosis efectiva han sido 75,7 $Gy.cm^2$ y 10,5 mSv para angiografías abdominales; 29,0 $Gy.cm^2$ y 7,6 mSv para arteriografías diagnósticas de miembros inferiores; 104,5 $Gy.cm^2$ y 23,6 mSv para drenajes biliares; 90,5 $Gy.cm^2$ y 21,5 mSv para varicoceles; y por último, 39,5 $Gy.cm^2$ y 9,6 mSv para nefrostomías.

1. Introducción.

Los procedimientos de Radiología Vascular e Intervencionista (RVI) han aumentado de forma sustancial durante los últimos años. Esta "cirugía mínimamente invasiva" ha reducido complicadas intervenciones quirúrgicas. En contraposición, estos procedimientos han incrementado el uso de las radiaciones ionizantes, lo que supone un crecimiento de los valores de dosis a pacientes y al personal profesionalmente expuesto [1].

Los procedimientos de RVI son exploraciones "complejas" en las que se usa grafía y escopia. Como cualquier exploración que utiliza rayos X, estos estudios radiológicos han de someterse a un Control de Calidad que determine las dosis a pacientes, lo cual es requisito legal en nuestro país desde enero de 1996 [2]. Además, con la aprobación de la nueva directiva en el Consejo de la Unión Europea [3], los Estados Miembros deben estimar los valores de referencia en exploraciones complejas. Estos requerimientos legales deben ser establecidos en cualquier país de Nivel Sanitario I. Dicha disposición legal entrará en vigor antes del 13 de mayo del 2000.

El objetivo de este trabajo ha sido estimar las dosis a pacientes (dosis efectiva) en las exploraciones de Radiología Vascular e Intervencionistas (RVI) en los Hospitales Universitarios de Málaga y de Tenerife, como primer paso para evaluar los riesgos radiológicos a los pacientes. Los procedimientos seleccionados se han agrupados en angiografías abdominales (A.Abd), arteriografías diagnósticas de miembros inferiores (A.MMII), drenajes biliares (DB), varicoceles (Var) y nefrostomías (Nefro).

2. Material y Método.

2.1. Equipamiento y calibraje.

2.1.1. Málaga.

La calibración del equipo Siemens Angioskop Digitron III fue realizada por el Servicio Técnico de la casa Siemens, durante todo el tiempo de la investigación. Además, la Unidad de Protección

Radiológica del H.Universitario de Málaga verificó el mismo mediante un NERO-6000M, encontrando que los parámetros de reproducibilidad, linealidad y eficacia presentaron un C.V. inferior al 5.1 %. Este equipo incorpora el sistema Digimatic Z115, que optimiza la técnica radiológica (kVp, mAs) para cada proyección. La cadena de formación de imágenes esta compuesta por un intensificador de imagen Digitron con 3 tamaños circulares: 33,27 y 17 cm de diámetro, cámara giratoria de TV y monitores Videomed. La formación de la imagen digital se realiza a través de un convertidor analógico digital de 10 bits/pixel. Los formatos de imagen que posee son: 256x256 y 512x512 pixeles. La fluoroscopia puede ser de dos tipos: convencional o digitalizada continua. Este equipo no posee fluoroscopia pulsada [4].

2.1.1. Tenerife.

La calibración del equipo INTEGRIS V3000 fue realizada por el Servicio Técnico de la casa Philips. Además, el Servicio de Protección Radiológica del H.Universitario de Canarias verifico el mismo mediante una cámara de ionización NERO 4000 M+, encontrando que los parámetros de reproducibilidad, linealidad y eficacia presentaron un C.V. inferior al 3 %. Adicionalmente se comprobó la concordancia entre el valor de dosis obtenido a partir de la exposición medida con el NERO y la dosis calculada a partir de PDA medido con Diamentor M2. La concordancia fue del orden del 98 %.

El equipo de sustracción digital, un Philips INTEGRIS V3000 con tubo de rayos Super Rotalix metálico, incorpora el sistema APR que posibilita la optimización automática de la técnica radiológica (kVp, mAs) para cada proyección. La cadena de formación de imágenes esta compuesta por un intensificador de imagen Pentaview con 5 tamaños circulares: 38, 31, 25, 20 y 17 cm de diámetro, cámara giratoria de TV y monitores HM 20 S. La formación de la imagen se realiza a través de un convertidor analógico digital de 10 bits/pixel y con un procesador de imagen interno de 16 bits/pixel. Los formatos de imagen que posee son: 512x512, 512x1024, 1024x1024 y 1280x1024 pixeles. La fluoroscopia puede ser de tres tipos: convencional, la digitalizada continua y la digitalizada pulsada [5].

2.2. Método dosimétrico.

En ambos centros asistenciales, el producto de la dosis-área (DAP) ha sido determinado mediante una cámara de ionización plana Diamentor M2, calibradas por el Servicio Técnico PTW (Frieburg-Alemania). Para el cálculo de la dosis efectiva se han seleccionado proyecciones diseñadas por Hart et al [6,7] para exploraciones radiológicas simples y complejas de digestivo. Nosotros hemos agrupado los procedimientos de RVI según la zona irradiada, seleccionando la proyección que más se ajusta a los campos irradiados. Para facilitar los cálculos se ha utilizado el programa Eff-Dose V 1.02 [8], basándose en cuatro parámetros: kilovoltaje medio, filtración total del haz de rayos X, DAP y proyección seleccionada. Además, este programa permite la estimación de la dosis efectiva con los factores propuesto por ICRP-60 [9] y no por los factores antiguos de ICRP-26 [10].

2.3. Exploraciones seleccionadas.

Un total de 226 procedimientos han sido analizados: 143 en el Hospital de Tenerife y 83 en el Hospital de Málaga. Las **angiografías abdominales** engloban las arteriografías de aorta abdominal, renales, celiaco-mesentéricas y hepáticas. La proyección "Abdomen PA" ha sido seleccionada como la más apropiada para este tipo de procedimientos [7,8]. Las **arteriografías de miembros inferiores** analizadas sólo son de tipo diagnóstico. La proyección "Pelvis PA" ha sido considerada la más apropiada para este tipo de procedimientos [7,8]. Los **drenajes biliares** reúnen a las colangiografías-transparieto-hepáticas (CTPH), drenajes biliares y las extracciones de litiasis biliares. La proyección "Riñón PA" ha sido escogida como la mejor para este tipo de procedimientos [7,8]. Para las embolizaciones de la vena espermática **(Varicoceles)** la proyección "Pelvis PA" ha sido considerada la más ajustada [7,8]. Por último, la proyección "Riñón AP" ha sido seleccionada para los procedimientos de **nefrostomías** [7,8].

3. Resultados.

En la tabla I se muestra el número y tipo de exploraciones, así como las características técnicas en escopia y grafía.

Tabla I.- Exploraciones y parámetros técnicos empleados.

Explo	MALAGA					TENERIFE				
		Escopia		Grafía			Escopia		Grafía	
Tipo	Nº	kV	mA	kV	mA	Nº	kV	mA	kV	mA
A.Abd.	29	85	4,5	81	43	16	86	5,4	78	47
A.MMII.	12	83	3,2	71	45	35	73	3,9	66	45
D.B.	18	89	3,9	82	48	18	92	5,7	82	42
Var.	10	79	4,3	81	42	20	77	4,4	72	42
Nefro.	14	91	3,5	80	44	54	87	5,6	78	40

La tabla II presenta los valores promedio de DAP en $Gy.cm^2$ y E en mSv.

Tabla II.- Producto dosis-área y dosis efectiva.

Explo	Proy.	MALAGA		TENERIFE		**PROMEDIO**	
	NRPB	DAP	E	DAP	E	**DAP**	**E**
Tipo	R-262	($Gy.cm^2$)	(mSv)	($Gy.cm^2$)	(mSv)	($Gy.cm^2$)	(mSv)
A.Abd.	Abdom. PA	90	12,7	61	8,2	**75,7**	**10,5**
A.MMII.	Pelvis PA	28	8,9	30	6,2	**29,0**	**7,6**
D.B.	Riñón PA	59	9,0	150	38,2	**104,5**	**23,6**
Var.	Pelvis PA	106	25,7	75	17,3	**90,5**	**21,5**
Nefro.	Riñón AP	23	5,5	56	13,6	**39,5**	**9,6**

4. Discusión.

La trascendencia de obtener valores de referencia de dosis a pacientes en procedimientos de RVI radica en poder estimar el riesgo radiológico que supone someterse a estas exploraciones.

Es importante reseñar la diferencia de resultados en DAP, y por lo tanto en E, entre ambos centro asistenciales. La forma de realización de estos procedimientos es similar en ambas Unidades de RVI. Las posibles causas de estas diferencias son multifactoriales: formación en protección radiológica del personal, el uso de tiempos largos de escopia y el tipo de la misma (preferible convencional o estándar a escopia de alta-dosis) y la diferencia entre la experiencia del radiólogo senior con el residente de radiodiagnóstico.

En A.MMII, Vañó et al [11] obtuvo un valor de DAP de 66,63 $Gy.cm^2$, Steele et al [12] 42,91 $Gy.cm^2$ y Thwaities et al [13] 26,26 $Gy.cm^2$.

Geterud et al [14] presentó unos valores de E (con factores de ICRP-26) de 4,2 mSv en procedimientos de extracción de litiasis renal, que podría corresponder con la misma zona de irradiación que las nefrostomías.

5. Conclusión.

Actualmente no existen publicaciones como la NRPB R-262 que establezcan relaciones entre DAP ú otro tipo de magnitud, y la dosis efectiva en procedimientos de RVI. Quizá los valores de dosis en órganos (paso previo a la obtención de la dosis efectiva) puedan ser calculados mediante colocación de dosímetros de termoluminiscencia (TLD-100) en un Phantom Laboratory (35 rodajas con 902 posibles localizaciones) simulando los campos y técnicas de las exploraciones de RVI [15].

Por último, creemos que deben seguirse las recomendaciones propuestas por la OMS [16]:

1. Todo personal de RVI debe tener una educación adecuada mediante programas de formación.
2. Deben estimarse la dosis a pacientes y poner todos los medios posibles para reducir al máximo dicha dosis (Criterio ALARA).
3. Los radiólogos vasculares deben conocer las dosis de radiación a pacientes. Esto es posible si se colocan en los nuevos equipos digitales sistemas de medición de la DAP.
4. Los pacientes deben ser controlados para observar posibles problemas de piel en la zona irradiada.
5. Los Hospitales deben establecer valores de referencia de DAP y realizar controles de calidad de las imágenes, para cada procedimiento de RVI.

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ESTIMACIÓN DE LA DOSIS EFECTIVA A PACIENTES EN EXPLORACIONES BARITADAS DEL APARATO DIGESTIVO EN MÁLAGA (ESPAÑA)

[1,2]Rafael Ruiz Cruces, MD, PhD; [1,2]Manuel Pérez Martínez, PhD; [2]Manuel F. Ruiz del Pino, MD; [3]Juan López Hidalgo, MD; [1]Manuel Martínez Morillo, MD, PhD; [1,2]Antonio Díez de los Ríos Delgado, PhD.

[1]Dpto. de Radiología y M.Física. Facultad de Medicina. Universidad de Málaga.
[2]Grupo de Investigación en Protección Radiológica. Universidad de Málaga.
[3]Unidad de Radiología Digestiva. Servicio de Radiodiagnóstico. Hospital Universitario "Virgen de la Victoria" de Málaga.

Resumen

El presente trabajo de investigación tiene como objetivo el presentar valores de referencia de dosis a pacientes en exploraciones complejas (escopia más grafia). Se ha utilizado una cámara de ionización plana para obtener los valores del producto de dosis-área ($Gy.cm^2$). Mediante el método descrito en el report NRPB R-262 se han determinado por separado en cada proyección empleada los valores de dosis efectiva (mSv). Los valores del producto de la dosis-área y dosis efectiva han sido 5,77 $Gy.cm^2$ y 1,20 mSv para esófagograma; 47,48 $Gy.cm^2$ y 6,42 mSv para estudios esófago-gastro-duodenales; 67,02 $Gy.cm^2$ y 12,55 mSv para tránsitos intestinales; 66,71 $Gy.cm^2$ y 18,85 mSv para enteroclisis; y por último, 77,13 $Gy.cm^2$ y 11,39 mSv para enemas opacos.

1. Introducción.

Los estudios de radiodiagnóstico suponen la fuente artificial de irradiación más importante en países de un entorno socioeconómico elevado [1]. Esto ha supuesto el establecimiento de unos criterios para estimar el correcto funcionamiento de sus equipos y garantizar una buena calidad de imagen [2].

Las exploraciones radiológicas denominadas complejas, aquellas que utilizan escopia y grafia, son estudios rutinarios en cualquier centro asistencial del país. En exploraciones simples si existen valores de referencia de dosis a pacientes. Esto valores de referencia pueden variar dependiendo de las características técnicas y de la fisonomía del paciente. En España, esta normativa queda recogida en el BOE 23/01/96 [3].

En exploraciones baritadas del apto. Digestivo no existen valores de referencia designados por la legislación española. Tras aparecer la directiva 97/43/EURATOM (30/06/97) [4] los Estados miembros de la Comunidad Europea deberán asegurar el establecimiento de restricciones de dosis a pacientes en todas las exploraciones de radiodiagnóstico. Dicha disposición legal entrará en vigor antes del 13 de mayo del 2000.

El objetivo de este trabajo es presentar los valores del producto dosis-área (DAP) y la estimación de la dosis efectiva (E) en exploraciones baritadas: esófagograma (Eso) esófago-gastro-duodenal (EGD), tránsito intestinal (TI), enteroclisis (Ent) y enemas opacos (EO). Este trabajo ha sido realizado en el Hospital Universitario "Virgen de la Victoria" de Málaga.

2. Material y Método.

El equipo utilizado para realizar las exploraciones baritadas ha sido un Philips Diagnost 90 S, con generador trifásico de 50 Hz. Este equipo optimiza la dosis de radiación mediante un fotoexposímetro que ajusta los parámetros técnicos según el espesor del paciente. El calibrado de este equipo fue realizado por el Servicio Técnico y comprobado por la Unidad de Protección Radiológica del Hospital Universitario de Málaga, mediante un analizador no invasivo del haz de radiación (NERO-6000 M) de la casa Victoreen, junto al programa DXS II y con un ordenador portátil. Se han determinado la reproducibilidad, la exactitud del kV, la linealidad del mAs y la capa hemirreductora (HVL).

El total de exploraciones analizadas han sido: 29 Esófagograma, 24 Esófago-Gastro-Duodenal, 19 Tránsito Intestinal, 20 Enteroclisis y 22 Enema Opacos. El esófagograma consiste en la visualización con contraste de bario del esófago en toda su extensión. Para ello hemos utilizado las proyecciones RAO (oblicua anterior derecha), LAO (oblicua anterior izquierda), y LPO (oblicua posterior izquierda). La exploración EGD visualiza el esófago, estómago y duodeno en sus cuatros porciones. Para su realización se han empleado las tres proyecciones descritas para el Esófagograma más LAO, RAO y AP-PA (antero-posterior o postero-anterior) en estómago; LPO y RAO en duodeno. El tránsito intestinal consiste en visualizar todo el territorio yeyuno-ileal, terminando el estudio cuando el contraste de bario llega al íleon terminal (válvula ileocecal). Es importante reseñar que las dosis obtenidas en estas exploraciones no incluyen el estudio EGD, ya que el contraste debe atravesar todo este recorrido antes de comenzar a visualizarse el intestino delgado. Hemos establecido este criterio para comparar los resultados entre tránsito intestinal y enteroclisis. En este último procedimiento, el contraste de bario y metil-celulosa son introducidos directamente en el duodeno mediante una sonda nasogástrica, visualizándose el mismo territorio que el tránsito intestinal. Las proyecciones más utilizadas han sido: RAO y LPO de duodeno y AP de intestino delgado. Por último, el enema opaco muestra todo el intestino grueso en su trayecto, utilizándose para ello las siguientes proyecciones: AP de abdomen (vacío); AP, PA, RAO, LPO y LAO de colon; RAO y LPO de recto; LAO en ángulo hepático y RAO en ángulo esplénico.

Los valores del producto dosis-área han sido obtenidos por una cámara de ionización plana Diamentor M2. Este equipo fue calibrado por el Servicio Técnico de la casa PTW Frieburg-Alemania. A partir de estos valores obtenidos por separado, tanto en escopia como en grafía, se determinaron los valores de dosis efectiva (E) en cada proyección utilizada mediante el método propuesto por Hart et al. [5] y descrito en el report NRPB-R262 [6]. Para el cálculo directo se empleó el software Eff-Dose V1.02 [7] que permite la estimación de los valores de dosis en 29 órganos y la dosis efectiva por los métodos de ICRP-60 [1] e ICRP-26 [8].

Además, se ha estimado la dosis entrada en superficie (DES), dividiendo el valor de DAP entre el área irradiada en cada exploración.

3. Resultados.

Los parámetros estimados en la calibración del equipo Philips presentaron unos coeficientes de variación de ± 5 %.

En la tabla I se muestran el número y tipo de exploraciones, la edad media, las características técnicas en escopia y grafía, la filtración total del haz, así como el espesor medio de la zona irradiada y el cálculo de su área.

Tabla I.- Exploraciones y parámetros técnicos empleados.

Explo.	Nº	Edad Media	Escopia kV	Escopia mAs	Grafía kV	Grafía mAs	Filtra. Total*	Espesor cm	Area cm^2
Eso	29	51,9	70-90	2-3	95-105	15-18	3,5	24,5	447,3
EGD	24	56,8	70-90	2-3	95-105	23-29	3,5	24,9	497,2
TI	19	48,7	80-100	2-3	95-105	45-65	3,5	25,7	520,1
Ent	20	41,2	80-100	2-3	95-105	45-70	3,5	23,9	461,3
EO	22	52,7	80-100	2-3	93-100	45-75	3,5	24,7	484,9

* La filtración total es la suma de la filtración total del haz más la filtración añadida por la Diamentor M2.

La tabla II presenta los valores promedio de DAP en $Gy.cm^2$ (total, escopia y grafía), DES en Gy, E en mSv y tiempo total (T) de realización en segundos.

Tabla II.- Producto dosis-área, dosis entrada en superficie, dosis efectiva y tiempo total.

Explo.	DAP ($Gy.cm^2$) Total	DAP Escopia	DAP Grafía	DES (Gy)	E (mSv)	T (s)
Eso	5,77 ± 3,27	3,18	2,59	0,13 ± 0,09	**1,20 ± 0,72**	141,9
EGD	47,48 ± 23,52	30,97	16,51	0,99 ± 0,47	**6,42 ± 1,99**	346,3
TI	67,02 ± 30,78	47,04	19,98	1,29 ± 0,57	**12,55 ± 7,13**	552,1
Ent	66,71 ± 30,90	45,23	20,97	1,49 ± 0,70	**18,85 ± 9,31**	706,2
EO	77,13 ± 29,69	51,82	25,31	1,64 ± 0,69	**11,39 ± 3,26**	392,7

4. Discusión.

La dosis efectiva (E) es la mejor magnitud para medir el riesgo radiológico [1]. Sin embargo, esta magnitud no puede ser medida directamente. Debe ser estimada mediante la DAP o la DES. En cada caso, es necesario tener en cuenta factores de conversión. En estudios complejos, se emplea la DAP porque resulta fácil de utilizar y no interfiere en la realización de los procedimientos por parte del personal de radiología. Hart et al [6,7] han propuesto unos valores de correlación directa (con un error asumido del 25%) entre E/DAP que son 0,3 $mSv/Gy.cm^2$ para enema opaco y 0,2 $mSv/Gy.cm^2$ para estudios de papilla de bario. Con estos valores y teniendo en cuenta nuestras estimaciones de DAP, los valores de E serían distintos: 1,16 mSv en Eso; 9,50 mSv en EGD; 13,41 mSv en TI; 13,34 mSv en Ent; 23,15 mSv en EO.

En un estudio comparativo entre países europeos [9] los valores medios de DAP obtenidos para estudios de papilla de bario (sin clara distinción de exploración) son: Reino Unido 19 $Gy.cm^2$, Francia 20 $Gy.cm^2$ y Norte Italia 38 $Gy.cm^2$.

En España, Vañó et al [10] presenta unos valores de 39,90 $Gy.cm^2$ en EGD y 45,19 $Gy.cm^2$ en enemas opacos.

5. Conclusión.

Es importante que los estados miembros de la Comunidad Europea, así como el resto de los países de Nivel Sanitario I, establezcan unos valores de referencia en exploraciones complejas del aparato digestivo. Además, debemos estimar las dosis efectivas para valorar el posible riesgo radiológico de estas exploraciones.

Para reducir las dosis a pacientes en estos procedimientos debemos tener presente algunos importantes parámetros:

1. Buen protocolo de petición de estos procedimientos por los médicos especialistas.
2. Buena formación en el manejo de las técnicas de radiodiagnóstico por parte de los radiólogos y de los médicos internos residentes (MIR).
3. Proyectos de formación en protección radiológica para MIR, radiólogos y digestólogos.
4. Más concretamente, realizar cortos períodos de escopia, colimar los campos al máximo y utilizar parámetros técnicos optimizados según los pacientes.

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ESTIMACIÓN DE RIESGO GENÉTICO Y DETRIMENTO EN EXPLORACIONES DE RADIOLOGÍA VASCULAR INTERVENCIONISTA EN MÁLAGA (ESPAÑA)

Rafael Ruiz Cruces, MD, PhD; Manuel Pérez Martínez, PhD; María Isabel Fernández Vázquez, GrN; Antonio Díez de los Ríos Delgado, PhD.

Grupo de Investigación en Protección Radiológica. Dpto. de Radiología y M.Física. Facultad de Medicina. Universidad de Málaga.

Resumen

El objetivo es estimar las magnitudes poblacionales en procedimientos de radiología vascular intervencionista (RVI). Se presentan los valores de dosis genéticamente significativa (DGS), dosis somáticamente significativa (DSS) y detrimento (G). Las determinaciones hacen referencia a la población de Málaga (577.486 habitantes), calculándose a partir de valores del producto dosis-área, dosis en órganos y dosis efectiva. A simple vista, estas exploraciones complejas deben contribuir con cifras más altas (debido a que suministran mayor dosis de radiación) que las exploraciones simples. Sin embargo, nuestros valores demuestran lo contrario: DGS = 0,8 μGy; DSS = 1,04 mSv y G = 0,85 cánceres radiogénicos / año. Estas cifras contrastan con las determinadas en exploraciones simples para la misma población, DGS = 158,59 μGy; DSS = 3,19 mSv y G = 0,69 cánceres radiogénicos / año. Aunque las causas sean multifactoriales, la principal radica en que la edad media de los pacientes que se someten a exploraciones de RVI es muy superior a la edad media de los pacientes que se realizan exploraciones simples. Estos cambios son más acentuados en la DGS, que afectaría a la dosis en gónadas y a la descendencia del paciente después de la irradiación.

1. Introducción.

Además de la preocupación de los países por estimar las dosis de radiación a los pacientes de forma individual [1] deben tenerse en cuenta como afectan estas dosis a la población en general. Esto ha supuesto el establecimiento de magnitudes que estimen los riesgos radiológicos a la población: dosis genéticamente significativa, dosis somáticamente significativa y detrimento [2].

Los estudios de RVI digitales son exploraciones radiológicas denominadas complejas ya que utilizan escopia y grafia. Estos estudios son cada vez más frecuentes debido a sus ventajas desde el punto de vista médico [3]. Sin embargo, esto ha supuesto un incremento de las dosis de radiación a pacientes [4,5]. La cuestión que surge inmediatamente es saber si este aumento de forma individual, incrementa las estimaciones de riesgo en la población.

El objetivo de este trabajo es estimar la contribución de las exploraciones de RVI a las magnitudes poblaciones: dosis genéticamente significativa (DGS), dosis somáticamente significativa (DSS) y el detrimento (G). Este trabajo ha sido realizado con los valores de dosis a paciente obtenidos por el Grupo de Investigación en Protección Radiológica de la Universidad de Málaga, en el Hospital Universitario "Virgen de la Victoria".

2. Material y Método.

Los valores de dosis órganos en exploraciones de RVI han sido obtenidos de Ruiz Cruces et al [6]. Se ha seguido la metodología propuesta en este trabajo [6], atribuyéndole proyecciones descritas para procedimientos de radiología simple y complejas de digestivo [7]. Para su cálculo se ha utilizado el programa Eff-Dose V1.02 [8].

La dosis genéticamente significativa (GSD) depende de las dosis de radiación recibidas en gónadas y de la posible descendencia que puedan tener estos pacientes. Fue definida por la UNSCEAR [9] como: " La dosis que si fuera recibida por cada uno de los miembros de la población podría causar el mismo daño genético a la población, que el producido por las dosis recibida individualmente." La función matemática es:

$$GSD = \frac{\Sigma_{jk}(N_{jk} D_{jk} P_{jk})}{\Sigma_k N_k P_k}$$

donde:
D_{jk} es la media de dosis órgano recibida por cada subgrupo de edad y sexo (k), conteniendo N_{jk} individuos, que se someten a la exploración j; P_{jk} es la esperanza de hijos por grupo de edad y sexo (k) que se someten a la exploración j; N_k es el número total de individuos por grupos de edad y sexo (k); y P_k es el promedio de la esperanza de hijos individual por grupo de edad y sexo (k).

La pirámide poblacional se muestra en la Figura 1 [10].

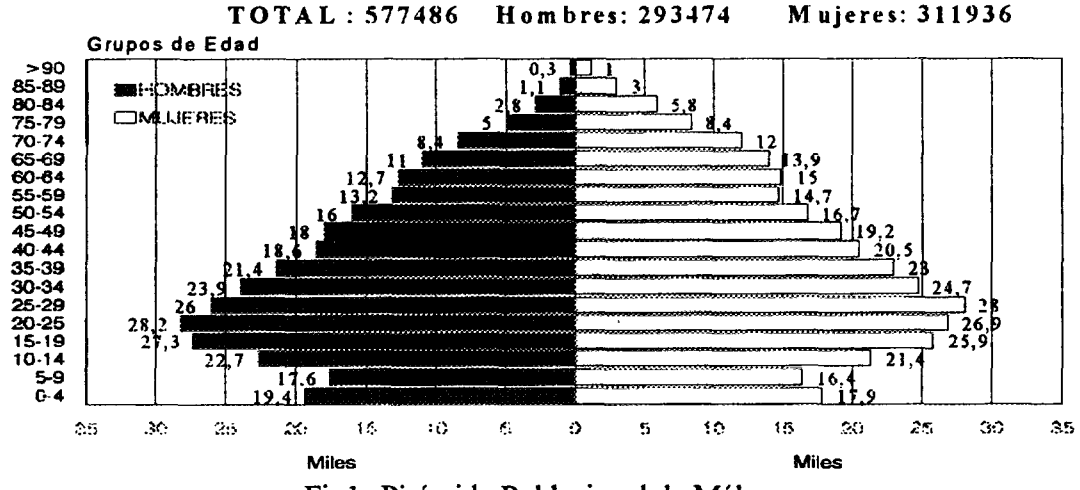

Fig1.-Pirámide Poblacional de Málaga.

La esperanza de hijos depende de la tasa específica de natalidad y del número de personas supervivientes para una cohorte primaria de 100.000 habitantes. La tabla I muestra los valores de esperanza de hijos.

Tabla I.- Esperanza de hijos.

Grupo de edad	Mujer	Hombre
15-19	1,33	1,43
20-24	1,16	1,36
25-29	0,78	1,07
30-34	0,35	0,61
35-39	0,10	0,24
40-44	0,02	0,13
45-49	0,001	0,01
>50	0	0,005

Por otro lado, la dosis somáticamente significativa (DSS) se puede definir como "la dosis en cada miembro de una población que produciría el mismo número de cánceres mortales, que

la dosis en los individuos que han sido irradiados en dicha población". Wall [11] analiza su fórmula:

$$S.S.D = \frac{\Sigma N_{jk} * D_{sjk} * p_{sk} * E_{sk}}{\Sigma N_{jk}}$$

donde:
s: variable órgano o tejido, k: variable subgrupo por edad y sexo, j: tipo de procedimiento.
D: dosis equivalente media en cada órgano, E: esperanza de vida, **N**: número de pacientes por grupo de edad y sexo; **p**: Factores de riesgo específicos para cada órgano.

El resultado de una posible lesión como consecuencia del uso de las radiaciones ionizantes fue expresado [2,12] en cuanto a DETRIMENTO (**G**) ó perdida de salud:

$$G = \Sigma (r_T * D_T * s_T)$$

donde:
r_T es la incidencia de un efecto nocivo en un tejido (T) por unidad de dosis, s_T es el factor de ponderación que expresa la severidad del efecto y D_T es la dosis media recibida por el tejido T.

Las exploraciones seleccionadas para estimar estas magnitudes han sido: arteriografías cerebrales, hepáticas, celiacas, mesentéricas, renales, diagnósticas e intervencionistas de miembros inferiores; colangiografías transparieto-hepáticas, drenajes biliares, extracción de litiasis biliares, colocación de prótesis de Wallstent biliar, colocación de prótesis de Hickman, nefrostomías, pielografías percutáneas, cambios de catéter renal, dilataciones ureterales y colocación de dobles jotas. La suma de todos estos procedimientos representa el 91 % del total anual (1312 exploraciones).

Estos procedimientos han sido separados por grupos de edad y sexo, para poder calcular el número total de pacientes que se someten a cada uno de estos estudios radiológicos. Por falta de espacio no podemos incluir las 15 gráficas y tablas de cada uno de ellos.

3. Resultados.

Los resultados finales obtenidos han sido:

DGS =	0,8 μGy.
DSS =	1,04 mSv.
G =	0,85 cánceres radiogénicos / año.

4. Discusión.

En un trabajo realizado en la misma población y referente a exploraciones simples [13,14] los valores encontrados fueron: DGS = 158,59 μGy; DSS = 3,19 mSv y G = 0,69 cánceres radiogénicos / año. A pesar de que las exploraciones complejas suministran más dosis a los pacientes de forma individual, sus contribuciones a las magnitudes colectivas son menores. Esto puede atribuirse a que estos procedimientos son menos solicitados y la edad media de los pacientes supera con creces a la edad media de las exploraciones simples.

Este contraste de valores es más evidente en la DGS, ya que está se relaciona directamente con las dosis en gónadas y la descendencia de estos pacientes. Salvo en los

procedimientos de varicoceles, en los que la edad media es de 23,9 años, en el resto de los estudios la media se sitúa entre los 44,8 años de los Hickman y los 67,0 años de las arteriografías hepáticas.

Por último, sólo el detrimento (G) en exploraciones complejas supera el valor estimado para las exploraciones simples.

5. Conclusiones.

Nosotros queremos con este trabajo aportar datos que puedan ser comparados con otros estudios realizados en otros países.

Como conclusiones más importantes podemos decir:

1. Las exploraciones complejas de RVI contribuyen a las DGS y DSS con valores menores que las exploraciones simples.
2. El detrimento o pérdida de salud es algo mayor en las exploraciones complejas que en exámenes radiológicos simples.
3. Aunque estas cifras sean bajas, no debemos nunca olvidar el objetivo principal de la protección radiológica: justificar, optimizar y reducir las dosis.

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ESTIMACION DE RIESGO GENETICO Y DETRIMENTO EN EXPLORACIONES BARITADAS DEL APARATO DIGESTIVO EN MALAGA (ESPAÑA)

Rafael Ruiz Cruces, MD, PhD; Manuel Pérez Martínez, PhD; Antonio Díez de los Ríos Delgado, PhD.

Grupo de Investigación en Protección Radiológica. Dpto. de Radiología y M.Física. Facultad de Medicina. Universidad de Málaga.

Resumen

El objetivo es estimar las magnitudes poblacionales en estudios baritados del aparato digestivo. Se presentan los valores de dosis genéticamente significativa (DGS), dosis somáticamente significativa (DSS) y detrimento (G). Las determinaciones hacen referencia a la población de Málaga (577.486 habitantes), calculándose a partir de valores del producto dosis-área, dosis en órganos y dosis efectiva. A simple vista, estas exploraciones complejas deben contribuir con cifras más altas (debido a que suministran mayor dosis de radiación) que las exploraciones simples. Sin embargo, nuestros valores demuestran lo contrario: DGS = 0,9 μGy; DSS = 1,89 mSv y G = 0,28 cánceres radiogénicos / año. Estas cifras contrastan con las determinadas en exploraciones simples para la misma población, DGS = 158,59 μGy; DSS = 3,19 mSv y G = 0,69 cánceres radiogénicos / año. Aunque las causas sean múltiples, la principal puede ser la mayor edad media de los pacientes que se someten a este tipo de exploraciones. Estos cambios son más acentuados en la DGS, que afectaría a la dosis en gónadas y a la descendencia del paciente después de la irradiación. Estos resultados deben ser cotejados con otros trabajos realizados en otros países.

1. Introducción.

Además de la preocupación de los países por estimar las dosis de radiación a los pacientes de forma individual [1] deben tenerse en cuenta como afectan estas dosis a la población en general. Esto ha supuesto el establecimiento de magnitudes que estimen los riesgos radiológicos a la población: dosis genéticamente significativa, dosis somáticamente significativa, dosis efectiva colectiva, dosis efectiva per capita anual y detrimento [2].

Los estudios baritados del aparato digestivo son exploraciones radiológicas denominadas complejas ya que utilizan escopia y grafía. La solicitud por parte de los especialistas de estas exploraciones radiológicas es muy frecuente en cualquier centro asistencial. En nuestro Servicio de Radiodiagnóstico se realizan una media de 2178 estudios baritados, de los cuales 198 son esófagogramas, 902 son tránsitos esófago-gastro-duodenales, 200 son tránsitos intestinales, 174 son enteroclisis y 704 son enemas opacos. Aunque no son exploraciones tan demandadas como las radiografías simples de tórax, abdomen o del sistema osteoarticular, debemos estimar cuál es el riesgo que producen a la población en general.

El objetivo de este trabajo es calcular la contribución de estas exploraciones a las magnitudes poblaciones: dosis genéticamente significativa (DGS), dosis somáticamente significativa (DSS) y el detrimento (G). Este trabajo ha sido realizado con los valores de dosis a paciente obtenidos por el Grupo de Investigación en Protección Radiológica de la Universidad de Málaga, en el Hospital Universitario "Virgen de la Victoria".

2. Material y Método.

En la tabla I se presenta los valores de dosis órganos. Se ha seguido la metodología propuesta para procedimientos de radiología simple y complejas de digestivo [3]. Para su cálculo se ha utilizado el programa Eff-Dose V1.02 [4].

Tabla I.- Promedio de Dosis órgano (mGy) en estudios con bario.

	Esófago	*EGD*	*T.Intest.*	*Entero*	*Enema*
Adrenales	4,09	14,88	7,30	2,87	7,28
Cerebro	0,03	0,03	0,01	0,00	0,00
Mama	2,90	3,75	1,72	0,27	0,17
Cristalino	0,03	0,03	0,01	0,00	0,00
Vesícula	0,44	11,21	16,45	27,96	15,15
Estómago	0,42	15,02	31,61	18,06	11,51
Duodeno	0,04	14,94	53,4	104,62	19,32
I.Delgado	0,05	12,42	42,55	85,53	16,77
I.Grueso	0,01	6,27	19,22	35,24	18,41
Corazón	2,77	3,97	2,04	0,65	0,79
Riñón	0,37	32,38	25,52	7,85	48,19
Hígado	1,31	4,59	3,77	8,38	8,84
Pulmón	3,46	4,56	1,92	0,53	0,67
Ovario	0,01	3,46	23,80	79,01	15,55
Páncreas	1,59	13,69	15,11	7,07	11,46
Piel	0,79	4,39	6,61	10,13	8,82
Bazo	0,73	24,02	26,76	5,48	12,36
Testículo	0,00	0,06	0,32	3,12	14,06
Timo	1,60	1,99	0,76	0,06	0,12
Tiroides	1,40	1,65	0,57	0,00	0,00
Vejiga	0,00	0,91	5,29	30,99	21,77
Utero	0,01	3,37	27,81	99,58	17,39
Esófago	4,23	5,61	2,25	0,77	0,82
Músculo	0,80	4,97	8,71	14,82	9,85
Cabeza	0,54	0,57	0,17	0,00	0,00
Tronco	1,66	8,76	14,98	22,86	15,10
Extremidad	0,00	0,00	0,04	1,92	3,31
Hueso	2,15	5,91	7,55	8,46	12,83
MEDIA	**1,23**	**4,35**	**7,02**	**8,02**	**11,52**

La dosis genéticamente significativa (GSD) depende de las dosis de radiación recibidas en gónadas y de la posible descendencia que puedan tener estos pacientes. Fue definida por la UNSCEAR [5] como: " La dosis que si fuera recibida por cada uno de los miembros de la población podría causar el mismo daño genético a la población, que el producido por las dosis recibida individualmente." La función matemática es:

$$GSD = \frac{\sum_{jk}(N_{jk} D_{jk} P_{jk})}{\sum_{k} N_k P_k}$$

donde:

D_{jk} es la media de dosis órgano recibida por cada subgrupo de edad y sexo (k), conteniendo N_{jk} individuos, que se someten a la exploración j; P_{jk} es la esperanza de hijos por grupo de edad y sexo (k) que se someten a la exploración j; N_k es el número total de individuos por grupos de edad y sexo (k); y P_k es el promedio de la esperanza de hijos individual por grupo de edad y sexo (k).

La pirámide poblacional se muestra en la Figura 1 [6].

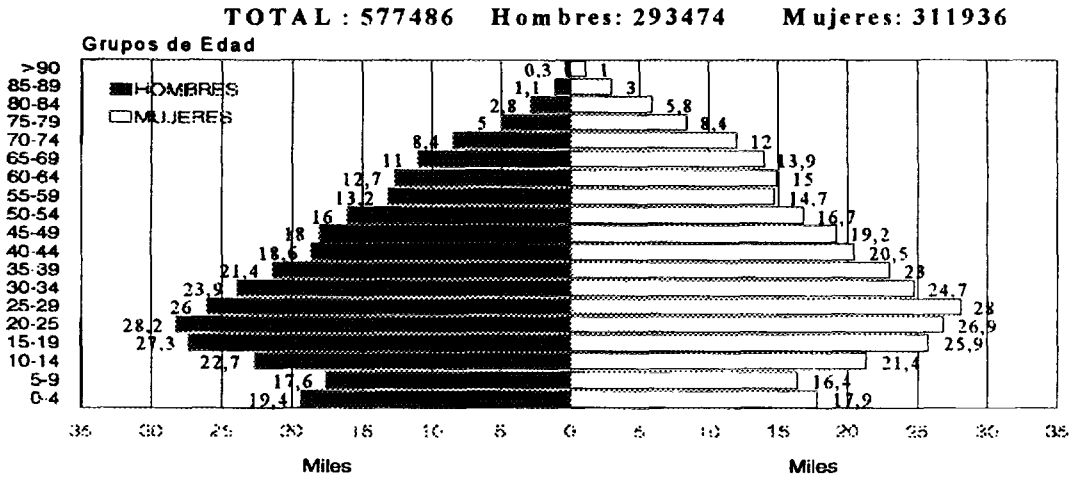

Fig1.-Pirámide Poblacional de Málaga.

La esperanza de hijos depende de la tasa específica de natalidad y del número de personas supervivientes para una cohorte primaria de 100.000 habitantes.

Por otro lado, la dosis somáticamente significativa (DSS) se puede definir como "la dosis en cada miembro de una población que produciría el mismo número de cánceres mortales, que la dosis en los individuos que han sido irradiados en dicha población". Wall [7] analiza su fórmula:

$$S.S.D = \frac{\sum N_{jk} * D_{sjk} * p_{sk} * E_{sk}}{\sum N_{jk}}$$

donde:
s: variable órgano o tejido, k: variable subgrupo por edad y sexo, j: tipo de procedimiento.
D: dosis equivalente media en cada órgano, E: esperanza de vida, **N**: número de pacientes por grupo de edad y sexo; **p**: Factores de riesgo específicos para cada órgano.

El resultado de una posible lesión como consecuencia del uso de las radiaciones ionizantes fue expresado [8] en cuanto a DETRIMENTO (**G**) ó perdida de salud:

$$G = \sum (r_T * D_T * s_T)$$

donde:
r_T es la incidencia de un efecto nocivo en un tejido (T) por unidad de dosis, s_T es el factor de ponderación que expresa la severidad del efecto y D_T es la dosis media recibida por el tejido T.

Las exploraciones seleccionadas para estimar estas magnitudes han sido: esófagograma, que consiste en visualizar todo el territorio del esófago; esófago-gastro-duodenal, que comprende el estudio anterior más la exploración baritada del estómago y del duodeno; tránsito intestinal y enteroclisis, ambos sirven para diagnosticar patologías en el yeyuno-íleon, diferenciándose sólo en la forma de administrar el bario; y por último el enema opaco, que obtiene información de todo el colon o intestino grueso.

Estos procedimientos han sido separados por grupos de edad y sexo, para poder calcular el número total de pacientes que se someten a cada uno de estos estudios radiológicos Por falta de espacio no podemos mostrar todas gráficas y tablas de cada uno de ellos

3. Resultados.

Los resultados obtenidos son
DGS = 0,9 μGy, DSS = 1,89 mSv y G = 0,28 cánceres radiogénicos / año

4. Discusión.

En un trabajo realizado en la misma población y referente a exploraciones simples [9,10] los valores encontrados fueron DGS = 158,59 μGy, DSS = 3,19 mSv y G = 0,69 cánceres radiogénicos / año A pesar de que las exploraciones complejas suministran más dosis a los pacientes de forma individual, sus contribuciones a las magnitudes colectivas son menores Esto puede atribuirse a que estos procedimientos son menos solicitados y la edad media de los pacientes supera con creces a la edad media de las exploraciones simples

5. Conclusiones.

Nosotros queremos con este trabajo aportar datos que puedan ser comparados con otros estudios realizados en otros países

Como conclusiones más importantes podemos decir

1 Las exploraciones baritadas del aparato digestivo contribuyen a las magnitudes poblacionales con valores menores que las exploraciones simples
2 Aunque estas cifras sean bajas, no debemos nunca olvidar el objetivo principal de la protección radiológica justificar, optimizar y reducir las dosis

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IAEA-CN-67/185

EVALUACION DE DOSIS A PACIENTE DURANTE EL TRATAMIENTO CON LITOTRICIA EXTRACORPOREA (ESWL)

Autores: M. Fco. Rodríguez; J. R. Román
Servicio de Física Médica. Hospital Universitario de Valme. Ctra. de Cádiz s/n. 41014- Sevilla.

Resumen

La litiasis urinaria se presenta cada vez más frecuentemente. Aproximadamente el 12% de la población tendrá una piedra en el tracto urinario en algún momento de su vida. La piedra produce los cólicos severos que duelen en el transito por el uréter. Éste probablemente es uno de los peores dolores y experiencia de los humanos. Aquéllos que lo han padecido nunca se olvidarán de él.
El tratamiento con litotricia extracorpórea consiste en pulverizar o romper en trozos los cálculos ubicados en el riñón o uréter. Esto se realiza mediante ondas de choque generadas por un cañón y focalizadas en el cálculo. El centrado y seguimiento se realiza con Rayos X. En una, o varias sesiones se elimina el cálculo sin necesidad de intervención quirúrgica, con su riesgo y coste asociados. Pero el alto número de pacientes tratados al año y las dosis suministradas a los pacientes durante su diagnóstico, tratamiento y posterior seguimiento, nos han llevado a este trabajo.

1. INTRODUCCION

1.1. Los cálculos renales

La litiasis urológica o cálculos urinarios se presentan aproximadamente de 7 a 10 de cada 1,000 admisiones en el Hospital [1]. La mayoría de piedras, 70 a 80 por ciento, está principalmente compuesta de cristales de oxalato de calcio; el resto está compuesto de sal de fosfato del calcio, ácido úrico o estruvite (magnesio, amonio y fosfato). De vez en cuando, las piedras dañan los riñones y reducen su función causando infección u obstrucción, pero muchos pacientes con piedras sólo padecen el dolor del transito de la piedra, infección urinaria y sangrado, junto con la molestia de la hospitalización y la incomodidad de los procedimientos del urólogo. Una explicación simplificada de la litogénica urinaria sería la sobresaturación y cristalización de ciertas sales en la orina, influido por la presencia de inhibidores de la precipitación cristalina, fenómenos de epitaxia y factores anatómicos. Las piedras de calcio comprenden más de la mitad del total [2].

1.2. Diagnóstico

La mayoría de las piedras contienen calcio que las hace radiopacas (blanco) en la radiografía. Algunas piedras son demasiado pequeñas para ser vistas o simplemente no son perceptibles debido al gas de intestino o los huesos. Así 34% no son detectables mediante radiografía de Abdomen (KUB). Radiopacas o no, casi el 100% de todas las piedras son descubiertas por TAC. La dosis de la radiación de CT es aproximadamente tres veces la dosis de KUB a menos que el radiólogo tenga un protocolo para reducción de dosis. Las piedras son ecogénicas y su descubrimiento por ecografía (ultrasonidos) es inversamente proporcional a la obesidad de paciente y directamente proporcional a la experiencia del examinador. La mayoría de las piedras más pequeñas de 0.003 m no se detectan mediante ecografía. La opción más reciente para el paciente con cólico renal típico es el TAC helicoidal. El método más frecuente es la detección del cálculo mediante la combinación de KUB y ecografía [3]. En el presente trabajo no se han evaluado la dosis que conlleva la detección y diagnóstico del cálculo renal.

1.3. Litotricia extracorpórea por ondas de choque (ESWL)

La ESWL se usó primero en Alemania en 1980 y se aprobó para el uso en los Estados Unidos en 1984. La idea es usar trenes de ondas de choque (shockwaves) para pulverizar el cálculo ("lithos" es griego para "piedra" y "tripsis" es griego para "rompiendo") a un estado como arena, para que pueda expulsarse naturalmente sin cirugía. Un problema importante es enfocar los trenes de ondas para que destruyan sólo la piedra y no dañen el cuerpo [4]. El ESWL ha demostrado ser eficaz para el tratamiento de piedras: disminuye tiempo de tratamiento y no necesita preparación previa [2].

2. MATERIALES Y METODOS

2.1. Centro de Estudio.

El estudio ha sido realizado en el Hospital Universitario de Valme de Sevilla (España), el equipo utilizado ha sido un LITHOSTAR PLUS de Siemens, tipo C, de membrana electromagnética y un sistema biplano de rayos X, número de serie 1098 e instalado en 1.988. En la actualidad lleva realizado mas de 8.300 tratamientos. (Fig. 1)

TABLA I. DATOS DEL CENTRO [1]

Población asistida:	350.000 pers.
Ingresos relacionados con cálculos urinarios:	0.7%
Tratamientos con ESWL anuales:	800
Edad Media:	49 (16)
Sexo:	54% Mujeres
Sesiones Medias:	1.8
Eficacia:	68%

3.2. Medidas realizadas

Se han tomado medidas correspondientes a 150 pacientes distribuidos en los dos planos de seguimiento (81 Plano I y 69 Plano II)

Los datos de los pacientes estudiados son los siguientes:

TABLA II. PACIENTES ESTUDIADOS

Total Pacientes:	150
Edad Media:	54 (24)
Sexo:	59% Mujeres
Peso:	75 (26)
Sesiones Medias:	1,8
Eficacia:	74%

En cuanto a implicación radiológica que conlleva el centrado y seguimiento la podemos diferenciar en: un disparo radiográfico previo de gran formato y otro al final del tratamiento de menor superficie, varios minutos de escopia para centrado y seguimiento en ambos planos y disparos de escopia de alto régimen también para los dos planos.

Por todo esto elegimos como parámetro de control el producto dosis x área (PDA) y para medirlo utilizamos una cámara de transmisión marca PTw modelo 57523 con calibración en 1.997 que se instaló en los colimadores de ambos planos. Las medidas de superficie fueron realizadas mediante disparo radiográfico sobre dosis a la altura promedio de la piel del paciente y los de chasis de control con una cámara de ionización RADCAL modelo 2025 con calibración en 1.996 sobre unos recipientes de agua simulando al paciente.

Para el calculo de la dosis a la entrada (ESD), a partir el producto dosis x área medido con la cámara de transmisión se ha utilizado la siguiente expresión matemática [5]:

$$Dp = 10{,}0 \cdot Frd \cdot Fpt \cdot PDA \cdot Ap$$

donde:

Dp: dosis a la entrada de la superficie del paciente en mGy

Frd: Factor de retrodispersión (se ha tomado como 1,35 en todos los casos [6])

Ft: Factor de corrección por la presión y la temperatura

PDA: Lectura de la cámara de transmisión ($cGy \cdot cm^2$)

Ap: Area irradiada en la superficie del paciente (cm^2)

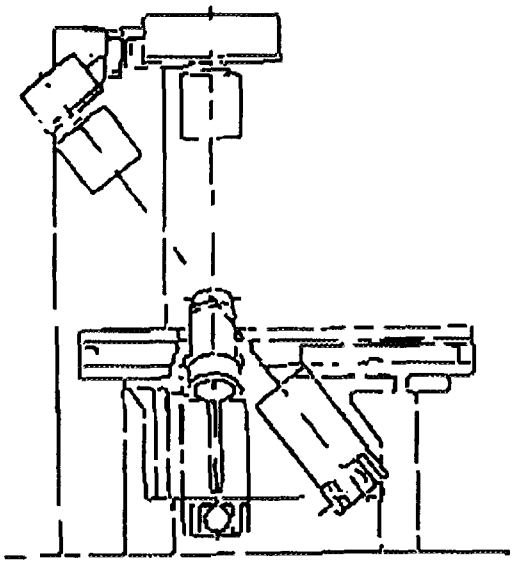
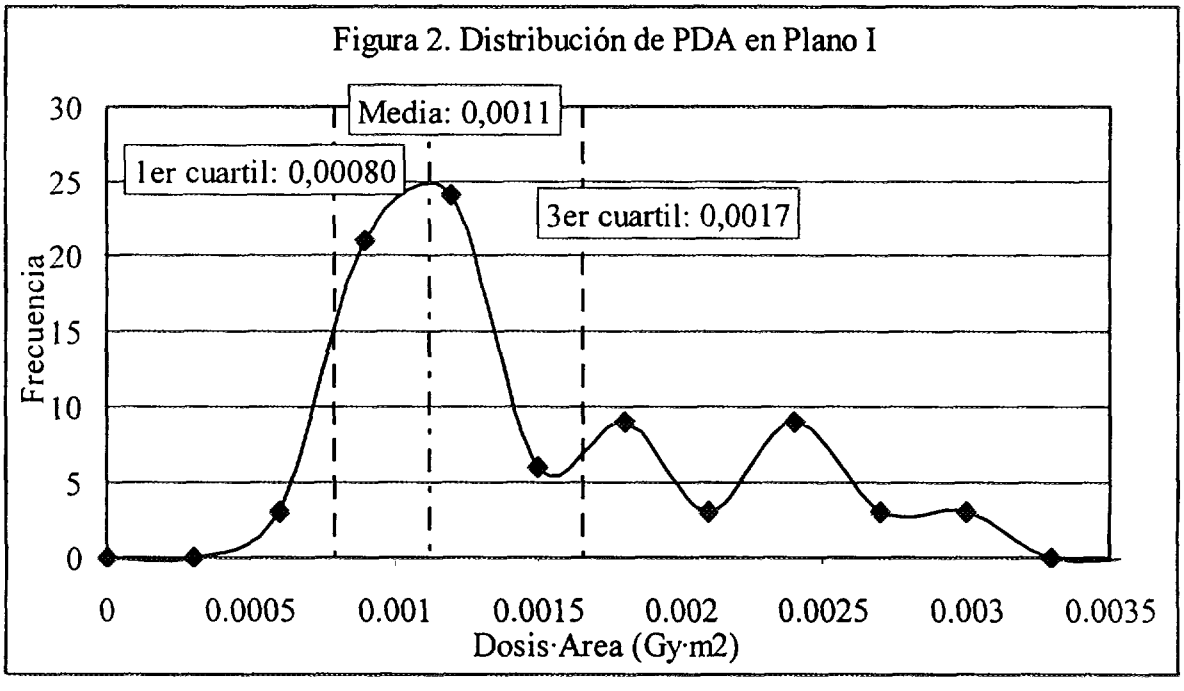


Figura 1. Esquema Lithostar de Siemens



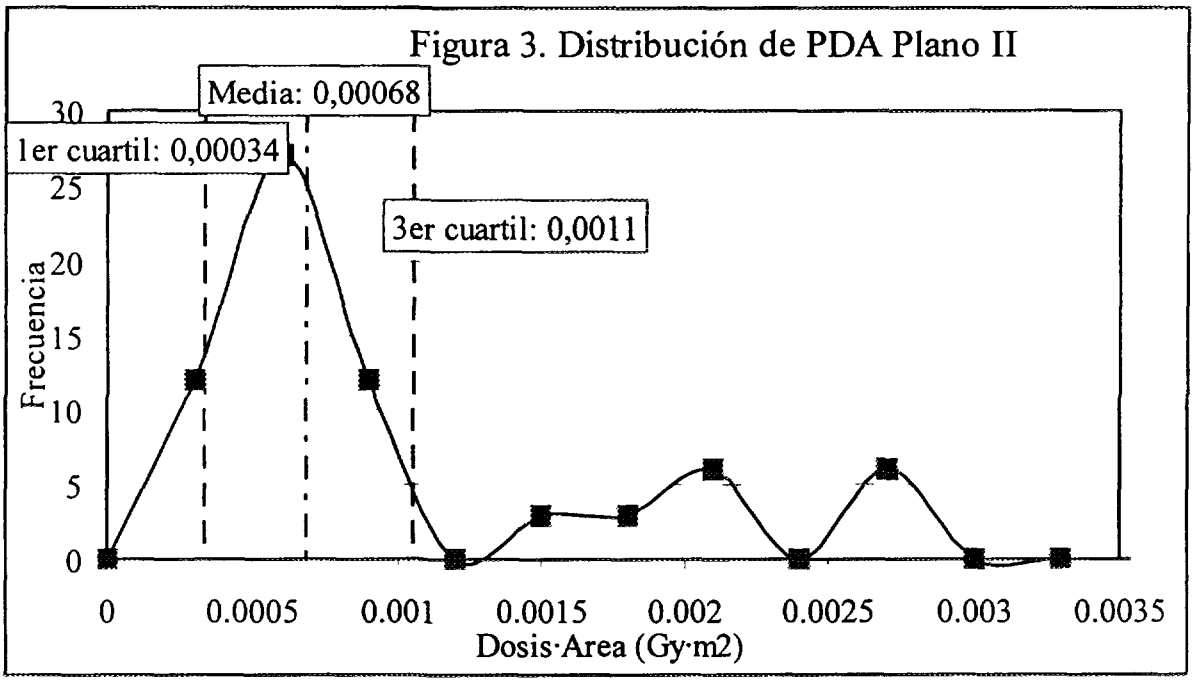


Figura 3. Distribución de PDA Plano II

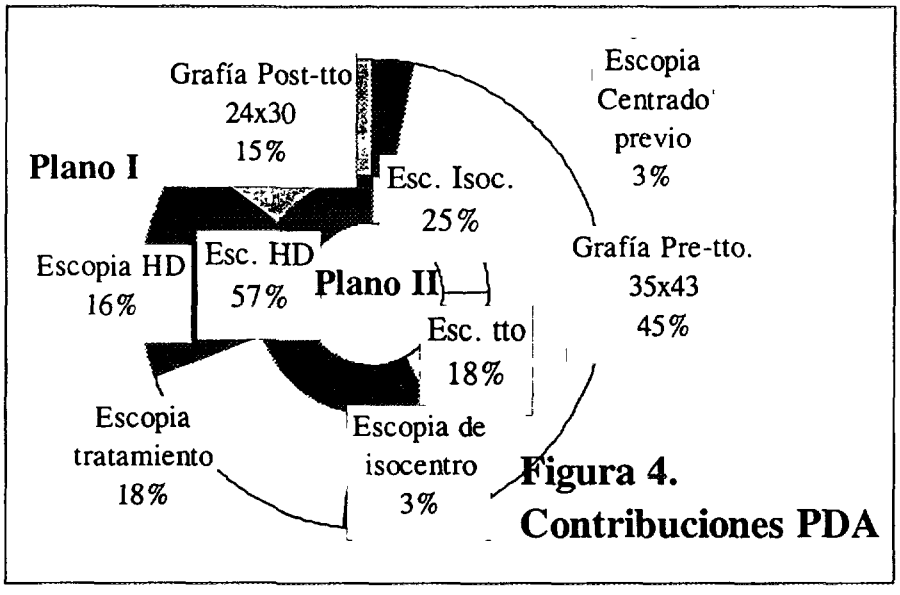


Figura 4. Contribuciones PDA

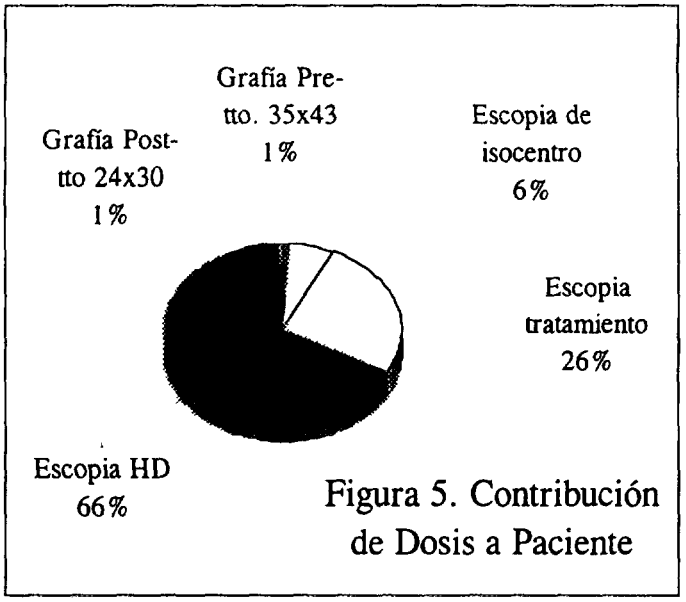


Figura 5. Contribución de Dosis a Paciente

3. RESULTADOS

Las figuras 2 y 3 representan la curva correspondiente al histograma de frecuencias de los PDA de cada plano. Los datos se presentan en la Tabla III. El PDA es mayor en el plano I debido a que el centrado y localización previa se hacen en este plano así como los disparos radiográficos inicial y final. La escopia de Alta Definición es el concepto que más contribuye al total del PDA y Dosis total.

TABLA III. PDA (GY·M²)

	Plano I	Plano II	Total
Pacientes	81	69	150
Media	0,001123	0,000681	0,001804
Mínimo	0,000529	0,000198	0,000727
Máximo	0,002923	0,002674	0,005597
1er Cuartil	0,000797	0,000337	0,001134
3er Cuartil	0,001656	0,001055	0,002711

Las contribuciones correspondientes a los diversos conceptos relacionados en el protocolo radiológico de la ESWL se representan en la figura 4.

La distribución de la dosis en piel se representa en la figura 5 y en la tabla IV.

TABLA IV. DOSIS EN PIEL (GY)

	Plano I	Plano II	Total
Escopia Centrado previo	0.0014		0.0014
Grafía Pre-tto. 35x43	0.0027		0.0027
Escopia de isocentro	0.0044	0.0263	0.0307
Escopia tratamiento	0.0762	0.0563	0.1325
Escopia HD	0.0912	0.2450	0.3362
Grafía Post-tto 24x30	0.0027		0.0027
Total	0.1786	0.3275	0.5061

4. CONCLUSIONES

Es necesario tener no solo en cuenta las medidas de radioprotección, sino la evaluación de las energías no ionizantes suministradas por la ESWL. Tanto en prevención de efectos secundarios como en términos de eficacia, puesto que repercute de forma directa en el índice de repetición de sesiones y por tanto de dosis suministrada. Las dosis medidas son superiores a las de la radiología convencional, aunque inferiores a las de la radiología intervencionista, por lo que sería conveniente establecer dosis de referencia; nos preocupa especialmente las dosis en gónadas y la dosis en piel en pacientes muy gruesos [7]. Se ha insistido muy especialmente en la colimación, se ha mejorado el sistema de imagen (cámaras y monitores), la revisión periódica del equipo según el Protocolo Español de CCRX y sobre todo concienciando a usuarios sobre todas las medidas especificas de radioprotección. El tratamiento de ESWL debe usarse con cautela en niños.

AGRADECIMIENTOS

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ESTUDIO EPIDEMIOLÓGICO MEDIANTE LA TÉCNICA DE ABERRACIONES CROMOSÓMICAS EN DISTINTAS MUESTRAS DE POBLACIÓN

M. Jesús Prieto*, Mercedes Moreno*, Marina Gómez**, Pilar Olivares*, Rafael Herranz**.

* Servicio de Dosimetría y Radioprotec ción. HGUGM.

** Servicio de Oncología Radioterápica. HGUGM.

RESUMEN

El Hospital General Universitario Gregorio Marañón (HGUGM) cuenta con un laboratorio de dosimetría biológica, desde hace ya diez años, para la realización de estimaciones dosimétricas en individuos con sospecha de sobreexposición a radiaciones ionizantes.

Para este objetivo es preciso disponer de estudios de frecuencia basal de aberraciones cromosómicas en una muestra de población control. Por ello, se ha realizado un estudio en 72 individuos pertenecientes a la Comunidad de Madrid (CAM), no expuestos a radiaciones ionizantes por su profesión o por razones sanitarias. Han sido analizadas 500 metafases por individuo (36000 metafases), obteniéndose una frecuencia basal de 0.7 dic/1000 células analizadas. Se han considerado parámetros como edad, sexo y consumo de cigarrillos y se ha comprobado que los resultados muestran una dependencia lineal con la edad y el consumo de cigarrillos y no presentan variación con el sexo.

Actualmente, se está realizando un estudio (27500 metafases analizadas) en una muestra de población expuesta a bajas dosis de radiaciones ionizantes, esto es, individuos profesionalmente

expuestos que ni de forma puntual han superado los límites de dosis establecidos. La frecuencia estimada hasta la fecha es de 0.9 dic/1000 células analizadas, sin diferencias significativas con respecto a la población control.

INTRODUCCIÓN

La dosimetría biológica (estimación de dosis por medio de parámetros biológicos) trata de medir la respuesta biológica de un individuo a las radiaciones ionizantes, y para ello se va a utilizar el propio organismo del individuo como indicador de la lesión.

Para la estimación de dosis en individuos con sospecha de sobreexposición a radiaciones ionizantes, se utiliza internacionalmente como método de rutina el estudio de aberraciones cromosómicas en linfocitos de sangre periférica (1,2,3), ya que se ha demostrado una relación dosis-efecto capaz de realizar una estimación de dosis fiable (4,5).

Se ha comprobado que las radiaciones ionizantes no inducen nuevas ni diferentes lesiones cromosómicas en los linfocitos de sangre periférica, solamente aumentan su frecuencia, siendo necesario tener en cuenta que existe un nivel basal que es preciso conocer.

Como es imposible en la mayor parte de los casos disponer de la frecuencia basal de aberraciones cromosómicas en cada caso particular, se puede establecer la frecuencia basal en determinados grupos de población (6), lo que nos permite conocer los niveles basales de alteraciones cromosómicas.

Existen publicaciones sobre la frecuencia de dicéntricos en distintas poblaciones, estas varían entre 0.0 en una población de recién nacidos de Edimburgo (7) hasta 2.8/1000 células en Brookhaven (8) estimándose una media aproximada de 1.3 dic/1000 células analizadas.

En el laboratorio de dosimetría biológica del Hospital General Universitario Gregorio Marañón se ha llevado a cabo un estudio de una muestra de población no expuesta a radiaciones ionizantes y pertenecientes a la Comunidad de Madrid, en la que se han tenido en cuenta factores como la edad (6,9), el sexo (6) y el consumo de cigarrillos (6,8,9) para ver si estos parámetros influyen en la frecuencia basal de alteraciones cromosómicas.

Debido a la incertidumbre que existe con las bajas dosis de radiación, en la actualidad se esta realizando un estudio en una muestra de personal expuesto a bajas dosis de radiación. La finalidad es analizar si la frecuencia basal en estos individuos sufre un incremento frente a la población control.

METODOLOGÍA

1. Obtención de las metafases y análisis cromosómico (10)

La obtención de las muestras se realiza mediante venipunción estéril, extrayendose de 5 a 10 ml de sangre periférica que se introducen en tubos que contienen heparina de litio como anticoagulante.

Se establecen los cultivos de 0.8 ml de sangre completa o de Buffy Coat en 10ml de medio MEM y RPMI 1640 enriquecidos con suero fetal de ternera, antibióticos y phitohemaglutinina. se añade bromodeoxiuridina (8-10 microgr/ml) a todos los cultivos para calcular el porcentaje de segundas divisiones.

La incubación se realiza durante 48 horas, añadiéndole el inhibidor mitótico colcemide (10 microg/ml) a las 46 horas. Transcurrido el periodo de incubación, se realiza la fijación de los cultivos con carnoy, formado por metanol y ácido acético en proporción 3:1. Previamente se han sometido a choque hipotónico con CLK 0.55M a 37ºC (4). Se realizan dos tipos de tinciones: Giemsa convencional (11 ,12) y Fluorescencia plus Giemsa (FPG) (13).

El análisis citogenético se realiza con microscopio óptico de alta resolución a 100 y 1000 aumentos. Se analizan 500 metafases completas por cada individuo, anotándose todas las aberraciones cromosómicas encontradas.

2. Selección de los individuos no expuestos a radiaciones ionizantes

Se han evaluado 72 individuos sanos, pertenecientes a una muestra de la población de la Comunidad de Madrid, no expuestos a radiaciones ionizantes por su profesión o por razones sanitarias, nacidos en la CAM o con más de 30 años de residencia: 36 mujeres (18 fumadoras y 18 no fumadoras) y 36 varones (18 fumadores y 18 no fumadores) y agrupados en los siguientes intervalos de edad: 18-20 años; 21-30 años; 31-40 años; 41-50 años; 51-60 años; 61-65 años.

Se han estudiado 500 células por cada individuo, lo que hace un total de 36.000 metafases analizadas.

3. Selección de los individuos expuestos a bajas dosis de radiaciones ionizantes.

Se han seleccionado 64 individuos pertenecientes al Servicio de Radiodiagnóstico del HGUGM y expuestos profesionalmente a bajas dosis de radiaciones ionizantes. 32 mujeres (16 fumadoras y 16 no fumadoras) y 36 varones (16 fumadores y 16 no fumadores), agrupados en intervalos de edad (mayores de 35 años y menores de 35 años). También se ha tenido en cuenta el tiempo que llevan trabajando expuestos a radiaciones ionizantes (menos de 5 años; entre 5 y 10 años; entre 10 y 15 años; más de 15 años).

El número total de células que se espera sean analizadas es de 32.000, pero hasta la fecha se tienen estudiadas un total de 27.500 metafases.

RESULTADOS Y DISCUSIÓN

1. Población Control:

Se estimó una frecuencia de 0.00072 dicéntricos/célula es decir 0.7 dicéntricos de cada 1000 células analizadas.

Se realizó el análisis estadístico de los resultados en colaboración con la NRPB para comprobar si factores como la edad, el sexo y el consumo de cigarrillos (6) influyen en la frecuencia basal de aberraciones cromosómicas. Para ello se ha utilizado el análisis de la varianza de acuerdo a

: 2 log l_0 / l_m que se corresponde aproximadamente con una distribución de Chi cuadrado y donde l_o son las observaciones deseadas para un ajuste perfecto y l_m son las observaciones deseadas para un ajuste particular.

Descripción de los modelos utilizados:

1. Se valora el conjunto de la población incluyendo todos los factores evaluados.
2. Se evalúa la desviación en relación con el sexo.
3. Evaluación de la desviación en relación con el tabaco.
4. Se toma el factor edad como una regresión lineal.
5. Se evalúan los puntos 3 y 4 de forma conjunta.
6. Se evalúa el punto 3 en relación con grupos de edad.

Modelos	Desviación en escala	Grados de libertad	P
1	40.02	23	0.015
2	38.63	22	0.016
3	34.27	22	0.046
4	35.31	22	0.036
5	29.56	21	0.100
6	21.90	17	0.190

El análisis estadístico muestra que el número de dicéntricos aumenta con la edad y el consumo de tabaco y no presenta variabilidad en relación con el sexo.

2. Personal expuesto a bajas dosis de radiaciones ionizantes:

Se estima hasta el momento una frecuencia basal de 0.00087 dic/célula, es decir, 0.9 dicéntricos/1000 células analizadas. El análisis estadístico de los resultados para evaluar como influyen la edad, el sexo, el tabaco y el tiempo trabajado expuestos a bajas dosis no se puede realizar hasta que este concluido definitivamente el estudio.

La conclusión de lo expuesto es que si tenemos en cuenta que la frecuencia basal en una muestra de población control es de 0.7dic/1000células y que la obtenida en una muestra de población de individuos profesionalmente expuestos a radiaciones es de 0.9dic/1000células, claramente se deduce que no existe diferencia significativa entre las dos poblaciones, ya que un dicéntrico en 500 células analizadas se considera como alteración basal (6). Este avance de los datos permite, por tanto, extraer consecuencias muy importantes a tener en cuenta desde el punto de vista de la protección radiológica.

Por último señalar que el número de células que faltan por estudiar para finalizar este segundo estudio es muy pequeño frente al número de células ya analizadas, esto nos hace pensar que los resultados finales de frecuencia basal en individuos profesionalmente expuestos a bajas dosis de radiaciones ionizantes no van a modificar mucho los resultados obtenidos hasta el momento. Sólo queda, por tanto, analizar como estadísticamente afectan los distintos parámetros tenidos en cuenta en el estudio.

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Background dose subtraction in personnel dosimetry

T. Picazo, N. Llorca, J. Alabau

Centro Nacional de Dosimetría. Avda. Campanar 21. 46009 Valencia. Spain.

Abstract: In this paper it is proposed to consider the mode of the frequency distribution of the low dose dosemeters from each clinic that uses X rays as the background environmental dose that should be subtracted from the personnel dosimetry to evaluate the doses due to practice. The problems and advantages of this indirect method to estimate the environmental background dose are discussed. The results for 60 towns are presented.

Introduction: Some of the dose limits proposed in the Basic Safety Standard of the IAEA[1] are very close to the detection limit of the more usual personnel dosimetry systems and fall within the scope of fluctuations of the environmental dose, therefore it is important to estimate this background as well as possible.

At this moment the Centro Nacional de Dosimetria (CND)[2] considers an average background environmental dose for Spain of 60 μGy per month of use. Some areas in Spain have a higher environmental dose, what makes that the reported yearly dose of an unused dosemeter may surpass the limit for pregnant workers or public (1 mSv). Also this insufficiently subtracted background dose contributes substantially to the collective dose.

The aim of this paper is to propose a method to estimate the background dose that should be subtracted from the readings of the dosemeters for each working centre that uses X rays without incurring in the cost of directly measuring it.

Assuming that most of the dosemeters used in a hospital are either not necessary or do not receive any irradiation, the proposal is to consider the mode (most frequent dose) of the frequency distribution of the low doses for that hospital as the background environmental dose that should be subtracted from

personnel dosimetry. This assumption may not be valid when only one or very few dosemeters are used and requires that enough statistic be accumulated over several months.

Materials and methods: The CND, which provides personnel dosimetry to most public owned hospitals in Spain since 1977, uses a dosimetry system[2] based on LiF phosphor. The data base of the system keeps all the data necessary to re-evaluate the dose, including raw data, calibration and sensitivity factors, light source readings, dates of issue and reading of the cards, etc.

When the calibrated readings of the unfiltered TLD pellets (used to give the shallow dose) are represented in a frequency histogram it appears a peak that approximates closely a log-normal distribution. The doses are divided by the number of months that each the dosemeter has been used (two months for a dosemeter timely returned for evaluation) in order to take account of dosemeters used longer.

In this study, the dosemeters used in areas where radioisotopes may be present (nuclear medicine, etc.) are excluded from the analysis. The width of the peak is characterised by the standard deviation calculated over the points of the peak up to and including the first one whose frequency is less than 1/10 of the highest frequency.

Results: The low doses measured since 1995 have been analysed and background estimated for 118 working centres whose highest frequency is over 100. For presentation the data are averaged over the hospitals in each town. Table 1 shows the estimated background (μGy per month) and the width of the distribution for 60 towns. Figure 1 shows the distributions for two hospitals located in areas of different environmental radiation.

Table 1: Background proposed for each town. Width defined as the standard deviation of the distribution. All values in μGy per month

Town	Dose	Width	Town	Dose	Width
Osuna	38	9	Manzanares	64	10
Alcázar de San Juan	40	10	Lleida	64	12
Arrecife de Lanzarote	41	9	Girona	64	13
Fuerteventura	41	10	Gijón	64	15
Tortosa	41	12	Puertollano	65	12
Pamplona	42	12	Badalona	66	12
Ecija	44	11	Santa Cruz de Palma	67	14
Alcañiz	46	10	Barbastro	67	12
Sevilla	47	11	Calatayud	69	12
Bilbao	47	12	Reus	70	15
Cabra	48	10	Burela	71	11
S.Sebastián de Gomera	50	11	Pontevedra	71	19
Hospitalet	50	11	Toledo	71	16
Teruel	50	12	Ciudad Real	73	15
Zaragoza	50	13	Barco de Valdeorras	73	14
Dos Hermanas	50	11	Alcalá de Henares	74	13
Fuenlabrada	50	17	Pozoblanco	74	12
Ceuta	51	13	El Ferrol	78	15
Móstoles	51	16	Guadalajara	79	12
Córdoba	51	10	Madrid	79	15
Albacete	52	13	Santiago	80	17
Valdepeñas	54	11	Monforte de Lemos	80	14
Las Palmas	56	11	Alcorcón	81	14

Barcelona	57	11	Talavera de la Reina	81	14
Cuenca	58	12	La Coruña	84	19
Hellín	58	13	Coslada	90	13
Santa Cruz de Tenerife	59	11	Lugo	90	16
Leganés	60	14	Orense	92	14
Getafe	61	12	Calde	103	15
Huesca	63	13	Vigo	104	23

Possible difficulties with this method: The method has several possible sources of error or difficulties with the interpretation of the results that we have tried to estimate:

- The method is not valid if there are not enough points in the histograms because data corresponds to a new customer of the system or because the number of users is small. To avoid this problem only the distributions in which the highest frequency is over 100 are used.
- Averaging over towns may be problematic if different hospitals in the same town have very different background. for instance Vigo has two hospitals, one is in the centre of town and the other is a granite building on a hill outside Vigo; the difference between their estimated background is 24 μGy/month and in Table 1 it can be seen that the distribution for Vigo is wider than the rest.
- The energy distribution of the environmental radiation could introduce a bias because of the energy dependence of the TLD pellets. This effect should not be important because the energy dependence of LiF phosphor is not big (at most 40%) and because most of the environmental radiation has energy higher than the 20-70 keV where this TLD shows clear energy dependence[3]. The study of the pellet under a $10g/cm^2$ filter (used to estimate deep dose) does not show a distribution significantly different from the pellet without filter (used to estimate shallow dose) (see figure 2).
- Travel irradiations as well as any other sources of error that are not constant in time should smooth after several months are included in the study. On the other hand any persistent bias would show

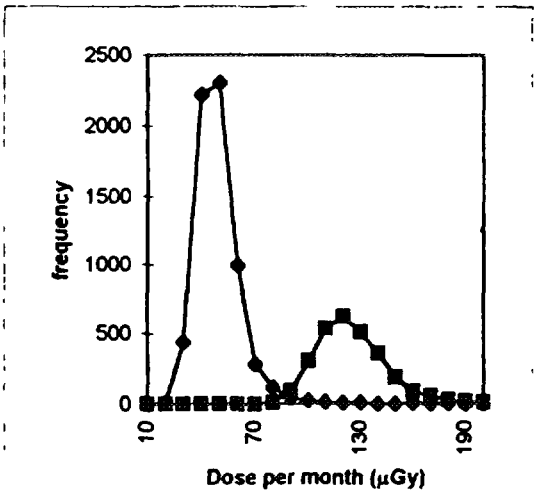

Figure 1: Frequency histograms for 2 hospitals.

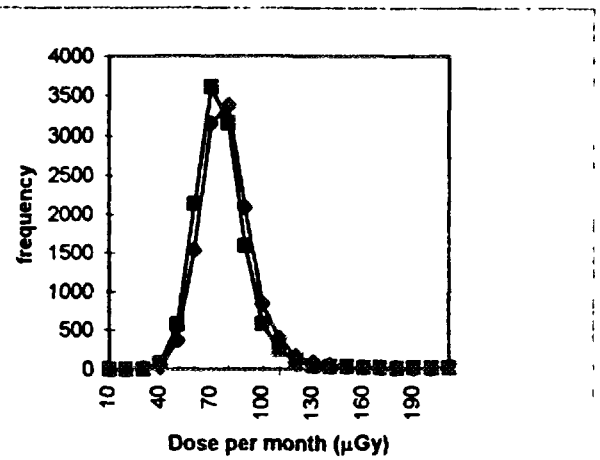

Figure 2: Deep and shallow dose for one hospital.

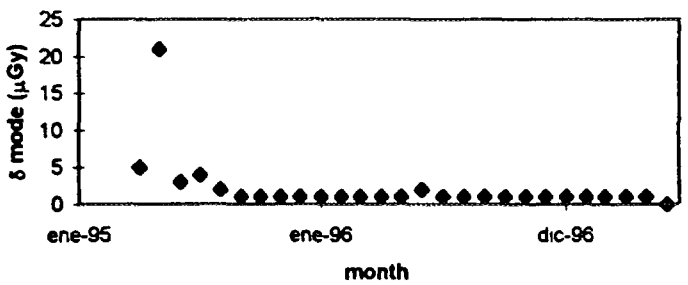

Figure 3: Deviation of the mode from the background for one hospital as data acumulates every month.

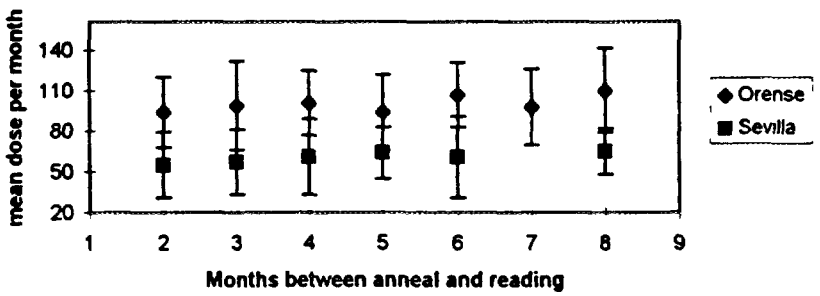

Figure 4: Variation with time of use of mean doses in two towns (doses per month in μGy). Error bars are standard deviation

clearly on the distributions, for instance a 10% bias in the sensitivity times calibration factors would stand up in distributions whose width are of the same order. In Figure 3, which shows the time evolution of the mode for a hospital with low statistics, it can be seen that the convergence of the mode to its final value is fast.

- Some of the dosemeters are not returned to the CND for evaluation at the end of the month and are therefore used longer. To estimate whether the same background per month should be subtracted in these dosemeters, we consider the distribution of their readings as function of the number of months of use. The mean and standard deviation of the doses less than 0.4 mGy per month, for two towns whose background deviate from the global average, are shown in figure 4.

Advantages of this method: We see some advantages in using this method to estimate the background dose:

- It is cheap. As it consists in the study of data already stored in the data base for other reasons, its cost is essentially zero.
- It represents the actual irradiations received by the dosemeters and, therefore, includes the different use of the dosemeters in each hospital.
- Knowing this background for each hospital, even if it is not used in the dose reports, it is possible to make, each month, a quality control check of the dosimetry readers. Subtracting this background from the readings and drawing the frequency histogram, it appears a peak centred in zero. Any deviation or widening of this peak may show a problem to be studied.

Effect on the collective dose: As the average dose is very small, the effect on the collective dose of subtracting the background dose that is proposed instead of an average background dose can be substantial. Recalculating from the data base the doses to professionals in a province with high environmental dose (Orense), the collective dose changes from 0.37 Sv.person (as reported now) to 0.12 Sv.person (for 1996).

Conclusion: When the environmental dose at a working centre that uses X rays has not been measured and more than a few (10) dosemeters are used, we estimate that it as acceptable to use as a background dose, to be subtracted from the readings of the dosemeters before applying energy corrections, the mode (most frequent value) of the distribution of the calibrated readings of the unfiltered pellets after enough statistic is accumulated (highest frequency higher than 100 and more than 5 months of data). When the number of dosemeters is small or the statistics too low to use this method, we propose to use the average background in the town.

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[1]PROYECTOS DE INVESTIGACIÓN SOBRE DOSIMETRÍA BIOLÓGICA REALIZADOS EN EL HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN

Pilar Olivares*, Rafael Herranz**, Marina Gómez**, Mercedes Moreno*, M Jesús Prieto*

* Servicio de Dosimetría y Radioprotección

** Servicio de Oncología Radioterápica

Abstract

Research efforts and special projects on biological dosimetry carried out since 1988 are addressed in chronological order Objectives, results obtained and studies progressing are described

1988

Los primeros pasos del laboratorio se inician en junio de 1988, con la financiación del Consejo de Seguridad Nuclear (CSN), para la realización de un proyecto de investigación epidemiológico y cromosómico consistente en la valoración de bajas dosis de radiación y, en la determinación de efectos sobre profesionales con riesgo de exposición radiológica

1989-1990

A la vista de los resultados que se obtienen, en 1989 se da prioridad a los estudios cromosomicos. estableciéndose un nuevo proyecto de investigación (CSN 1989/90) para la realización y estandarización de técnicas de Dosimetría Biológica. La finalidad de este nuevo proyecto es poder estimar dosis en individuos con sospecha de sobreexposición a radiaciones ionizantes mediante la aplicación practica del método citogenético del estudio de aberraciones cromosómicas en linfocitos de sangre periférica

Los objetivos durante este período de tiempo se centran en

1 Elaboracion de una curva de calibracion dosis-respuesta de rayos X Se utilizo un generador de rayos X de 300 Kvp, tasa de dosis de 98 4 R/min, rango de dosis entre 0 y 400 cGy y ocho dosis

[1] Con la financiación del Consejo de Seguridad Nuclear

puntuales de 0, 25, 50, 75, 100, 200, 300 y 400 cGy. Se realizó el análisis citogenético estudiándose el número de dicéntricos para cada dosis y la tasa de dicéntricos/célula; tras el análisis estadístico de los resultados se obtuvo la curva de calibración dosis-efecto que corresponde a una ecuación lineal cuadrática característica de radiaciones de baja LET. (1)

2. Curva de calibración para neutrones: Se utilizó una fuente de Californio 252, con una tasa de dosis de 0.002795 Gy/h a un metro de distancia, con cinco dosis en el rango entre 0 y 0.2 Gy. Para la irradiación de las muestras se utilizó el mismo tiempo de exposición variando la distancia de la muestra a la fuente. Se realizó el análisis citogenético y el análisis estadístico de los resultados obteniéndose una curva de calibración que responde a una ecuación lineal, característica de radiaciones de alta LET. (1,2,3)

3. Optimización del laboratorio de dosimetría biológica en el Hospital General Gregorio Marañón (HGUGM), puesta a punto de técnicas de cultivo y métodos de tinción en colaboración con el Oak Ridge National Laboratory. (4,5,6)

4. Realización de estudios de dosimetría biológica incluidos en la atención a casos con sospecha de sobreexposición a radiaciones ionizantes, que acuden al Centro de Radiopatología y Radioprotección Nivel II. (durante este período se llevaron a cabo 21 estudios). (3,6,)

1990-1992

En septiembre de 1990 el CSN concede una beca personalizada para realizar trabajos de Dosimetría Biológica en el HGUGM (1990/92). Los objetivos durante este tiempo se centran en:

1. Elaboración de curva de calibración dosis-efecto para rayos gamma: Se utilizó una fuente de Cesio-137, tasa de dosis de 27.27 R/min y las muestras se colocaron a 40 cm de distancia. Se impartieron cinco dosis puntuales (50, 100, 150, y 200cGy) y el tiempo de irradiación fue de

segundos para todas las dosis. Se realizó el estudio citogenético y el tratamiento estadístico de los resultados obteniéndose la curva de calibración dosis-efecto que corresponde a una ecuación lineal cuadrática correspondiente a radiaciones de baja LET. (1,3)

2. Inicio de un estudio cromosómico de la población basal de individuos pertenecientes a la Comunidad de Madrid. (28 individuos analizados)

3. Realización permanente de estudios de dosimetría biológica en individuos con sospecha de sobreexposición a radiaciones ionizantes. (Se realizaron 14 estudios en este tiempo). (7).

Durante este período (el 27/06/90), se firmo un Convenio General de Colaboración entre el CSN y la Consejería de Salud de la Comunidad Autónoma de Madrid, dentro del campo de la Protección Radiológica a desarrollar mediante acuerdos específicos.

1992-1994

Se firma un primer Acuerdo Específico sobre Dosimetría Biológica (1992/93) y se concede una nueva beca personalizada (1992/94). Los objetivos durante este período son:

1. Montaje del laboratorio de dosimetria biológica.

2. Elaboración de una nueva curva de calibración dosis-efecto para rayos gamma: Se realizó una nueva curva de calibración para rayos gamma, pues la mayor parte de los individuos que acuden con sospecha de sobreexposición, están expuestos a rayos gamma, sobre todo los positivos. Además la curva previa solo disponía de cinco dosis puntuales y era conveniente aumentar los puntos a dosis bajas. Se realizó la irradiación de las muestras en una máquina de telecobaltoterápia "Eldorado 78", las muestras se irradiaron envueltas en bolus equivalente a tejido biológico para que se produzca

el equilibrio electrónico y en varias fases debido a que a dosis bajas es necesario estudiar un elevado número de células. La tasa de dosis fue de 23.85 cGy/min, el tiempo de irradiación inferior a 15 minutos en cada dosis, la distancia de la muestra a la fuente de 98.9 cm y el rango de dosis entre 10 y 400 cGy. Posteriormente las muestras se mantuvieron a 37ºC durante una hora para que se completase la reparación enzimática. Se realizo el análisis citogenético teniendo en cuenta el número de di y tricéntricos en cada dosis y posteriormente el análisis estadístico con la colaboración de la NRPB, comprobándose que los resultados siguen una distribución de Poisson. Se obtuvo la correspondiente curva de calibración para rayos gamma. (8)

3. Finalización del estudio cromosómico de la población basal de individuos pertenecientes a la CAM: (44 individuos analizados durante este período). Se estableció una frecuencia basal de 0.7 dic/1000 células analizadas, dato que esta en concordancia con las publicaciones existentes. La muestra global estaba formada por 72 individuos (36000 metafases). (9)

4. Análisis y valoración de dosis en casos reales con sospecha de sobreexposición a radiaciones ionizantes: se realizaron 18 estudios durante este período. (10,11)

1994-1995

Se firma un segundo Acuerdo Específico sobre Dosimetría Biológica (noviembre 1994/1995). Los objetivos durante este período son:

1. Realización del análisis estadístico de la población basal de individuos pertenecientes a la CAM: Con la colaboración de la NRPB, se realizo el análisis estadístico de los resultados para ver si parámetros como la edad, el sexo y el consumo de cigarrillos influían en la frecuencia basal, comprobándose que esta presenta una dependencia lineal con la edad y el consumo de cigarrillos y no presenta variación con el sexo. (9,12)

2. Inicio del estudio de la frecuencia basal de dicéntricos en individuos expuestos de forma continuada a bajas dosis de radiaciones ionizantes: Se seleccionó una muestra de 64 individuos dentro del Servicio de Radiodiagnóstico del HGUGM, debido a que éstos, presentan riesgo de irradiación externa pero no de contaminación interna. (57 individuos analizados).

3. Estudio citogenético en irradiaciones localizadas: Se ha realizado el estudio de dicéntricos en cuatro pacientes sometidos a tratamiento radioterápico (campos pélvicos). Se estudiaron aproximadamente 3000 células por paciente; el estudio se ha hecho antes del tratamiento, tras la primera sesión, la quinta, la decimoquinta y la veinticinco. En dos de los pacientes se realizó un estudio a los seis meses después de finalizar el tratamiento para ver el decay de los dicéntricos.

4. Análisis y valoración de dosis en casos reales con sospecha de sobreexposición a radiaciones ionizantes: Se realizaron 15 estudios durante este período. (13,14)

1996-1999

Se firma un tercer Acuerdo Específico (octubre 1996/1999). Los objetivos durante estos tres años son:

1. Puesta en marcha de la técnica FISH (Fluorescence in situ hibridation) para el estudio de aberraciones cromosómicas estables inducidas por las radiaciones ionizantes: Se han seleccionado tres sondas diferentes, las de los cromosomas 1 y 2 que van a permitir analizar los intercambios producidos entre estos dos cromosomas y una sonda centromérica para diferenciar si estos cambios son translocaciones o dicéntricos.

2. Elaboración mediante la técnica FISH de curvas de calibración para rayos gamma y rayos X.

3. Calibración, estandarización y control de calidad de la técnica FISH en colaboración con otros laboratorios.

Además de los trabajos mencionados, se continúa realizando de forma rutinaria la valoración de dosis en casos reales con sospecha de sobreexposición a radiaciones ionizantes, asimismo se esta llevando a cabo la finalización del estudio de aberraciones cromosómicas en una muestra de población expuesta a bajas dosis.

Las referencias que se mencionan a continuación son las publicaciones de los trabajos descritos anteriormente.

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DESARROLLO DE LA TÉCNICA FISH PARA SU APLICACIÓN EN DOSIMETRÍA BIOLÓGICA, EN EL HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN

Mercedes Moreno*, M. Jesús Prieto*, Marina Gómez**, Pilar Olivares*, Rafael Herranz**.

*Servicio de Dosimetría y Radioprotección. HGUGM

**Servicio de Oncología Radioterápica. HGUGM

RESUMEN

En el Hospital General Universitario "Gregorio Marañón" (HGUGM) de Madrid, se viene realizando de manera rutinaria desde 1989, el análisis citogenético para estimación de dosis, en personas que se sospecha pudieran haber estado expuestas de forma accidental a radiaciones ionizantes. La metodología de uso habitual es el estudio de aberraciones cromosómicas encontradas en linfocitos de sangre periférica. La técnica, recomendada por la OIEA en su publicación nº 260 (1986), permite establecer una relación nº de dicentricos-dosis a través de curvas de calibración dosis-efecto elaboradas in vitro. Esta metodología de estimación de dosis, presenta una serie de limitaciones que pueden ser parcialmente eliminadas, mediante la aplicación de nuevas técnicas de citogenética molecular, como el *PAINTING* cromosómico mediante hibridación *in situ* con fluorescencia (FISH). En el HGUGM se está llevando a cabo un trabajo de investigación para la estandarización de la mencionada técnica, que incluye, la elaboración de las curvas de calibración dosis-efecto, la utilización de la nomenclatura de aberraciones adecuada, y la intercomparación de los resultados con otros centros a nivel internacional. En este trabajo se exponen los primeros resultados, que se refieren basicamente, a la descripción en detalle de la técnica de FISH seleccionada para el desarrollo del proyecto.

La técnicas internacionalmente aceptada para la estimación de dosis absorbida tras exposición a radiaciones ionizantes, es el análisis de aberraciones cromosómicas en linfocitos de sangre periférica (1). El tipo de aberración cromosómica seleccionada son los dicentricos, por su baja frecuencia basal en la población general, y por ser facilmente identificados al microscopio en preparaciones metafásicas obtenidas mediante técnicas de citogenética convencionales (2). La metodología está basada en que la irradiación *in vitro* e *in vivo* de los linfocitos sanguineos produce la misma frecuencia de dicéntricos por unidad de dosis, de forma que se puede calcular la dosis absorbida por un individuo expuesto, mediante la comparación de la tasa de dicentricos observada, con curvas de calibración dosis-respuesta obtenidas previamente *in vitro* (1) (3).

El principal problema que se presenta se debe a que los dicentricos, derivados de intercambios cromosómicos asimétricos, son letales para la célula en división, por lo que terminarán siendo eliminadas; por ello no es posible utilizarlas para estimaciones dosimétricas en personas expuestas tiempo atrás, ni en exposiciones crónicas.

Las translocaciones reciprocas, aberraciones cromosómicas derivadas de intercambios simétricos, no son letales para la célula en división, pudiendo ser trasmitidas a lo largo de los sucesivos ciclos celulares (4). Tradicionalmente, se requerían técnicas de bandeo diferencial para reconocer este tipo de lesiones, por lo que se desestimó su utilización con fines dosimétricos de rutina, dada su gran complejidad de análisis y la gran cantidad de tiempo necesario para llevar a cabo los estudios. El desarrollo del "painting" cromosómico mediante FISH, permite colorear de manera específica cromosomas homologos enteros, a través de su hibridación con sondas concretas de DNA, ligadas

a un determinado fluorocromo (5) (6), de forma que se pueden identificar rapidamente las aberraciones cromosómicas, y calcular la frecuencia de las translocaciones en las que estén implicados los cromosomas coloreados (7) (8) (9) (10).

En este trabajo se expondrán los primeros resultados del desarrollo del painting cromosómico mediante FISH en el Laboratorio de Dosimetría Biológica del HGUGM.

METODOLOGIA

1. Preparación de metafases

Se utilizan, como en dosimetría biológica tradicional, las técnicas citogenéticas de cultivo y procesamiento clásicas, basadas en la desarrollada por Morhead y col., por ello se describen de forma muy resumida: Se establecen los cultivos de linfocitos de 48 horas a 37°C, en medio MEM enriquecido con suero fetal de ternera al 15%, añadiendo antibióticos, glutamina y phitohemaglutinina, las 2 últimas horas de cultivo se realizan en presencia del inhibidor mitótico colcemnid, para detener el ciclo de división en metafase. Tras choque hipotónico con ClK (0.075 M) a 37°C durante 10 min, se realiza la fijación, en tres pasos con metanol:Ácido acético en proporción 3:1, y la extensión en portas limpios, que son almacenados a -20°C o utilizados inmediatamente.

2. "*PAINTING* " mediante hibridación *in situ* (FISH)

Se realiza mediante un coctail de sondas específicas para los cromosomas 1 y 2 marcadas con digoxigenina, que son calentadas a 70°C durante 10 min para su desnaturalización, a continuación se mantienen a 37°C durante 1.30 horas para evitar la hibridación de las secuencias repetidas (7).

Por otro lasdo se lleva a cabo la desnaturalización de los cromosomas metafásicos introduciendolos en una solución de formamida/2xSSC al 70% durante 2 min a 70°C, a continuación se desidratan en series de etanol al 70 80 y 95% y se secan al aire La hibridación se realiza situando 20 µl de la mezcla de sondas en el porta, se cubre y sella y se incuba durante hasta el dia siguiente a 37°C en una cámara humeda en la oscuridad Se retira el cubreobjetos y se realizan los lavados post-hibridación en Formamida/2SSC al 50% (PH 7) a 43 °C durante 15 min y en 0 1SSC (PH 7) a 60°C durante 15 min, se pasa por PBD, y sin dejar secar el porta se añaden 30 µl de sonda pancentromérica marcada con biotina, previamente desnaturalizada a 72°C durante 5 min, se cubre y sella, y se introduce en una cámara humeda para su incubación a 37°C en la oscuridad, hasta el día siguiente Se retira el cubreobjetos y se procede al lavado para sondas satélite con formamida/2SSC (PH 7) al 50% durante 15 min a 37°C y con 2SSC (PH 7) a 37°C durante 8 min Se realiza la detección apropiada mediante Antidigoxigenina marcada con Rodamina, para las sondas painting, y Avidina marcada con fluoresceina para la sonda pancentromérica, se incuba en la oscuridad, introduciendolos en una cámara humeda a 37°C durante 10 min La tinción de contraste se realiza con DAPI 0 05 microgr /ml en una solución antifadeo

3. Análisis cromosómico

Se realiza al microscopio con un equipo de epifluorescencia, que dispone de filtro sencillo para DAPI, permitiendonos visualizar las metafases a 10x y con un filtro triple (DAPI-FITC-Rodamina), que nos permite analizar las metafases a 100x aumentos

Los cromosomas 1 y 2 aparecen totalmente teñidos en color rojo, los centromeros de todos los cromosomas de color verde y el resto de color azul claro sobre fondo oscuro Esto permite identificar perfectamente los intercambios cromosómicos que se produzcan entre los cromosomas 1-2 y el resto, y por otro lado nos permite la identificación de todos los dicéntricos

Se ha diseñado el protocolo de FISH para su aplicación en dosimetría biológica. Se han seleccionado 3 sondas diferentes, dos de ellas para "pintar" cromosomas enteros que nos van a permitir analizar los intercambios cromosómicos que se se produzcan entre los cromosomas 1 y 2 y el resto, y una tercera que nos permitirá diferenciar claramente si estos intercambios, son traslocaciones o dicéntricos. Las principales problemas a resolver son: si podemos comparar los resultados obtenidos con esta metodología con los que se obtienen con la técnica citogenética de análisis de dicéntricos utilizada clásicamente en dosimetria biológica; utilización de una nomenclatura adecuada que permita una clasificación correcta de los intercambios cromosómicos detectados; intercomparación de resultados entre los diferentes centros. Para resolver la primera cuestión, es necesario conocer la proporción del genoma hibridado y extrapolarlo a todo el genoma (8), y además, enlazando con la segunda cuestión, establecer claramente que intercambios deben ser tenidos en cuenta, para poder equiparar los resultados con ambas metodologías.

Por la metodología utilizada, hemos seleccionado el sistema PAINT (11) de nomenclatura para clasificar los intercambios cromosómicos. Este sistema, siendo compatible con el Sistema Internacional de Nomenclatura Cromosómica, simplifica su utilización con fines dosimétricos. Pretendemos incluir en nuestro analisis de resultados, todas las aberraciones encontradas, incluyendo las que no se tienen en cuenta con el sistema PAINT, esto nos permitirá realizar diversas comparaciones con la dosimetría biológica clásica.

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INDUCCION DE FACTORES DE APOPTOSIS EN CELULAS TUMORALES HUMANAS POR BAJAS DOSIS DE RADON

J. Soto*, A. Martín*, S. Cos**, D. González-Lamuño***

*Cátedra Física Médica. **Cátedra Fisiología. ***Cátedra Pediatría.
Facultad Medicina. Universidad Cantabria. España.

Resumen

La posibilidad de modificación de genes relacionados con apoptosis en células tumorales obliga a realizar una experimentación multidisciplinar que describa sus condiciones y características. En este trabajo se utilizan bajas dosis de radiación debidas al radón en la irradiación de células tumorales de mama humanas. Una vez irradiadas, las células se incuban durante tres días al cabo de los cuales se procede a su contaje y a la extracción del ARN total. Mediante técnicas de biología molecular, transcripción inversa y reacción en cadena de la polimerasa, se estudia la expresión de genes implicados en apoptosis. Los resultados encontrados indican que en la línea celular utilizada, MCF-7, se expresan los genes bcl-2, bcl-x_L y bax. En las células irradiadas los niveles de expresión de bcl-x aumentan con respecto a las control y se induce la expresión de la forma bcl-x_S cuya proteína es inductora de apoptosis.

1. Introducción

Determinados estudios epidemiológicos sugieren la existencia de menores frecuencias de aparición de tumores en poblaciones expuestas a bajas dosis de radiación debidas al radón (^{222}Rn) [1,2]. Un hecho semejante sólo parece poder justificarse por un efecto del radón sobre el sistema inmunitario o por la inducción de procesos de apoptosis en células tumorales [3,4]. El estudio de esta última posibilidad es especialmente interesante y puede hacerse de manera experimental. En este trabajo exponemos la metodología y los resultados encontrados referentes a la modificación de factores de apoptosis al irradiar con radón, a dosis moderadamente elevadas, células tumorales humanas.

2. Método

Para estudiar los efectos del radón sobre células tumorales hemos usado una línea estable, MCF-7, obtenida de efusión pleural de una paciente con carcinoma mamario metastásico. Las células se conservan en botellas a 37°C donde exhiben antigenicidad a la superficie. En cada experiencia se toma una cierta cantidad y se diluye en un medio nutriente hasta conseguir una concentración de $3 \cdot 10^5$ células/cm^3. Las células se siembran en placas Petri poniendo en cada una de ellas 1 cm^3 de disolución y añadiendo 4 cm^3 de medio nutriente, después de lo que se dejan 3 horas para que se fijen a las placas. Transcurridas éstas se quita todo el medio de cada placa y se sustituye por medio fresco al que se le ha añadido radón.

El medio de cultivo conteniendo radón se obtiene por difusión del gas desde una muestra líquida que contiene radio (^{226}Ra) y disolución del gas en el medio nutriente contenido en un tubo estéril. Los tubos con líquido nutriente obtenidos de esta manera se cierran y se miden con una cadena de espectrometría gamma, una vez que el radón ha alcanzado el equilibrio radiactivo con sus descendientes de vida media corta, para calcular la concentración de radón disuelto.

El medio nutriente se calienta después a 37°C en los mismos tubos cerrados. A continuación se filtra para asegurar su carácter aséptico, tomando porciones de 5 cm^3 que se añaden a las placas. Estas se mantienen en cámara de incubación durante 3 días, transcurridos los cuales se sacan de la cámara y se cuenta el número de células existentes en cada placa mediante un hemocitómetro.

Una vez contadas, se procede a la extracción del ARN total mediante lisis celular con detergentes, en presencia de agentes inactivadores de enzimas que degradan el ARN, disoluciones fraccionadas o extracción orgánica, centrifugación y precipitación. El producto obtenido se corre por electroforesis en gel para asegurar la calidad del ARN total obtenido.

A partir del ARN obtenido se sintetiza una cadena de ADN complementaria mediante síntesis inversa, utilizando hexámeros como cebadores de la reacción. Posteriormente se procede a la amplificación de regiones específicas de genes implicados en apoptosis mediante la reacción en cadena de la polimerasa (PCR). Para ello, se han diseñado oligonucleótidos específicos cuyas secuencias son complementarias a los fragmentos de ADN que flanquean la región que se quiere amplificar.

La expresión de los distintos genes estudiados se determina de manera semicuantitativa mediante electroforesis de los productos de PCR, modificando las condiciones y ciclos de la reacción, de tal modo que no se llegue a la fase de saturación. Como referencia se ha usado el gen de la deshidrogenasa GAPDH. Los productos amplificados se han

visualizado tras electroforesis en agarosa y/o acrilamida con bromuro de etidio. A partir de la comparación entre los resultados encontrados en las células irradiadas y las control, hemos procedido a la reamplificación de los productos que solamente aparecen en las primeras. Estos productos se estudian por fin mediante un secuenciador capilar de DNA por secuenciación de sus bases

3. Resultados

Utilizando la metodología descrita hemos hecho distintas experiencias usando dosis bajas de radiación debidas al radón. La dosis recibida por las células se calcula en cada caso a partir de la concentración de radón existente inicialmente en el medio de cultivo en equilibrio con sus descendientes. Se considera que en el proceso de filtración y distribución a las placas, el medio pierde la totalidad del radón disuelto, que pasa al aire, y la dosis se evalúa calculando la energía total depositada por sus descendientes de vida media corta. El valor típico de las dosis usadas ha sido de 1 mGy.

El recuento de las células después de 3 días en cámara de incubación da, en todos los casos, un crecimiento menor de las poblaciones irradiadas que de las control. Las poblaciones celulares irradiadas alcanzan un promedio de un 80% de la población control, con una elevada significación estadística de la diferencia entre ambas. El crecimiento de las células irradiadas es comparable, aunque ligeramente mayor, al obtenido en otras experiencias anteriores, [5].

Hemos aplicado la técnica de la PCR con un número elevado de ciclos para determinar la expresión de los genes relacionados con apoptosis bax, bcl-2 y bcl-x. Los genes bcl-2 y bcl-x regulan apoptosis protegiendo las células de una gran variedad de estímulos fisiológicos y patológicos. Existen dos tipos de tránscritos de bcl-x cuyos productos tienen función antagónica. El tránscrito largo bcl-x_L se traduce en un péptido que protege de apoptosis, igual que lo hace bcl-2, mientras que el tránscrito corto bcl-x_S la induce. Los resultados encontrados señalan la expresión de los genes bax, bcl-2 y bcl-x en la línea celular utilizada, siendo bcl-x_L el que se expresa en mayor cantidad.

Como consecuencia de la irradiación con bajas dosis de radón se observan diferencias en la expresión de los genes estudiados. El gen bax presenta un aumento de expresión, poco significativo, en las células irradiadas con respecto a las control. El tránscrito largo inhibidor de apoptosis bcl-x_L tiene un aumento significativo de expresión en las células irradiadas. En ellas se expresa también la forma corta bcl-$_S$ inductora de apoptosis, que no lo hace en las células control. Estos resultados indican que las dosis bajas de radiación tienen un papel importante en la proliferación de células tumorales induciendo la expresión de genes tanto represores como inductores de apoptosis.

4. Conclusiones

De entre los resultados encontrados en el presente trabajo queremos destacar :

La irradiación con radón a bajas dosis disminuye el crecimiento de las poblaciones de células tumorales humanas, MCF-7, usadas.

La línea celular utilizada expresa los genes relativos a apoptosis bax, bcl-2 y bcl-x.

La irradiación con bajas dosis aumenta significativamente la expresión de bcl-x_L, y, de manera poco significativa, de bax. En las células irradiadas, y no en las control, se expresa la forma corta bcl-$_S$ que se traduce en un péptido inductor de apoptosis.

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APROXIMACIÓN CONCEPTUAL Y FUNCIONAL AL DISEÑO DE ESTRATEGIAS OPTIMIZADAS DE INTERVENCIÓN PARA LA RESTAURACIÓN AMBIENTAL TRAS ACCIDENTE NUCLEAR GRAVE

C. Vázquez, J. Gutiérrez. CIEMAT. Avenida Complutense 22, 28040 Madrid. España

Resumen

El presente trabajo constituye una aproximación a los criterios que pueden utilizarse en el establecimiento de metodologías de optimización de estrategias de intervención para la recuperación ambiental tras accidente, problema complejo, aún no bien resuelto ni conceptual ni funcionalmente. En este sentido la ponencia resume los desarrollos, sobre este tema, que el Programa de Protección Radiológica por Intervención del CIEMAT está realizando dentro de sus proyectos de investigación en curso.

1. INTRODUCCION

Un accidente nuclear con repercusión ambiental produce, entre otras consecuencias, un incremento del riesgo radiológico que, en muchos casos, si no se tomaran decisiones inmediatas podría ser inaceptable para la salud de la población a corto, medio y largo plazo. Estas decisiones inmediatas se refieren, en general, a restricciones de permanencia de las personas en determinados lugares, o del consumo de los alimentos allí producidos, aunque también pueden consistir en la aplicación de cualquier otro procedimiento de reducción de dosis, como la retirada de la contaminación o su emplazamiento de un modo más conveniente. En todo caso la intervención inmediata tratará de establecer controles e introducir barreras entre la contaminación y la población a lo largo de un determinado periodo de tiempo.

Si en el accidente se han liberado radionucleidos de vida larga, la prolongación en el tiempo de estas decisiones inmediatas puede resultar excesivamente costosa para la sociedad, lo que lleva a plantearse la cuestión de una intervención para la restauración ambiental de los entornos contaminados. Tal intervención debe estar sujeta, obviamente, a los principios generales de Protección Radiológica, por lo que deberá estar justificada (de modo que proporcione más beneficios que perjuicios) y optimizada (la forma, escala y duración de la misma se dirigirán a maximizar el beneficio neto).

El establecimiento de metodologías para la optimización de estrategias en este tipo de intervenciones se dirige, por tanto, al análisis de las opciones de actuación existentes que sean aplicables y a la identificación de las que pudieran paliar mejor los efectos negativos de la situación de restricción y control, reduciendo el riesgo radiológico remanente tras las decisiones inmediatas, con el menor costo social. El análisis de algunas de las consecuencias que podrían derivarse de estas intervenciones puede ser muy complejo. Tal es el caso, por ejemplo, de los posibles impactos sobre el bienestar social y/o el mercado interior y exterior, los efectos secundarios sobre el medio ambiente, las consecuencias políticas de una decisión, etc. Todas estas consideraciones sobrepasan ampliamente el ámbito de la protección radiológica, por lo que el análisis que se presenta aquí toma en consideración únicamente costos, reducción de riesgo radiológico, y efectos sobre el rendimiento y calidad de los productos.

2. DESARROLLO CONCEPTUAL

El resultado ideal tras la restauración ambiental sería la eliminación de cualquier barrera artificial o control administrativo preexistente, garantizando que el riesgo radiológico residual fuese suficientemente bajo como para que la población pudiera vivir, en el futuro, sin que el accidente representase ya ninguna restricción de comportamiento. La contaminación residual entonces se podría considerar incluida en el fondo natural.

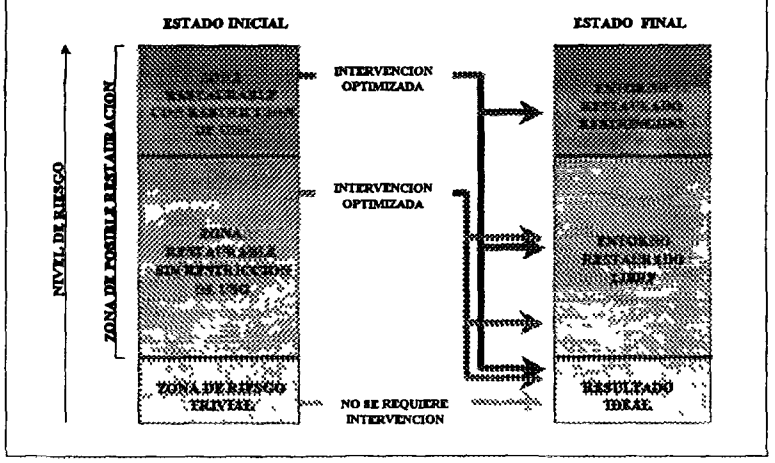
Cuando se presenta un caso de restauración ambiental, se supone que el riesgo individual de la población está ya controlado por los niveles de intervención preexistentes. Durante la optimización, normalmente, se manejarán dosis suficientemente bajas como para que se les pueda aplicar la condición de linearidad dosis respuesta. Bajo esta perspectiva, la dosis colectiva evitada se considera una magnitud adecuada para valorar la reducción del riesgo radiológico.

Consideraciones de equidad en la distribución del riesgo podrían dar preferencia a dosis bajas sobre mayores grupos de población frente a dosis relativamente más altas sobre un grupo de personas más reducido. El mismo tipo de consideraciones tendería a valorar más la dosis que recibirían las poblaciones no directamente beneficiadas por la práctica responsable del accidente frente a la dosis sobre el resto de la población. En esta aproximación, no se toman en cuenta estos matices y se valora de igual modo la dosis que pudiera impartirse a través de la cadena alimentaria, que el mercado distribuirá entre un grupo de población muy amplio, y la dosis que un reducido grupo de individuos pueda recibir por irradiación externa desde un entorno urbano contaminado. En cuanto a la distribución de la dosis colectiva a lo largo del tiempo, se considera más adecuado no aplicar ningun factor de descuento sobre las dosis futuras.

La optimización de una intervención, maximizando el beneficio neto, puede conducir a algunas situaciones pintorescas como se ilustra en el siguiente caso hipotético: Tras el análisis, una determinada contramedida agroquímica resulta seleccionada por representar el máximo beneficio neto. Es moderadamente efectiva en cuanto a la reducción de la transferencia de contaminación a los cultivos, es barata, no genera residuos y además aumenta considerablemente el rendimiento de producción sin otros efectos secundarios negativos. En estas circunstancias, la contramedida optimizada podría incluso llegar a producir un aumento de dosis colectiva, resultado que no es en absoluto aceptable. Parece por tanto razonable exigir que en el proceso de optimización se introduzca algún requisito que garantice una reducción de riesgo radiológico de al menos un determinado porcentaje, lo que también contribuye a que los resultados de la decisión se vean menos afectados por las incertidumbres asociadas a los modelos de predicción.

Por otro lado, ni la justificación ni la optimización de la intervención garantizan que la opción seleccionada reduzca el nivel de dosis residual a un valor suficientemente bajo para alcanzar la situación de restauración ideal que, como se ha visto anteriormente, sería el nivel más parecido posible al estado previo al accidente. Esto podría valorarse comparando la tasa de dosis residual con las tasas de dosis que la población recibía antes del accidente o,de modo más sencillo, comparando el incremento de dosis con lo que habitualmente se considera como un riesgo trivial en la mayor parte de los casos. Estos conceptos de trivialidad se han tenido en cuenta en la elaboración de criterios de exención(1). El OIEA en sus BSS especifica 10μSv o 1 mSv*persona respectivamente como valor de dosis individual y de dosis colectiva anuales para la exención de practicas y fuentes.

FIG REPRESENTACION ESQUEMATICA DE LOS DISTINTOS CASOS QUE PUEDEN PRESENTARSE AL ANALIZAR UNA RESTAURACION AMBIENTAL Y RESULTADOS POSIBLES



La aproximación adoptada para el análisis se esquematiza en la Figura en la que se distinguen dos valores de referencia expresados como valores de tasa de dosis o sus derivados en términos de concentración de actividad. El valor superior está conectado con los niveles establecidos para restricciones de uso y consumo. Si los valores medidos o calculados para un determinado escenario de contaminación superan los niveles de restricción de uso el escenario se considerará previamente restringido. En este caso la optimización de la intervención valorará el beneficio neto de la intervención frente a la situación de restricción previa. De no existir ninguna opción de restauración capaz de reducir los niveles por debajo de los de restricción, el escenario ya "intervenido" deberá seguir sometido a vigilancia y control.

Como referencia inferior se consideran las tasas de dosis antes indicadas para la exención. Si el incremento de dosis individual, debida a la contaminación existente en el escenario a restaurar, es inferior a 10μSv, a través de todas las vías posibles, el escenario se considera ya libre de toda restricción, no siendo necesario analizar la conveniencia de ningún tipo de actuación. En caso contrario se efectúa un análisis

de decisión multiatributo para determinar las opciones óptimas y obtener la mejor estrategia de intervención. El resultado de aplicar dicha estrategia conducirá a un escenario restaurado al nivel de la capacidad técnica existente en el momento y, normalmente, deberían aceptarse los valores residuales para mantener un modo de vida normal.

Podría darse el caso en que, bajo otra perspectiva diferente a la que ha servido de base para este análisis anterior, otras opciones de descontaminación pasaran a ser las optimas si se tomasen en consideración uno o más nuevos criterios de evaluación (social, político...). En general, la valoración de estos últimos se realizaría añadiendo el "juicio de experto" del responsable de la toma de decisión sobre el análisis previo realizado.

3. DESARROLLO FUNCIONAL

La ejecución de esta, en principio, simple aproximación filosófica, requiere una fuerte complejidad técnica. La evaluación de la respuesta de una determinada opción de intervención, sobre un escenario de contaminación específico, ha de partir del impacto desde la fecha prevista para la intervención, en caso de que ésta no se llevase a cabo. Esto es, ha de evaluarse, a partir de esta fecha, la dosis a la población, a través de todas las potenciales vías de exposición y, en caso de tratarse de un escenario bajo restricción de uso, el coste de garantizar el cumplimiento de tal restricción. Esta evaluación proporcionará una idea de hasta que punto es importante tratar de restaurar el entorno.

Una vez conocido el impacto radiológico procedente del escenario contaminado bajo estudio, la etapa siguiente es valorar la aplicabilidad, en ese escenario concreto, de las distintas opciones de descontaminación existentes (entendiendo descontaminación como sinónimo de reducción de dosis) y los beneficios y daños que se derivarían de tales actuaciones.

En general, los escenarios de contaminación pueden ser muy complejos (conteniendo incluso ecosistemas diferentes) y no hay soluciones universalmente aplicables. Los modelos requeridos para la determinación de los flujos de contaminación a lo largo del tiempo tampoco son de aplicación general sino que dependen de otra serie de características locales. Estas realidades conducen a la necesidad de descomponer los escenarios de contaminación hasta un punto en el que ya sean factibles las evaluaciones del impacto y de la aplicabilidad de opciones de descontaminación, utilizando un modelo único de comportamiento.

La aproximación adoptada consiste en analizar en profundidad los mecanismos responsables de los flujos de los radionucleidos hasta la población a través de todas las posibles vías de exposición (transferencias en entornos urbanos, suelos, cultivos, ganado, industria alimentaria, otros procesos industriales, sistemas seminaturales: pastos, bosques, matorral,etc.), y los modelos de evaluación disponibles. Este análisis permitirá dividir los distintos entornos en una serie de **componentes** caracterizados por determinados atributos responsables del comportamiento de los diferentes radionucleidos contaminantes. Cualquier escenario contaminado puede de este modo representarse por valores específicos para cada uno de los **atributos de los componentes** que lo integran, permitiendo así la aplicación de modelos adecuados de cálculo de impacto.

No todos los componentes, según acaban de definirse, pueden descontaminarse del mismo modo, con resultados idénticos, lo que justifica, en la aproximación adoptada, un nuevo desglose en diferentes **elementos de intervención** sobre los que el resultado de una contramedida debe quedar perfectamente determinado.

La evaluación de una contramedida puede a su vez realizarse identificando en ella atributos que reflejen aspectos de su comportamiento. Algunos de estos atributos dependen de ciertas características del componente sobre el que vayan a aplicarse, otros dependen sólo de la contramedida en sí y otros dependen, además, de factores externos. Todos ellos podrán, finalmente, valorarse y ponderarse adecuadamente por un sistema de decisión estándar, que clasificará opciones de acuerdo con los factores de ponderación y restricciones que se introduzcan.

4. APLICACIONES Y DESARROLLO FUTUROS

La metodología que ha sido expuesta en este trabajo ha constituido la base de la participación CIEMAT en uno de los proyectos multinacionales de colaboración sobre las consecuencias del accidente de Chernobyl (CHECIR, ECP-4 "Strategies of Decontamination") donde ha sido aplicada[2],[3],[4].

Actualmente se está tratando de ampliar la aplicación de esta metodología de modo que permita dar respuesta a un conjunto de escenarios potenciales de contaminación diferentes a aquellos sobre los que se haya hecho experimentación directa. Este proceso requiere una serie de extrapolaciones sobre cada uno de los parámetros de comportamiento (atributos) representativos de cada componente específico y utilizar métodos estocasticos para inferir la calidad de la respuesta dentro de determinados rangos de variabilidad de cada uno de los atributos, tratando de mantener una fiabilidad de resultados aceptable. De este modo se pretende obtener un conjunto de **componentes genéricos** utilizables para representar escenarios de contaminación diferentes a aquellos sobre los que se hayan obtenido datos experimentales.
La capacidad de elaboración de componentes genéricos adecuados depende básicamente del grado de conocimiento sobre los mecanismos de comportamiento de los radionucleidos en el medio ambiente y de la calidad de los modelos matemáticos disponibles para representar estos mecanismos.

Los trabajos que se realizan actualmente en este sentido siguen dos frentes convergentes. Por una parte, se está coordinando un proyecto multinacional dentro del Programa Específico de Seguridad de la Fisión Nuclear (4° Programa Marco de la UE), que cuenta, además, con financiación de CSN y ENRESA a través de sus respectivos Planes de Investigación. El proyecto, "Techniques and management strategies for environmental restoration" (TEMAS), trata de identificar cuantos escenarios especificos adecuadamente caracterizados puedan existir, a fin de obtener una serie de componentes genéricos representativos de la realidad de la comunidad europea. Por otro lado, otro proyecto, "Vulnerabilidad radiológica de los suelos españoles", trata de establecer una caracterización edafológica y agronómica de los suelos españoles que permita, en el futuro, la evaluación teórica del comportamiento de radionucleidos que pudieran depositarse accidentalmente sobre el suelo español.Este proyecto cuenta, asimismo con el soporte económico de CSN y ENRESA.

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NON-NEOPLASTIC CALCIFIED TISSUE PATHOLOGIES AMONG RADIUM WORKERS AND PLUTONIUM INJECTEES

J.H. STEBBINGS
Midwest Epidemiology Associates
Naperville, Illinois
United States of America

Abstract

NON-NEOPLASTIC CALCIFIED TISSUE PATHOLOGIES AMONG RADIUM WORKERS AND PLUTONIUM INJECTEES.

Two human studies of deterministic effects of radium and plutonium are summarized. Histopathology data from femurs of New Jersey radium workers demonstrate effects of radium at ~0.8 Gy skeletal dose. Toxicity ratio data from beagles suggest equivalent histopathological effects from ^{239}Pu may occur in humans at skeletal doses of ~0.12 Gy in compact bone or at ~0.01-0.02 Gy in spongy bone. These results support observations that subjects injected with plutonium in the 1940s showed bone changes typical of alpha radiation exposures, extensive osteoporosis with related fractures, and hearing disorders or vertigo relatable to bone damage and/or middle ear inflammation, all findings suggested by the clinical radium literature. A probable case of extensive pathologic calcification from a plutonium injection also occurred. In two cases suspect findings occurred at skeletal doses of ~ 0.05 Gy. It is hypothesized that subjects with collagen disorders and uremic insufficiencies, as well as females late in life, form subpopulations susceptible to non-stochastic effects of internal alpha-emitters. In general, bone fractures late in life secondary to osteoporosis are associated with increased disability, increased risk of institutionalization, and with diminished survival rates.

1. INTRODUCTION

William Looney predicted in 1958 [1] that the then current maximum permissible concentration of 0.1 microgram (3.7 kBq) of radium would be inadequate to prevent 'appreciable bodily injury.' Skeletal damage and roentgenographic changes were considered less difficult to project downward than bone tumor induction, and Looney emphasized the effect of accumulating dose beyond 40 years, and the increasing atrophy of the skeleton and its decreasing ability over time to repair skeletal damage. Looney suggested that the characteristic histopathological changes in bone specimens of radium subjects indicted that the "roentgenographic changes considered 'nondeleterious' may represent more extensive bone damage than is now appreciated."

William Sharpe presented first qualitative [2] then quantitative [3] evidence of histopathological effects in the bones of New Jersey radium workers, seeing characteristic pathology in nearly all subjects with preterminal ^{226}Ra burdens above his minimum detectable burden of 0.016 kBq. Reanalyses of Sharpe's data have yielded more precise quantitative estimates of the radium burden at which osteonecrosis can clearly be seen, and have demonstrated the clear statistical significance of the findings even in the lower dose range. These observations, conjointly with plutonium toxicity ratios from Jee et al. [4] for bone effects, suggested that plutonium is likely to damage human bone at quite low skeletal doses. These estimates of the sensitivity of human bone to plutonium damage supported new clinical observations on the plutonium injectees exposed in 1945-1947 [5]. These effects included specific and nonspecific bone changes, calcification, and hearing loss, changes also consistent with the clinical literature on radium poisoning [6, 7]. In this report we summarize briefly the findings of both the study of radium osteonecrosis and the related medical findings in the plutonium injectees.

2. LOW-DOSE RADIUM OSTEONECROSIS

2.1 Prediction of the necrosis ratio

Sharpe [3] accepted three findings in 25 radium-exposed individuals as characteristic of radium-related osteonecrosis: (1) bone and marrow "infarcts"; (2) increased quantities of fibrous tissue within the marrow, especially immediately adjacent to the endosteum; and (3) abundant granular basophilic calcification, often focal, associated with marrow or vascular space fibrosis. Sharpe's data were abstracted, as were updated radium dosimetry data [8]. Sharpe's primary dependent variable was the "necrosis ratio," the number of blocks of femur tissue containing osteonecrosis divided by the number of tissue blocks studied. In this analysis that ratio was used as the dependent variable in conventional linear regression models for critical dose-response estimates because of limitations of a Poisson model near its origin. For statistical inference, however, a Poisson regression approach was used, where the number of blocks with necrosis is the dependent variable, and the total number of blocks is the "offset." Dosimetry data were based on measurements of preterminal ^{226}Ra burden, estimates of ^{226}Ra and ^{228}Ra intake, and estimates of lifetime skeletal dose. There was little difference in statistical significance levels using the three alternative independent variables. The present analysis differs from that of Sharpe [3] in being restricted to the twelve females, exposed as radium dial workers. Males, primarily radium refinery workers, appear to have shown similar effects from radon progeny exposure rather than from ^{226}Ra body burdens. This presentation also excludes results for ^{228}Ra except as one source of total skeletal dose. Additional details are found in the primary report [9].

Poisson regressions for both preterminal ^{226}Ra burdens and skeletal radiation dose from both ^{226}Ra and ^{228}Ra among the twelve female radium dial workers were quadratic in form, with all terms statistically significant at the 0.001 level. The corresponding conventional regression estimates of the necrosis ratio are: 0.04160 x ^{226}Ra burden - 0.0004647 x ^{226}Ra burden^2 (kBq); or, 0.02233 x dose - 0.000125 x dose^2 (Gy).

Four subjects had high preterminal ^{226}Ra burdens, averaging 40 kBq with estimated skeletal doses averaging 72 Gy. Excluding these, the 5 females with necrosis ratios above zero had average preterminal ^{226}Ra burdens of 0.73 kBq, and estimated skeletal doses of 1.7 Gy. The three showing no radium osteonecrosis had preterminal burdens of 0.37 kBq and estimated skeletal doses of 0.26 Gy. In this range the dose-response relationships were linear. Both the constant and linear terms in the Poisson regression remained statistically significant at the 0.01 level. No intercept models were used for the conventional linear regression estimates in this low dose range. The equations are: 0.09816 x ^{226}Ra burden (kBq); and 0.05066 x dose (Gy).

2.2 Extrapolation to plutonium effects

Although the supralinear quadratic relationship of radium osteonecrosis on radium body burden or skeletal dose is of interest, in the context of concern for low doses of radiation the low-dose prediction equations are more relevant. The lowest observed non-zero necrosis ratio was 0.025; three additional values were in the range 0.038 to 0.041. For convenience, 0.04 was taken as the necrosis ratio corresponding to the level where bone damage is empirically observable without doubt. This point corresponds to the effect expected from ~0.8 Gy skeletal dose, or a preterminal burden of ~0.4 kBq ^{226}Ra. These estimates are from subjects exposed in early adult life as healthy workers, and may overestimate doses required to cause damage in susceptible subjects.

The data of Jee [4] on bone vasculature in beagles suggest toxicity ratios per unit skeletal dose of ~6.6:1 for ^{239}Pu relative to ^{226}Ra, and ~6:1 for injected ^{239}Pu in spongy bone versus compact bone. These toxicity ratios suggest that histologically observable damage to compact bone in humans may be expected from ^{239}Pu at ~0.12 Gy, and that equivalent damage would occur in spongy bone at skeletal doses of ~0.01-0.02 Gy. This supports the observations of bone effects in the plutonium injectees.

3. CALCIFIED TISSUE EFFECTS AMONG PLUTONIUM INJECTEES

Medical findings potentially related to plutonium burdens in 18 subjects injected while ill between 1945 and 1947 in a study of plutonium retention in man [5] were reviewed [10, 11]. Seven subjects dying less than one year after injection were excluded from study; five others had inadequate records. Useful medical and research records for six subjects existed, two of whom had died in their second year post-injection and had been exhumed. Reports of a radiologist experienced in reading radiographs of radium workers were available for three cases. Five persons had been injected with ~11 kBq ^{239}Pu; of these, subjects not dying in their second year had skeletal doses in 1975 of ~0.7-1.4 Gy; the two short-lived cases had skeletal doses of ~0.05 Gy. The skeletal dose in one case injected with 3.5 kBq ^{238}Pu was estimated at ~0.11 Gy in 1975.

Calcified tissue pathology consistent with plutonium effects occurred in all six cases. All three radiographs read by the experienced radiologist were suspect. A Black male with ^{238}Pu exposure had trabecular changes in the humeri and acromions and abnormal trabeculae in the mandible consistent with radium deposition. His reduced x-ray score of "3" corresponded on average to that from a preterminal burden of 7-13 kBq ^{226}Ra [12]. An exhumed male dermatomyositis case showed some intracranial densities and irregular mandibular trabeculations "possibly" due to radiation. A third young female Cushing's disease case was found on exhumation to have numerous very small very dense deposits on the surfaces of a number of bones, ascribed by the radiologist to the plutonium exposure. This case, with kidney damage, was at risk of pathologic calcification; it is proposed [11] on the basis of Selye's [13] studies of thorium that plutonium acted as a calciphylactic agent. Selye considered the collagen diseases dermatomyositis and scleroderma seen in this series as related to calciphylaxis.

Of the three subjects with only clinical data relating to bone changes, an abnormal metallic density of the metacarpal had been noted in 1950 in the one male, consistent with dense necrosis found in radium cases [12]. Consistent with the greater risk in females of osteoporosis, one female had severe degenerative changes and osteoporosis ultimately resulting in hip fracture prior to death, and the second, a long-standing scleroderma case, had two compression fractures of the spine. Disability resulted in both cases. The first of these also had increased radiographic density of the vault of the skull and in the region of the mastoid air cells, suggesting that plutonium had effects in that region similar to radium. In addition to this pathology in the mastoid region in one case, a second case developed vertigo about 7 years post-injection, and ~20 years prior to death was diagnosed as having bilateral conduction deafness, probably due to otosclerosis

With respect to the bone damage seen in these cases, two of three seen by the radiologist familiar with radiographs of radium workers showed patterns consistent with specific effects of radium, coarsened trabeculation and mandibular effects. Non-specific effects indistinguishable from osteoporosis were seen. Although Evans [12] described this as the simplest sign of alpha-irradiation of bone, it remains poorly studied. That radium poisoning could cause spontaneous fractures, often of the hip, was recognized early [6, 12]; again this outcome has not been adequately quantified in the literature. Hearing loss was found to be excessively common among radium workers studies by Sharpe [7], and loss of bone conduction was common. Aub et al. [6] had reported on two dial workers with hearing impairment due to temporal bone damage.

A case study of medical findings neither complete nor collected for research purposes cannot in itself be conclusive. In the context of occupational or environmental epidemiology such a "case study" at best demonstrates that findings are consistent with those expected on the basis of the literature. In this study there fortunately was a relevant clinical literature, that on radium, to furnish expectations. Numerous findings are fully consistent with the bone effects expected from alpha-emitter exposure. While one cannot conclude in each case that plutonium was the major, or even a significant contributory, cause, one certainly cannot conclude that no effects of the plutonium exposure occurred. Even in the two cases with short survival and skeletal doses of ~0.05 Gy possible or probable effects of the plutonium exposure were seen.

4. CONCLUSIONS

Histopathological effects on human bone at skeletal doses down to 0.12 Gy from ^{239}Pu in compact bone and 0.01-0.02 Gy in spongy bone are expected. Trabecular changes characteristic of alpha-emitter exposure was seen at ~0.11 Gy in an injectee given ^{238}Pu, and "possible" trabecular abnormalities were seen in a collagen disease case surviving less than two years with a bone dose ~0.05 Gy. Probable plutonium-induced pathologic calcification was also seen at a bone dose of ~0.05 Gy. Two female plutonium injectees with skeletal doses in the 1-2 Gy range suffered skeletal fractures typical of severe osteoporosis. That persons with collagen diseases, and females exposed late in life, are particularly susceptible to bone effects of alpha-emitters seems likely.

A proper perspective on risk from early bone damage requires evaluations of disability, of costs of institutionalization, and of decreased survival in the last years of life [11,14]. Osteoporosis or loss of bone strength is a major risk factor for bone fractures in the elderly, which are associated with 6-20% excesses of all-cause age-specific mortality for up to two years post-fracture. In one study survival was decreased nearly 20% for those with vertebral fractures. Assessment of risk from radionuclides should therefore include estimation of increments to age-specific risks of disabling events very late in life, and their contribution to premature mortality. Since these outcomes are non-specific and multifactorial, the task will be far more difficult than that of projecting bone cancer risks to low doses and late times.

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EXPOSICIÓN OCUPACIONAL EN RADIODIAGNÓSTICO EN CUBA DURANTE 1991-1994

Sáez D.G.,[*] Guevara C.R.,[‡] Larrinaga E.F.[‡] y Calzado Y.[‡]
[*] Centro de Control Estatal de Equipos Médicos.
[‡] Instituto de Medicina del Trabajo.
Ciudad Habana, Cuba.

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RESUMEN

Se presentan los resultados de la distribución de dosis de los trabajadores vigilados (TV) en radiodiagnóstico durante el período 1991-1994, por ser el período que sigue al último reportado por el Comité Científico de las Naciones Unidas para el estudio de los Efectos de las Radiaciones Atómicas (UNSCEAR). El análisis se realizó según las recomendaciones del UNSCEAR. Se observó una brusca disminución en el número de trabajadores expuestos a niveles medibles (TENM) a partir de 1991, estableciéndose una gran desproporción de éstos con respecto al número de TV. Los TENM con dosis mayores que los tres décimos del límite permisible de dosis vigente, poseen el peso de la contribución a la dosis colectiva recibida por los TV en el período con cerca del 22 %. Se realiza un análisis de la repercusión en los resultados del nuevo límite permisible de dosis para la exposición ocupacional. Se recomienda un mejoramiento del sistema dosimétrico y en general del sistema de protección radiológica, que incremente la calidad en el control de la exposición ocupacional en radiodiagnóstico.

INTRODUCCIÓN

En Cuba, la vigilancia radiológica individual de los trabajadores ocupacionalmente expuestos a rayos X de uso médico-diagnóstico es llevada a cabo por el Departamento de Higiene de las Radiaciones del Instituto de Medicina del Trabajo (DHR-IMT). Este servicio se brinda como promedio, a alrededor de 4000 trabajadores por año y se establece con el fin de tomar medidas preventivas acerca de las exposiciones profesionales del personal que labora con radiaciones ionizantes.

La vigilancia se sustenta en el control dosimétrico individual de los trabajadores expuestos, siendo un medio por el cual se pueden realizar valoraciones acerca de las exposiciones ocupacionales y relacionarlas con las condiciones laborales existentes.[1-3]

El propósito de este trabajo es realizar un análisis de los resultados de la dosimetría individual de los trabajadores vigilados correspondiente al período 1991-1994, en base a las recomendaciones del Comité Científico de las Naciones Unidas para el Estudio de los Efectos de las Radiaciones Atómicas (UNSCEAR). Se presentan los resultados de este período por ser el que sigue al último período reportado por UNSCEAR. [1]

MATERIAL Y MÉTODO

El sistema dosimétrico del DHR-IMT está basado en la dosimetría fílmica personal.[4] El criterio que se sigue para el registro de las dosis es:

- Si la dosis calculada es menor del nivel mínimo detectable (NMD), la dosis registrada es cero.
- Si la dosis calculada se encuentra dentro del 95 % del intervalo de confianza del velo de la película, la dosis registrada es el NMD, si la dosis calculada es mayor, se registra el valor obtenido.

- Para dosímetros perdidos la dosis registrada es cero.

De acuerdo con el nivel de dosis registrado, por cada trabajador, la UNSCEAR[1] clasifica a los trabajadores expuestos en 2 grupos:

- Trabajadores vigilados (TV): aquéllos que se reportan como ocupacionalmente expuestos a las radiaciones y se encuentran controlados dosimétricamente.
- Trabajadores expuestos a niveles medibles (TENM): aquellos trabajadores vigilados cuyas dosis son superiores al NMD y que por tanto indican la exposición real recibida.

Para el análisis de la exposición ocupacional la UNSCEAR[1] evalúa un conjunto de indicadores que caracterizan la distribución de dosis. Estos se sustentan sobre la base de la magnitud dosimétrica dosis efectiva,[2] por lo que el dosímetro personal debe estar calibrado en las magnitudes CIUMR[5,6] (Comisión Internacional de Unidades de Medidas de la Radiación), recomendadas para la vigilancia individual, que se relacionan con la dosis efectiva.

Los indicadores UNSCEAR referidos son:

- Dosis efectiva colectiva anual (S)
- Dosis efectiva media anual (Em)
- Coeficiente de distribución numérica NR_{15}: Este cociente nos permite conocer el porcentaje de los TV cuyas dosis efectivas anuales superan los 3/10 del límite permisible de dosis anual (LPD).
- Cociente de distribución de dosis efectiva colectiva anual (SR_{15}): Esta relación expresa la fracción de S correspondiente a los TV que obtuvieron dosis superiores a los 3/10 del LPD.

Para el procesamiento de la información se desarrolló una rutina de cálculo en computadora que permitió completar el programa existente en el departamento para el cálculo y registro de las dosis recibidas por cada TV.[4] Esta rutina, posibilita realizar de forma automatizada la caracterización de la distribución de dosis, utilizando los resultados dosimétricos de cada TV registrados en las bases de datos de los usuarios.

Según estos datos, se calcularon los indicadores UNSCEAR mencionados, para cada provincia y año del período evaluado, así como los indicadores globales para el país por año y los resultados para el cuatrienio seleccionado (1991-1994).

DISCUSIÓN DE LOS RESULTADOS

La tabla 1 presenta los resultados de la distribución de dosis de los TV del país para cada año y el cuatrienio analizado. Como se puede observar, la relación TENM/TV disminuye bruscamente de 1991 a 1992, resultando en alrededor del 5% para el cuatrienio. Además, también resultó una disminución de 1991 a 1992, de los indicadores de dosis relacionados con los TV (S y Em_{TV}). No obstante, la dosis efectiva media por año para los TENM (Em_{TENM}) se mantiene aproximadamente constante entre 1991-1993. Sin embargo, de 1993 a 1994, todos los indicadores sin excepción, vuelven a descender.

El cociente NR_{15} es pequeño y significó para el período sólo 14 TV con dosis superiores a los 3/10 del LPD. No obstante, si se observa el indicador SR_{15} para estos casos, se aprecia que llamativamente estos TV, poseen el 22 % de la dosis colectiva del período. De aquí la importancia de controlar las dosis de estos trabajadores, que aunque no superan el LPD, si aportan una contribución significativa a la dosis colectiva del cuatrienio.

Una idea más clara acerca de la importancia de este hecho se obtiene, si se asigna a estos TV, el promedio de la dosis efectiva que recibieron en el período los TENM. Si se realiza esta operación, resulta una reducción en la dosis colectiva acumulada por los TV en el período (1,4654 Sv) del 20,9 %, lo cual significa 305,7 mSv menos. La disminución que se alcanza justifica la toma de acciones para su reducción.

Tabla 1. Resultados de los indicadores UNSCEAR para los TV del país por año y para el período analizado.

Año	TV	TENM	TENM/ TV (%)	S (SvH)	Em_{TV} (mSv)	Em_{TENM} (mSv)	NR_{15}	SR_{15}
1991	4480	447	9,98	0,7484	0,17	1,66	0,0016	0,2041
1992	4426	152	3,43	0,2694	0,06	1,76	0,0009	0,3121
1993	4088	176	4,31	0,3115	0,08	1,76	0,0007	0,2936
1994	3975	129	3,25	0,1361	0,03	1,05	0,0000	0,0000
91-94	4242	226	5,33	0,3664	0,09	1,61	0,0008	0,2240

De igual manera a como se calculó el índice NR_{15} puede procederse para la obtención de un NR_{20} que nos permita conocer el porcentaje de los TV que superan el valor promedio por año (20 mSv) para garantizar el LPD recomendado por la ICRP[2] y las Normas Básicas Internacionales de Seguridad (NBIS)[7], y así mismo, calcular el coeficiente NR_6, que representa la proporción de TV que sobrepasan los 3/10 del nuevo LPD, caso último que es equivalente al cociente NR_{15} para el límite anterior, que pudiera continuar significando un indicador de interés, independientemente de que esta clasificación desaparece en las nuevas recomendaciones internacionales.

Al realizar ambas operaciones, resulta un índice NR_{20} para el cuatrienio superior a cero (0,0005), valor que corresponde en promedio por año a 2 TV que superan el nivel de 20 mSv, pero con resultados inferiores a 50 mSv. A pesar de que este valor es el promedio que debe cumplirse para garantizar el límite exigido de 100 mSv en 5 años, nivel que sí no debe superarse, procede tomar medidas inmediatas sobre estos trabajadores, de manera que se establezcan las causas de estos valores excedidos.

Notable además, es el valor que se obtiene para NR_6, donde resulta que la introducción del nuevo LPD aumenta en 3.25 veces el número de TV promedio que en el período superan los 3/10 del LPD, incrementándose la contribución de éstos a la dosis colectiva del cuatrienio hasta el 59.4 %, resultado que ya pesa significativamente en el acumulado total.

Por tanto, la introducción del nuevo LPD debe traer aparejado la toma de medidas que refuercen la vigilancia de la exposición ocupacional en el puesto de trabajo, de manera que se pueda controlar mejor las dosis de los TV que llevan el peso de la dosis colectiva (TV con dosis mayores que 3/10 del LPD).

Finalmente, debe quedar claro que la efectividad de cualquier sistema dosimétrico no sólo radica en procedimientos estandarizados y en un personal capacitado, sino también, en aspectos de vital importancia como son, la organización del sistema dosimétrico desde la base, el uso correcto del dosímetro y una concientización de todos los TV acerca de la importancia de su uso y cuidado. De aquí que, las cifras que se presenten como resultados de la distribución de dosis, puedan ser representativas de las condiciones reales de exposición a la que estos trabajadores se encontraban sujetos y por tanto, indicadores válidos para la evaluación del riesgo a la radiación ionizante.

CONCLUSIONES

El análisis de los resultados de la vigilancia radiológica individual de los TV en radiodiagnóstico del país, nos permitió conocer la tendencia de la distribución de dosis de estos trabajadores en el período de 1991-1994, en concordancia con los indicadores UNSCEAR, resultados que pueden ser usados por dicho comité en su próxima evaluación.

Se observó una disminución en el número de TENM a partir de 1991, estableciéndose una gran desproporción de éstos con respecto al número de TV.

Los TENM con dosis mayores que 3/10 del LPD poseen el peso de la dosis colectiva recibida por los TV en el período, contribuyendo con el 22 %.

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VEINTE AÑOS DE EXPERIENCIA EN EL CONTROL DE BAJAS DOSIS DE RADIACIÓN

Ing. Carlos Eduardo CASPANI e Ing. Roberto LESCANO
RADIOFÍSICA SANITARIA. O. Gelabert 3586. (3000) SANTA FE- ARGENTINA
FACULTAD DE INGENIERÍA QUÍMICA, U.N.L .Sgo. del Estero 2829. (3000) SANTA FE-ARGENTINA
FAULTAD DE CIENCIAS BIOLÓGICAS Y BIOQUÍMICAS, UNL, Paraje El Pozo, (3000) SANTA FE- ARGENTINA.

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RESUMEN

Se introduce el tema destacando la importancia que tiene como contribución a la Dosis Colectiva, las dosis recibidas por los pacientes, operadores y público en general durante la exploración clínica con Rayos-X considerándola como una típica práctica de baja dosis de radiación. Se indican y justifican las acciones que se realizan para conseguir los objetivos y se explicitan los resultados operativos explicando el porque del indicador sanitario que se toma. Se concluye remarcando los conceptos que se deben destacar en el control de las dosis de radiaciones de Rayos-X utilizados en diagnóstico clínico e indicando donde poner énfasis para mejorar sustancialmente los resultados.

INTRODUCCION

Las dosis individuales recibidas por el paciente son dependientes del tipo de estudio, el tipo de equipo utilizado y de la experiencia del operador (tiene también su importancia la contextura del paciente), pero se tiene una idea aproximada de los niveles de radiación promedio en piel, y en gonadas de cada tipo de estudio.

Si bien en algunos casos existen diferencias de dosis en dos órdenes de magnitud es cierto que tambien se puede tener una idea de la cantidad de radiografías recibidas anualmente por la población y como es el valor de la pendiente de crecimiento .

Comparando esto con los niveles recibidos por otro tipo de usos (1), se ve claramente la incidencia de las prestaciones médicas en el total de dosis efectiva colectiva anual recibida por la población, no porque individualmente la dosis recibida sea grande si no porque su uso es masivo y reiterado.

Por lo que incidiendo en el uso excesivo e irresponsable de la prescripción de radiografías asi como con el QC de las instalaciones para evitar las repeticiones y disminuir la dosis promedio en las distintas prácticas se logra disminuir considerablemente la dosis efectiva colectiva anual . Las características de esta práctica son la casi absoluta falta de incidentes o accidentes pero que su altísima frecuencia de utilización la hacen comparable al peligro asumido en otras prácticas que involucran mucho menos individuos directamente pero en la que un accidente la convierten en una catástrofe .

Por ello no es exagerado afirmar que la humanidad se esta irradiando naturalmente (del espacio exterior y la tierra) pero que ha aumentado artificialmente y drásticamente la dosis colectiva efectiva por el uso de las radiaciones ionizantes de bajas dósis.

DESARROLLO:

Para encarar la tarea de radioprotección se desarrollan los siguientes programas :

a) Evaluación y Vigilancia: que tiene como objetivo general lograr que todas las fuentes de radiaciones ionizantes sean utilizadas en las mejores condiciones de radioprotección y cumplan con la filosofía de que la dosis recibida, individual y colectiva, sea tan baja como sea razonablemente posible (ALARA) (2).

Para ello se efectúa la evaluación en el lugar, observando la distribución del equipamiento dentro de la sala y su relación con el paciente, operador y público aledaño (sala de espera, secretaria, vecinos etc.), tipos más frecuentes y modalidades de su uso, medición de la dosis de fuga estando cerrada la salida del haz primario, medición de las dosis ambientales en condiciones de uso (con fantomas) en las áreas de trabajo del Personal Ocupacionalmente Expuesto (POE) y en los lugares aledaños a la instalación, dejando explícito en un acta formal las condiciones de radioprotección e indicando cuando corresponda las modificaciones a realizar para mejorarlas.

b) Educación Radiosanitaria: cuyo objetivo primordial es garantizar en cada servicio personal idóneo en radioprotección y dar amplia difusión de la temática incluso a nivel popular para fomentar la exigencia por parte de la comunidad del cumplimiento de las Normas de Radioprotección. Para ello se dictan Cursos de Radiofísica Sanitaria y se participa en Congresos, Mesas Redondas y Seminarios de la especialidad y afines, asi como también se publica en Revistas de la especialidad y relacionadas.

c) Dosimetría Personal: el objetivo es conocer las condiciones de trabajo de POE desde el punto de vista de la protección radiologica.

Al conocer la dosis personal de cada operario y sabiendo su actividad frente al paciente asi como los tipos mas frecuentes de radiografías, se puede estimar una dosis personal en buenas condiciones de radioprotección y compararla con la dosis medida.

d) Cálculo de blindaje y asesoramiento de instalación: tiene como objetivo asegurar que cada instalación cumpla con las mejores condiciones de protección estructural y con la distribución adecuada de los equipos y componentes.

Para ello se efectúa el cálculo de todas las instalaciones o se controla la memoria de cálculo presentada, también se asesora sobre los detalles de construcción de la protección estructural y sobre la disposición de los distintos componentes de la sala (puerta, ventana, comando, mesa, potter mural, etc.), sobre los distintos protectores individuales, incluso sobre la técnica más adecuada que cumpla con el requerimiento médico y disminuya la dosis en el paciente y en el operador.

RESULTADO:

El número total de equipos en toda la Provincia, según sus características es el de la tabla 1, también se muestran en esta tabla los datos sobre el Personal Ocupacionalmente expuesto, su capacitación, evaluación y control.

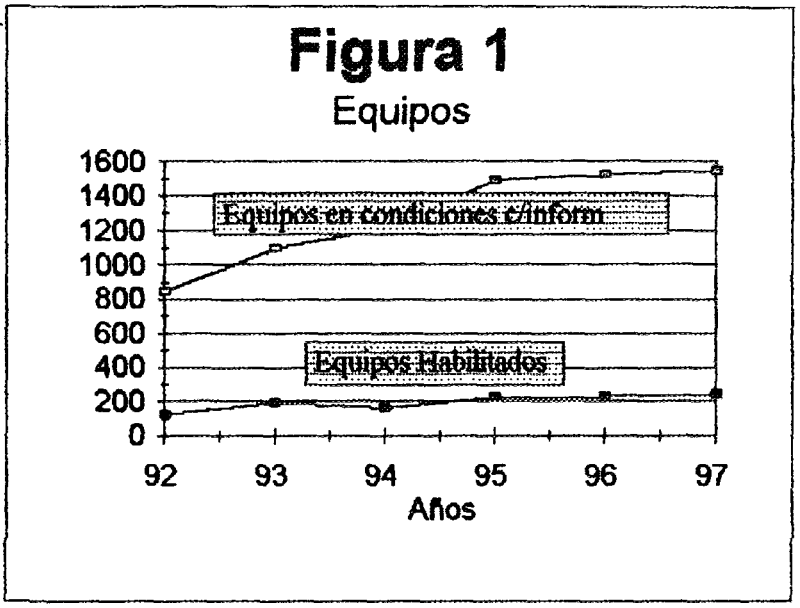
Tabla 1. Equipos y Personal Ocupacionalmente Expuesto

Radiodiagnóstico médico	957	Total de POE	3000
Radioscopía	239	Total de Cursos dictados	30
Radiografía odontológica	1323	Total de Personal capacitado	1500
Tomografía Computada	31	Personal con dosimetría	800
Investigación e Industrial	13	Inspecciones anuales	700
Radioterapia	28	Medidas promedio por inspección	6,5

El Total de Equipos por año que se encuentran en la Figura 1 son los que están habilitados y en condiciones de uso con tramite administrativo pendiente. Los restantes para completar el total de equipos instalados en la Provincia son instalaciones que tienen informe con indicaciones sobre detalles de radioprotección que debe cumplimentar.

El primer indicador utilizado era la dosis promedio anual en los lugares de trabajo del personal ocupacionalmente expuesto; pero ello no tiene en cuenta su forma de trabajo, es por eso que en la actualidad se toma la dosis promedio anual del POE.

Figura 1



Las Dosis promedio anual sacada de los datos de Dosimetria Personal Fildosimétricas se grafican en la Figura 2.

Las medidas de las dosis ambientales tomadas dentro del comando a la altura de las gonadas como promedio de mas de 900 medidas tomadas en cada año, se muestran en la Figura 3

Con los datos de la Figura 3 y considerando un promedio de irradiación efectiva de 18 segundos diarios por aparato, calculo que surge de tomar el total de radiografias anuales y dividirlas por el número total de equipos, se puede calcular una dosis personal esperada que si se compara con los datos de la Figura 2, se ve que estos últimos son casi un orden de magnitud mayor que los primeros.

Figura 2

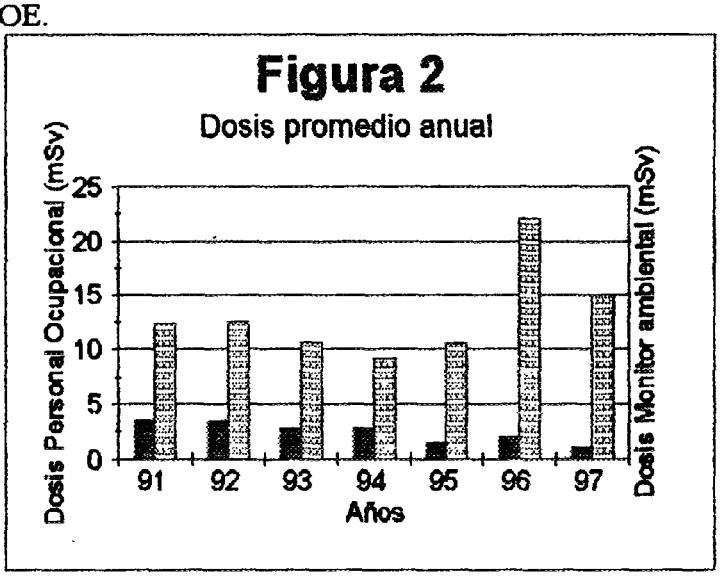
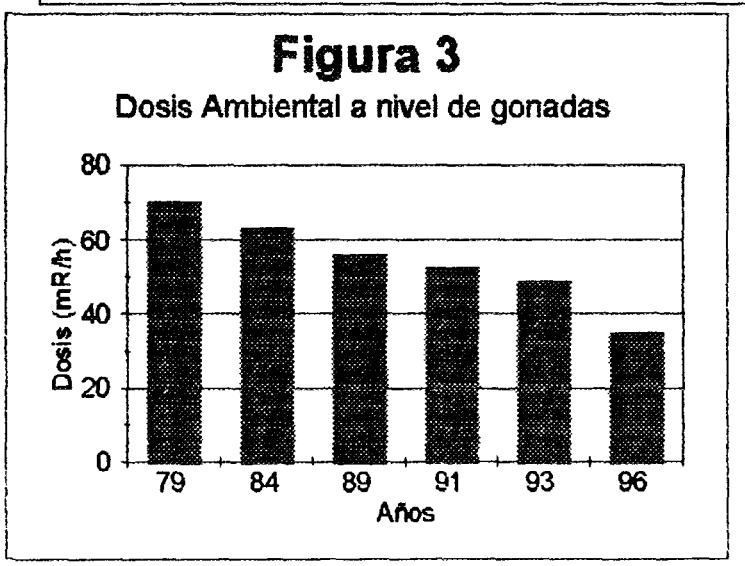


Figura 3



CONCLUSIONES:

Aplicando la filosofía del ALARA, el accionar del ente regulador debe enmarcarse dentro de la persuación adoptando el convencimiento como costumbre de trabajo o de lo contrario llegar a la sanción pecuniaria sin necesidad de recurrir a la aplicación de clausura o suspensiones .

También en concordancia con la filosofía del ALARA se pone especial énfasis en la prevención más allá que en la corrección o recuperación, para ello es imprescindible contar con normas claras que hagan posible y eficiente su aplicación, asi como asegurar que sea posible el control de su cumplimiento.

Haciendo un estudio de sensibilidad paramétrica surge claramente que realizando un estricto control en la fabricación o importación de equipos y la de elementos de protección se logran resultados espectaculares.

De nuestros resultados se ve la necesidad de propender a la presencia más continua del ente regulador, así como a desarrollar mayor cantidad de proveedores de insumos de Radioprotección, cuya falta o escasés provocan en muchos casos el no cumplimiento de las normas en forma y tiempo, esto podría ser la causa de la discrepancia entre las Figuras 2 y 3, que muestra que si bien las condiciones de la instalación son aceptables la práctica es tal que lleva a irradiarse mas allá de lo estrictamente necesario.

También de los resultados se desprende la necesidad de encarar una amplia difusión esclarecedora a nivel popular para que la población exija de sus prestadores el cumplimiento de las normas de seguridad radiológicas.

Escencialmente es imprescindible un mecanismo de comunicación de los Organismos Internacionales y Nacionales con cada uno de los responsables del control, e incluso si fuera posible con los responsables del uso de equipos generadores de radiaciones ionizantes, para mantenerlos permanentemente actualizados e informados sobre los cambios o novedades que se produzcan.

AGRADECIMIENTO:

Al Ministerio de Salud de la Provincia de Santa Fe por el soporte económico para desarrollar esta tarea, al Tec. Oscar ROITBARG por el aporte de las medidas ambientales y al Tec. Mario BRIZUELA por el tratamiento estadisticos de los datos de Dosimetría Personal.

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CONTAMINACION CON IODO-131 EN TERAPIA METABOLICA

R. García*, J. Luis*, A. Gómez*, V. Gonzalez*, J.R. Rodriguez**, M. Herrador*.
* *Servicio de Radiofisica. Hospital Universitario Virgen del Rocío. Sevilla.*
**Servicio de Medicina Nuclear. Hospital Universitario Virgen del Rocio. Sevilla.*

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RESUMEN

High-dose radioactive iodine therapy using ^{131}I is the treatment of choice for patients with thyroid cancer following thyroidectomy. Because of the large amount of activity which is excreted during hospitalization, contamination hazard from ^{131}I excretion via perspiration, saliva, breath and urine may arise. In twelve patients treated with doses of ^{131}I ranging from 1.85- 7.4GBq activity levels were measured in room surfaces, the toilet, patients saliva and skin. Removable activity from skin reached a maximum at 24h post-theraphy. Removable activity from room surfaces exceed the level of contamination which requires clean-up in a public area during patient's hospitalization. The relatively high activities present in the saliva and skin of these patients emphasizes the need for all individuals coming in contact with these patients to be made aware of the contamination hazard present.

INTRODUCCION

El tratamiento de pacientes con cancer de tiroides o hipertioridismo implica el uso de dosis de ^{131}I lo suficientemente elevadas como para producir un considerable incremento del riesgo de contaminación radiactiva por parte de los operadores y familiares.

Algunos estudios han cuantificado el grado de exposición interna y externa de los familiares de estos pacientes (1-4) pero existen pocos trabajos que estudien la contaminación potencial asociada a dosis superiores a 1.11GBq durante la hospitalización (5,6).

Esta memoria describe el procedimiento seguido para determinar la contaminación procedente de pacientes con cancer de tiroides tratados con dosis terapeúticas de ^{131}I superiores a 1.11GBq así como los resultados obtenidos.

MATERIAL Y METODOS

Doce pacientes con cancer de tiroides con dosis de tratamiento que oscilaron entre 1.85- 7.4 GBq participaron voluntariamente en este estudio. Nueve eran mujeres y tres hombres. Los pacientes estuvieron hospitalizados durante 72horas hasta que la tasa de exposición fue inferior a 6mR/h a 50cm.

Se tomaron frotis de piel y de los distintos objetos y superficies de la habitación mediante torundas de algodón empapadas en alcohol a las 24, 48 y 72h. En piel las muestras correspondieron a frente, cuello, torax, y manos. Tambien se tomaron frotis de la superficie del receptor del telefono, picaporte, mando a distancia del televisor, suelo del cuarto de baño y del inodoro. Además se obtuvieron muestras de saliva , para ello el peso de cada torunda se obtuvo antes y despues de la toma de muestras para deteminar la actividad por gramo de saliva.

Todas las muestras se midieron en contador de pozo previa verificación de su eficiencia y reproductibilidad.

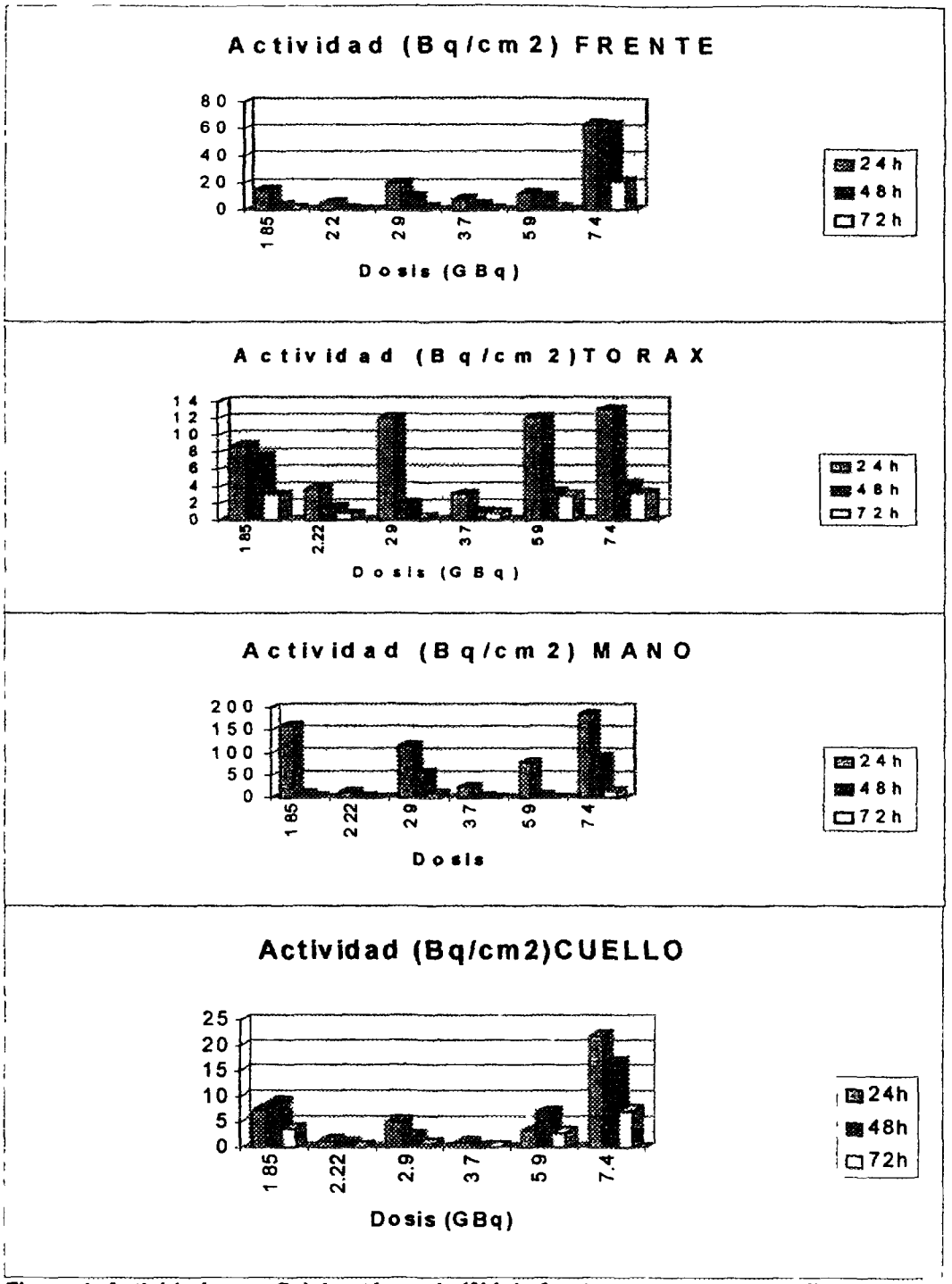

Figura 1. Actividad superficial cutánea de ^{131}I de frente, torax, mano y cuello.

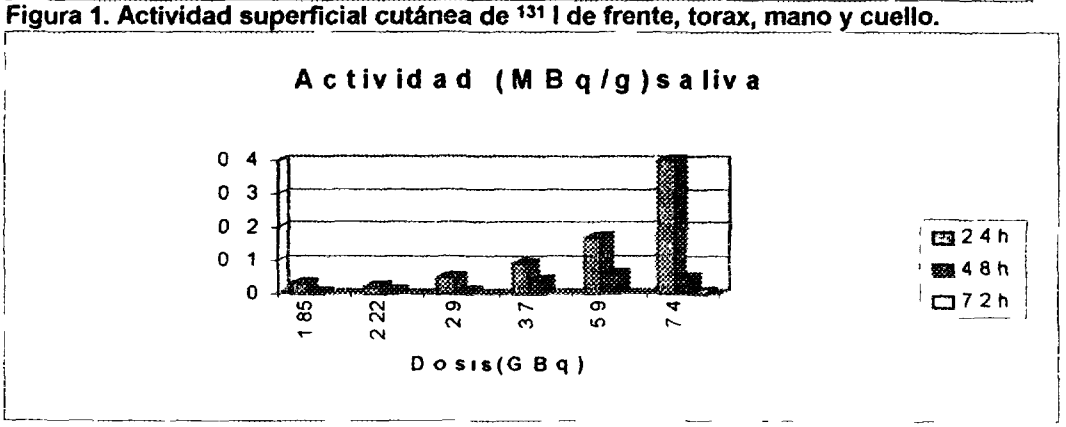

Figura 2. Actividad especifica en saliva

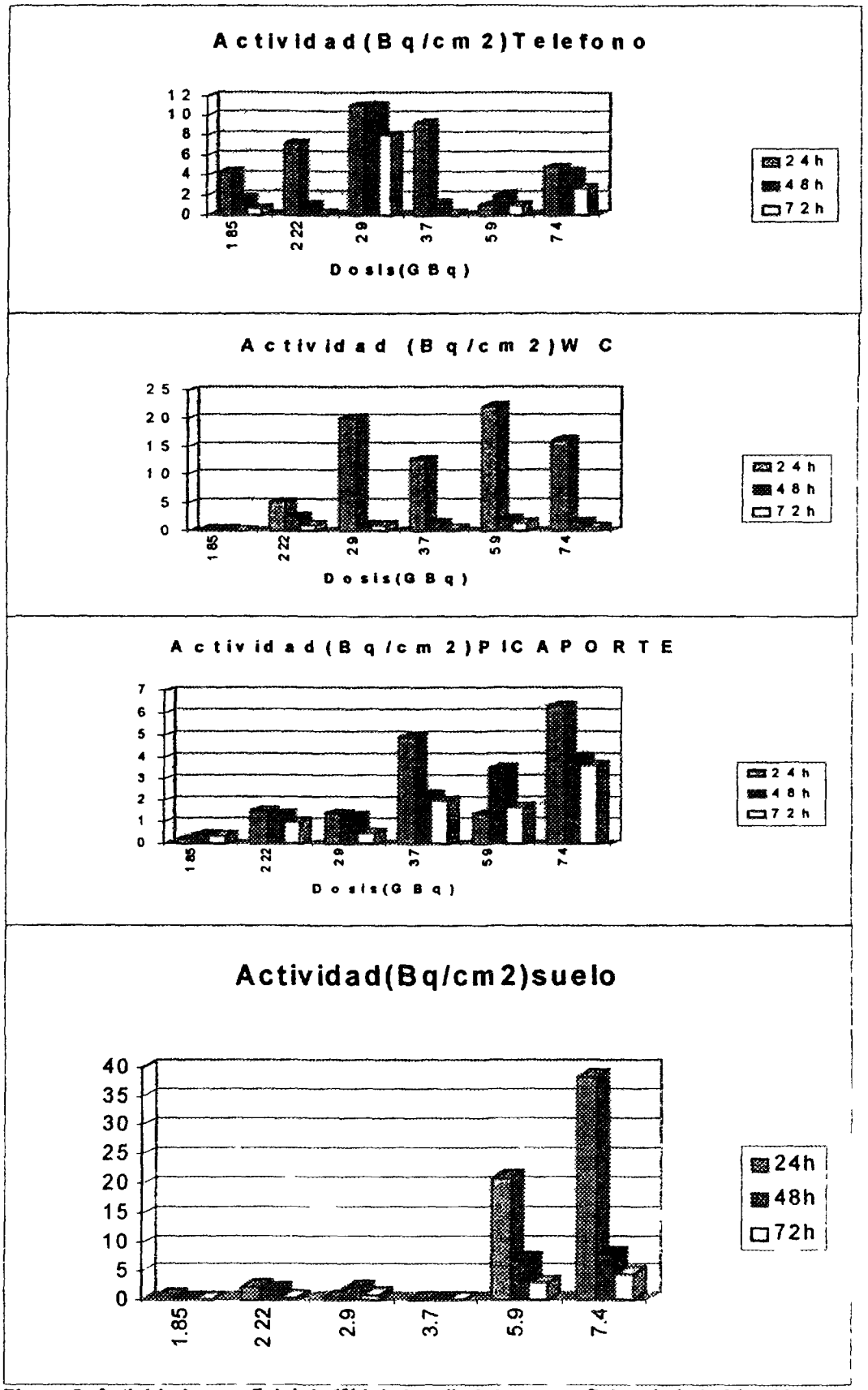

Figura 3. Actividad superficial de ^{131}I de las distintas superficies de la habitación.

RESULTADOS

Las actividades medias obtenidas sobre piel aparecen en la Figura 1. En las gráficas aparecen las dosis terapeúticas administradas a los pacientes (el número de pacientes en cada intervalo de dosis fue de 2) respecto a la actividad en Bq/cm^2. Los valores de actividad superficial obtenidos oscilaron entre 0.1 y 185 Bq/cm^2. El pico máximo se obtuvo en general a las 24h de la administración del tratamiento. Las unicas excepciones se presentaron en los frotis de cuello en 4 pacientes donde el pico se presentó a las 48h. No encontramos una correlación entre la dosis y las actividades de los frotis aunque los pacientes con dosis de 7.4GBq presentaron los niveles de actividad superficial mas altos.

Las actividades medias obtenidas sobre los distintos objetos y superficies de la habitación aparecen en la Figura 3. Las actividades obtenidas oscilaron entre 0.04 y 38.2 Bq/cm^2. Los niveles más altos en general se obtuvieron a las 24h- 48h, no existiendo una correlación clara entre la dosis y los niveles de contaminación aunque los pacientes con 7,4GBq en general presentaron los niveles más altos.

La actividad en la saliva muestra una correlación positiva entre la dosis de tratamiento y el tiempo. Los niveles de actividad oscilaron entre 0.01 y 0.4 MBq/g.

DISCUSION

Aunque el desarrollo del cancer es el principal afecto tardío provocado por la exposición a la radiación, en principio no existe actualmente evidencia que sugiera que la contaminación procedente de pacientes tratados con ^{131}I por hipertiroidismo o cancer de tiroides representen un problema de salud pública. Estos pacientes excretan radioiodo fundamentalente por orina y en menor proporcion saliva , sudor y aliento (6).

La actividad desprendible de piel alcanza su pico máximo a las 24h aunque no encontramos una correlacion con la dosis administrada. Entre las areas corporales la frente y las manos presentan los niveles mas altos de contaminación con niveles inferiores a 89 Bq/cm^2 a las 48h e inferiores 21 Bq/cm^2 a las 72h.

De acuerdo con las recomendaciones de la Comisión Internacional de Protección Radiológica (publicación nº57, 1989) el límite derivado para la contaminación superficial para las superficies y equipamiento en áreas controladas es de 30 Bq/cm^2 y para áreas vigiladas y públicas y superficie corporal es de 3 Bq/cm^2. Se observa, que en el momento del alta (transcurridas 72h), el límite de contaminación para la superficie corporal se supera para dosis de 7,4GBq. Respecto a la actividad superficial de los distintos objetos y de la habitación solo se superan los límites al alta en el mando del televisor en el suelo del baño y en algun caso en el telefono. Todo ello muestra la importancia de una buena higiene corporal durante el ingreso y despues del alta con el objeto de disminuir el grado de actividad superficial corporal .

La actividad en saliva muestra una correlación con la dosis de tratamiento y el tiempo siendo practicamente indetectable a las 72h. Los niveles encontrados por nosotros oscilaron entre 4 y 0.01 MBq/g siendo máximo a las 24horas. La alta actividad específica durante el eingreso refuerza la necesidad de instruir al personal que atiende a estos pacientes en técnicas para evitar contaminarse ante el contacto con saliva o vómito.

CONCLUSIONES

Encontramos niveles significativos de actividad en saliva y piel durante el tiempo del ingreso y a partir de las 72h en los pacientes que recibieron dosis superiores a 7,4GBq. Hasta las 72h no se alcanzan los niveles recomendados para actividad superficial en areas públicas. Es necesario por tanto dado los niveles de actividad superficial y en saliva instruir a los pacientes al alta para minimizar los riesgos de contaminacion a miembros del público.

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IAEA-CN-67/200

XA9745710

INSTRUMENTALIZACIÓN DE LA PROTECCIÓN RADIOLÓGICA EN EL SERVICIO ANDALUZ DE SALUD

Autores: M. Herrador Córdoba; J. García Rotllán.
Servicio de Radiofísica. Hospital Universitario Virgen del Rocío. Sevilla.
Servicios Centrales del Servicio Andaluz de Salud. Sevilla.

RESUMEN.

En Andalucía las aportaciones al riesgo radiológico de la industria nuclear y de la radiación natural son pequeñas y lo mismo ocurre con las aplicaciones médicas de carácter privado y la investigación, por lo que adquiere un elevado interés en el seno de la comunidad autónoma el modelo de actuación en protección operacional seguido por el Servicio Andaluz de Salud para las instituciones sanitarias públicas. En esta memoria se fundamenta y describe dicho modelo y los rendimientos obtenidos con el mismo hasta la fecha.

INTRODUCCIÓN.

Desde el punto de vista de riesgo radiológico la Comunidad Autónoma de Andalucía, puede ser caracterizada por las siguientes particularidades:

- Una tasa de exposición debida a la radiación natural de sólo $7{,}1 \cdot 10^{-6}$ R/h de promedio. (1)
- No existen en su territorio centrales nucleares, aunque contiene el único centro español de almacenamiento de residuos de baja y media actividad y una fábrica de procesamiento de material combustible clausurada.
- Más del 80% de las aplicaciones médicas de las radiaciones ionizantes, incluida la investigación sanitaria, se realizan en el ámbito público.
- El uso de fuentes radiactivas en investigación no sanitaria y docencia se concentra en centros públicos y su aportación al riesgo resulta muy baja.
- Las aportaciones de otras aplicaciones industriales son igualmente bajas.

Bajo estas premisas y teniendo en cuenta el protagonismo que en determinados aspectos de protección radiológica tiene la administración sanitaria, así como las implicaciones derivadas de su aplicación en centros sanitarios, es de entender el interés que tiene conocer cual ha sido la actuación de la administración sanitaria andaluza en este campo.

FASES DEL PROCESO DE NORMALIZACIÓN.

La Consejería de Salud y el Servicio Andaluz de Salud (SAS) han venido implementando desde el año 1988 el entramado de infraestructuras, personal y medios necesario para cubrir de forma razonable todas las instalaciones sanitarias públicas en materia de protección radiológica tanto a nivel normativo como operacional.

Asímismo, y a medida que el desarrollo obtenido lo ha permitido, también se han atendido demandas en asesoramiento de otras instituciones como el Parlamento de Andalucía, el Defensor del Pueblo Andaluz y el Ministerio del Interior.

El proceso de normalización de la protección radiológica en los centros sanitarios públicos de Andalucía se ha desarrollado a lo largo de estos años en las siguientes fases:

Asesoramiento. El Servicio Andaluz de Salud comisionó un equipo de expertos en protección radiológica para recabar la información referente al estado de todas sus instalaciones y determinar las actuaciones más urgentes.

Formación e información. Fué diseñado y dotado presupuestariamente un plan de formación en protección radiológica apoyado en el esfuerzo docente de los profesionales hospitalarios de este campo y al que tienen acceso todos los trabajadores de las instalaciones del SAS. Simultáneamente se incrementa la información interna en esta materia.

Regulación. En consonancia y como desarrollo local de la reglamentación del Estado Español y de la Unión Européa, el Servicio Andaluz de Salud establece los instrumentos jurídicos que facilitan la protección radiológica operacional en sus instalaciones.

Seguimiento. Se pone en marcha la Comisión Asesora en Protección Radiológica, que junto a sus propias estructuras administrativas, permite al Servicio Andaluz de Salud un seguimiento de la progresiva implantación y desarrollo de las Unidades de Protección Radiológica, así como de todos aquellos aspectos relacionados con la materia en sus instalaciones.

RENDIMIENTOS.

Los rendimientos obtenidos han sido considerablemente buenos, aunque aún resulta necesario el esfuerzo de la Administración, de las Instituciones Sanitarias y de los profesionales para conseguir su optimización.

Se confeccionó el censo de instalaciones y personal y se estudiaron las necesidades formativas e informativas de éste, tanto desde un punto de vista formal como operativo. Ello dió paso a la elaboración de un plan de formación e información, cuya dotación presupuestaria y puesta en marcha se fundamentan en las conclusiones de tales trabajos.

El desarrollo del plan de formación ha significado la realización de cursos de capacitación para supervisores, directores y operadores de instalaciones, cursos de garantía de calidad y actividades de divulgación e información, para lo que se ha contado con la colaboración del Consejo de Seguridad Nuclear (CSN), del Centro de Investigaciones Energéticas Medioambientales y Tecnológicas (CIEMAT) y con el esfuerzo de nuestros profesionales hospitalarios. Su número se eleva ya a los 116, todos ellos realizados en el seno de las instalaciones sanitarias públicas andaluzas con medios propios, y su calidad ha sido contrastada por el CSN y el CIEMAT. Como consecuencia se han cubierto, además, los requisitos legales de acreditación y/o licenciamiento del personal que manipula equipos o fuentes, o dirige el funcionamiento de las instalaciones.

La inclusión de artículos sobre protección radiológica en publicaciones internas del SAS (2) ha contribuido, a nivel informativo, a que diferentes profesionales sanitarios tomen conciencia de su necesidad y rentabilidad.

En el aspecto regulatorio el Servicio Andaluz de Salud ha publicado tres resoluciones: Resolución 7/96 de 21 de Febrero de Constitución de la Comisión Asesora en materia de Protección Radiológica, que establece las funciones, composición y funcionamiento de dicha comisión.

Resolución 15/96 de 3 de Mayo de Creación de Unidades de Radiofísica Hospitalaria, en la que se crean unidades diferenciadas de radiofísica hospitalaria en hospitales con instalaciones radiactivas de segunda categoría, según la clasificación española, y a partir de los profesionales que desarrollan en los mismos las funciones que la propia resolución establece.

Resolución 16/96 de 3 de Mayo de Ordenación Territorial de la Protección Radiológica en el ámbito del Servicio Andaluz de Salud, por la que se divide el territorio andaluz en doce áreas de cobertura en materia de protección radiológica aplicada a las instalaciones sanitarias públicas y se determina la unidad de radiofísica de referencia para cada una de ellas.

Por otra parte, el Plan Andaluz de Salud incluye en sus objetivos 112, 113 y 114 el compromiso de la Administración Sanitaria en protección radiológica (3).

El seguimiento de las diferentes actuaciones que en esta materia efectúan los distinton niveles administrativos lo realiza la Comisión Asesora que mantiene reuniones periódicas. Asímismo determina las necesidades anuales en materia de formación e informa de todo ello a la Dirección General de Asistencia Sanitaria. También efectúa reuniones monográficas y a demanda que facilitan la toma de decisiones integramente consciente por parte de la Administración.

Como culminación existen ocho unidades de radiofísica hospitalaria de las cuales seis se encuentran ya jerarquizadas y siete están reconocidas por el CSN como servicios de protección radiológica. En el resto de los hospitales de referencia ya existen radiofísicos desarrollando las misiones correspondientes y se está comenzando el proceso de diferenciación, reconocimiento y jerarquización.

CONCLUSIONES.

La aplicación de la protección radiológica en las instituciones sanitarias públicas de Andalucía se ha efectuado mediante un modelo desarrollado en cuatro fases que a su vez han dado origen a los cuatro pilares básicos en los que se fundamenta la gestión en protección operacional: asesoramiento, formación e información, normalización y verificación.

Los objetivos planteados en cada una de las fases, han sido alcanzados razonablemente y han contribuido a una mayor conciencia en la búsqueda del uso seguro y adecuado de las radiaciones ionizantes.

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ANALISIS DE SALUD EN UN GRUPO EXPUESTO A DOSIS BAJAS DE RADIACIONES IONIZANTES

F. DIAZ LEDESMA
Servicio Médico de Tecnatom, SA

H. CRESPO
Hospital Gregorio Marañon de Madrid

Madrid, Spain

Abstract

In order to evaluate the effects of exposure to low radiation doses, the health status of professional staff exposed to ionizing radiation is investigated. Based on archived material of medical and radiation exposure records taken over a time span of 13 years, a variety of medical parameters are explored. Findings of surveys made are given.

1.INTRODUCCIÓN

Dado el interés desencadenado en el momento actual por la valoración de los efectos de una exposición a **dosis bajas de Radiaciones Ionizantes,** el Servicio Médico de Tecnatom S.A. propone un estudio sobre el estado de salud de su población profesionalmente expuesta a radiaciones ionizantes.

Puesto que Tecnatom S.A. cuenta con el historial médico archivado a lo largo de **13 años** y estos datos se encuentran informatizados creemos de interés realizar un estudio evolutivo sobre los datos médicos recogidos en el archivo.

Las dosis medias anuales en nuestra empresa no superan los **5 mSv.** como queda representado en el **gráfico 1,** entre los años 1983 y 1996.

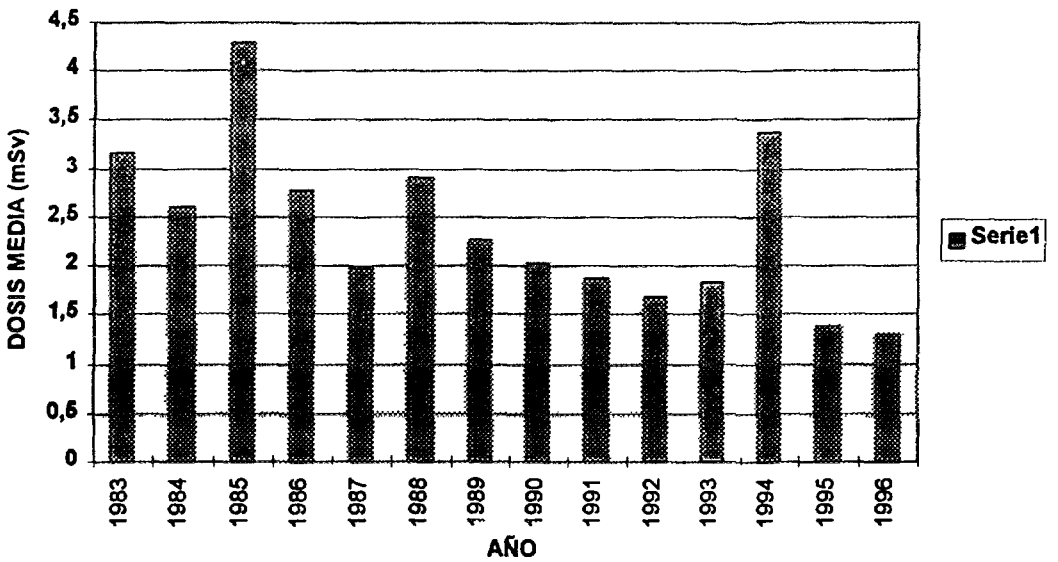


GRAFICO 1. DOSIS MEDIAS ANUALES DE TECNATOM.

En la distribución de las dosis de radiación ionizante acumulada en nuestros trabajadores el 74,25% se encuentra por debajo de 20 mSv, el 15,97 % se encuentra de 20 mSv a 60 mSv, el 8,24% de 60 a 120 mSv y, un 1,54 % corespondería a dosis de 120 a 160 mSv.

2.OBJETIVOS.

2.1. Valorar la evolución de la **hematología** en relación a la dosis recibida a lo largo de los **13 años,** considerando los siguientes parámetros:

2.1.a. Leucocitos.
2.1.b. Neutrófilos
2.1.c. Linfocitos.
2.1.d. Hematíes.
3.1.e. Plaquetas.

2.2. Estudio tiroideo realizado a nuestra población profesionalmente expuesta a radiaciones ionizantes.

2.3. Evaluación de algunos parámetros tumorales.

2.1.Estudio hematológico:

El tejido hematopoyético lo integran multitud de tipos celulares que se pueden agrupar en tres compartimentos, en función de su potencial proliferativo y de automantenimiento.

Compartimento de Células Madre Hematopoyéticas(CMH)
Compartimento de Células en maduración
Compartimento de Células Maduras

En nuestro estudio, hemos recogido los valores de leucocitos, linfocitos, neutrófilos, monocitos; hematíes y plaquetas en analíticas realizadas desde el año 1983 al año 1996, relacionandolo con la dosis acumulada.

2.2. Estudio Tiroideo:

Estudio de la función tiroidea

La función tiroidea consiste en la elaboración y posterior paso a la sangre de las **hormonas tiroideas,** tiroxina (T4) y triyodotironina (T3). Para la biosíntesis de éstas hormonas, es básica, la captación del yoduro de la sangre circulante.

La glándula tiroidea forma parte del sistema endocrino hipotálamo-adenohipofisario, y por tanto su principal regulación funcional está vinculada al hipotálamo-hipófisis, a través del conocido sistema de retroacción negativa.

La TRH es un tripéptido sintetizado en las células nerviosas hipotalámicas que tras su liberación alcanza la adenohipófisis liberando TSH. Esta ejerce acción en las células tiroideas liberando las hormonas tiroideas.

En nuestro estudio hemos considerado los sigientes parámetros:

- Determinación de **TSH** circulante en plasma para juzgar la situación funcional del eje hipotálamo-hipofisario.
- Determinación plasmática de **Tiroxina Libre.**

2.3. Evaluación de algunos parámetros tumorales: Marcadores tumorales:

El término **marcador tumoral** designa a aquellas sustancias detectables en líquidos orgánicos, especialmente en sangre periférica que pueden hacer sospechar la existencia o desarrollo de un tumor.

La utilidad clínica de estas sustancias, es función de su especificidad por una neoplasia determinada y de su sensibilidad. Como los productos de las neoplasias son semejantes a los de las células normales, es necesario establecer **un umbral** por encima del cual la probabilidad de que se trate de una elevación secundaria aumenta directamente con la cantidad de marcador.

Su elevación debe asociarse a otros métodos para apoyar un diagnóstico.

En algunos casos la cifra de marcador en el momento del diagnóstico puede tomar un valor pronóstico y de utilidad en el estadiaje.

De ellos los que utilizaremos en nuestro estudio serán:

3.a. Antígeno carcinoembrionario:

Su sensibilidad en estadios precoces es demasiado baja. Su valor se considera normal **hasta 5 ngr./ml.** Es útil sobre todo en el carcinoma colorectal y especialmente para la detección de recidivas de Carcinoma de colon.

3.b.Alfa Fetoproteina:

La cifra normal en suero es menor de 20 ngr./ml. Se detectó que estaba elevado en hepatocarcinomas (80%). Es útil en la detección de éstos tumores en grupos de riesgo (cirrosis hepática) y en el control de la respuesta al tratamiento.

3.c.Antígeno prostático específico(PSA):

Es normal hasta 2 -2.5 ngra./ml. Este marcador se eleva en el 60-90 % de pacientes con carcinoma de próstata.

3. MATERIAL Y MÉTODOS

3.a. LUGAR DEL ESTUDIO

Tecnatom S.A. Empresa cuyas actividades se han centrado en dos áreas principales: adiestramiento del personal de operación de Centrales Nucleares y las inspecciones preoperacionales y en servicio. En la actualidad cuenta con unos 500 trabajadores de los cuales 300 están considerados como profesionalmente expuestos a radiaciones ionizantes.

3.b. Población de estudio:

-Personal Profesionalmente expuesto a **Radiaciones Ionizantes.**

-Se trata de una población bastante estable.

-Con una media de edad de 39 años.

- Nivel socio-económico medio.

3.c Años sometidos a dosis bajas de radiaciones ionizantes: 13 años.

3.d. Fuente de información:

Datos recogidos del historial médico de los trabajadores archivados a lo largo de 13 años.

3.e.Tipo de estudio:

Recolección retrospectiva de la información analítica en el grupo expuesto a **radiaciones ionizantes**.

4.CONCLUSIONES

En nuestro estudio, como podemos ver en las gráficas, no existen importantes alteraciones en nuestra población.

1. ESTUDIO HEMATOLÓGICO:

Hemos recogido los valores de **leucocitos, linfocitos, segmentados, hematíes y plaquetas** desde el año 1983 hasta 1996 relacionando éstos valores con la dosis.

Dentro de los leucocitos, un pequeño número de casos presenta valores por encima de la normalidad, este grupo, corresponde a los trabajadores profesionalmente expuestos que presentan dosis más bajas, mientras que en el rango que presenta dosis más altas, las cifras de leucocitos están dentro de los límites de la normalidad. El estudio hematológico realizado a este pequeño número de empleados descarta patología hematológica.

El resto de los parámetros hematológicos estudiados, están dentro de los límites de la normalidad y no se observa ninguna alteración significativa a lo largo de los años estudiados.

Para una mejor visualización de la evolución de éstos parámetros hematológicos hemos calculado los valores medios anuales de cada dato hematológico relacionandolo con los valores medios anuales de dosis, donde se puede observar la despreciable variación que sufren los mismos.

2. ESTUDIO TIROIDEO:

En cuanto al **estudio tiroideo**, los valores de T4 libre y TSH están dentro de los límites de la normalidad como observamos en las gráficas.

3. ESTUDIO DE ALGUNOS PARÁMETROS TUMORALES:

Los valores de antígeno carcinoembrionario(CEA), Alfa fetoproteina y PSA se encuentran dentro de los límites de la normalidad.

FROM SCIENTIFIC EVIDENCE TO RADIATION PROTECTION

R.V. Osborne and N.E. Gentner
Health and Environmental Sciences Division,
Chalk River Laboratories, AECL, Ontario, K0J 1J0, Canada

ABSTRACT

The long-term effects on health from radiation at low dose rates depend on so many biological variables that simple generalizations are unlikely to be valid for any specific individual at any specific time. Increased incidence of cancers can be observed from moderate doses at high dose rates. At lower doses and lower dose rates evidence is less clear. Advances in molecular biology in the last decade are enabling striking progress to be made in understanding the cellular mechanisms that determine the responses to radiation and their underlying genetic control. Enough is known now to conclude that any response will depend on an individual's genetic makeup and may be varied in time for a given individual, depending, *inter alia* on the pattern of dose in time. Faced with this uncertainty, the pragmatic approach for protection remains that of basing the level of protection simply on the magnitude of the radiation dose, albeit not with the underlying idea that with every radiation event there is a fixed probability of causing cancer.

1. THE ISSUE

We have epidemiological evidence of health effects at moderate doses at high dose rates and from laboratory studies we have knowledge of many variables that affect the response to radiation events at the molecular, cellular, tissue and whole animal levels. The challenge is to make the best use of the knowledge in extrapolating from the epidemiological evidence in order to manage appropriately the radiation doses to workers and the public that can occur from exploiting technologies that involve radiation sources.

2. KEY OBSERVATIONS

What are the key observations that allow us to define the envelope for effects from low doses and low dose rates?

Increased numbers of cancers have clearly been observed in some populations at moderate doses and high dose rates.

> Most notable are the results from the A-bomb survivors in Hiroshima and Nagasaki [1]. UNSCEAR have provided detailed reviews of epidemiological evidence. It is noteworthy that a recent forum of experts in the field, gathered by the USA's Council of Scientific Society Presidents, came to a consensus that lowest dose at which deleterious effects from radiation had been significantly observed was about 100 mGy delivered acutely [2].

There is a variety of relationships between effects and combinations of dose and dose rate.

> For example, there is evidence that at lower dose rates the overall number of deleterious effects is smaller per unit dose.(e.g., reference [3].)

Some failures to observe significant risk in populations exposed to radiation doses reflect statistical limitations in the studies, and not necessarily the absence of risk.

> Conversely, obtaining a "best fit" estimate of the slope of a linear no-threshold model does not validate such a model to the exclusion of others. An examples of such studies is reference [4].

Given the general ideas on the multistep process involved in carcinogenesis and that radiation events can influence more than one step, there could be a variety of cellular targets and biological responses.

It could be, for example, that loss of heterozygosity resulting from extensive double strand damage is more important than a mutation at a single location. It is conceivable that timing along the multistep process could be changed, thereby affecting latency. The efficacy of DNA repair processes and inducibility of these processes by low doses of radiation are currently active research topics [5].

There is evidence that some people may be more susceptible than others to radiocarcinogenesis, at least at high doses, because of differences in genetic make up.

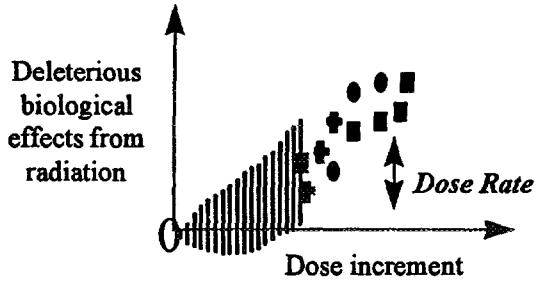
A considerable array of genes has been identified which is associated with increased risk of cancer. Cells of tissues in people who have one or more of these genes may already be some steps along the multistep path to cancer, reflected in such people having a higher risk (per unit radiation dose) from a radiation event affecting a later step, and no practical threshold that might otherwise arise because of the slow progress through initial steps. Conversely, some might argue that any stimulatory effect of low dose rates might be most beneficial in these cells. Accordingly, the extent and nature of genetically-predisposed differences in responses to low doses at low dose rates remains an open question but one of increasing interest [6].

The spatial and temporal characteristics of interactions of radiation with cellular constituents are quite different from those of chemicals.

One millisievert (mSv) from gamma radiation represents on average about one event or track per cell. At low dose rates of the order of a few mSv per year (or less) one has therefore to consider the impact of a few events per cell per year; i.e. only a small fraction of the body's cells are hit in any day. (The fraction is much smaller for higher LET radiations). This is quite different from the situation with chemicals where, even at what might be regarded as trace quantities of chemicals (say parts per 10^{12}), there are still many molecules per cell. Hence, if a cell does respond in any way to one event, for there to be any dose rate effect there has to be interaction between spatially- or temporally-distant events. Such interaction may result in a different response (for example, enhanced repair) to a later event compared with that to an earlier one - an adapted response. With the time and spatial separation of radiation events when there are only small increments on the background dose rate the possibility of such interactions seems remote; one would therefore expect a "linear" relationship between number of events (dose) and deleterious effects stemming directly from those. However, a radiation event may affect how the cell or its associated tissue handles non-radiation-related but potentially deleterious events that occur sufficiently soon and close enough. One could therefore have an increase in some deleterious effects, and a reduction in others because of a general increase in repair capability.

A general conclusion is that any net effect from radiation at low dose rates clearly depends on so many biological variables that simple generalizations one way or the other, even in a probabilistic sense, are unlikely to be valid for any specific individual at any specific time. Indeed, given that we do not have a random combination of continuous variables in a given population anyway, the concept of the population response being a simple stochastic one may not be valid either. Overall, there seems to be no *a priori* reason for assuming that there is a simple linear relationship of long term average biological response with dose. The pragmatic approach is to accept that the response to a small increment in radiation can only be described in terms of the envelope much as shown in Figure 1.

Figure 1. Schematic representation of the envelope within which we need to manage radiation doses. Actual symbols represent where deleterious effects have definitely been observed. We have to assume that we are protecting people whose dose increments - and therefore whose responses - are somewhere in the dashed area.



3. THE RESOLUTION

We do not know for any particular small increment in dose, what the actual ultimate influence on biological state will be; only its bounds. In any population the effects on individuals of small additions in the day-to-day radiation doses will be varied, both in time for a given individual and between individuals, depending *inter alia* on the individuals' genetic make ups and the spatial and temporal distributions of cellular doses. Eventually, a combination of sufficiently large doses and dose rate from natural background, medical and other man-made sources to people in a population could result in a biological response that is deleterious to some individuals.

How, then, do we achieve protection against the possible effects of exposure from man-made sources? If there is a "freebie" area (effectively a threshold, for possibly some proportion of the population), how do we apportion "credit" for doses that correspond to this area? How do we take account of doses received elsewhere?

First, we make the practical assumption that we do not have a detailed accounting of any individual's complete personal dose history, nor of their genetic make up, nor of their individual cellular responsiveness to radiation at any particular time.

Then, given the multitude of factors influencing radiation response, the only practical and equitable approach is to associate with increments of radiation dose from man-made sources (or any other) a probability of advancing an individual (whose position in the distribution we do not know) towards a deleterious biological response. The only reasonable assumption for a hypothetical individual somewhere in the distribution is that the bigger the dose, the proportionately bigger the likelihood of an advance towards an effect. (Note, this does not preclude that in some individuals from any particular additional radiation dose, there may be no actual effect, a much greater actual deleterious effect, or a beneficial actual effect, or even both some deleterious and some beneficial effects.). Such an approach protects the hypothetical average individual, accepting that we do not know the characteristics of each individual, only the estimated bounds of response from epidemiology.

Hence we might recommend a dose D that provides what is judged to be a reasonable factor below the dose/dose rate combination where effects can be observed in a given population. For doses below this, the level of protection accorded against any particular radiation dose will be commensurate with the value of the dose relative to D. Particular values of dose below D could be selected as particular decision levels, based on the relativity to natural background and the value of D, rather than from any attempt to assign explicit risk values and to manage on the basis of explicit risk values that are, in fact, insupportable.

However, this is the same approach in practice to that used if an assumption is made that the probability of a deleterious effect on health (cancer) increases in proportion to the radiation dose - one interpretation of the linear no-threshold model.

4. SUMMARY

A regulatory system that avoids the assignment of explicit risk values to low doses would still include a dose limit and the application of ALARA, fundamentally the same as present practice. The biological foundation, discussed above, reflects current radiobiological and molecular biological knowledge and is much more realistic than the present one which reflects an essentialist approach to biology in assigning a common, linear-in-dose response to individuals. This is an important difference. Implicit is the acknowledgment of the multiplicity of different individual responses that may be occurring at low dose rates, and the disconnection from the idea that every radiation event by itself has a fixed probability of causing cancer.

ACKNOWLEDGMENTS

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RISKS TO HEALTH FROM RADIATION AT LOW DOSE RATES

N. E. Gentner and R. V. Osborne
Health & Environmental Sciences Division
Chalk River Laboratories, AECL, Chalk River, Ontario K0J 1J0, Canada

ABSTRACT

Our focus is on whether, using a balance-of-evidence approach, it is possible to say that at a low enough dose, or at a sufficiently low dose rate, radiation risk reduces to zero in a population. We conclude that insufficient evidence exists at present to support such a conclusion. In part this reflects statistical limitations at low doses, and in part (although mechanisms unquestionably exist to protect us against much of the damage induced by ionizing radiation) the biological heterogeneity of human populations, which means these mechanisms do not act in all members of the population at all times. If it is going to be possible to demonstrate that low doses are less dangerous than we presently assume, the evidence, paradoxically, will likely come from studies of higher dose and dose rate scenarios than are encountered occupationally.

1. BACKGROUND

A linear relationship, without threshold, is applied for radiation protection purposes [1]. Many people believe this "LNT" model to be appropriate for relating the long-term possibility of health risks from ionizing radiation to dose. Evidence exists for such a relationship over a wide range of doses and dose-rates for many organisms for various endpoints, and over more limited ranges for humans. How likely is there to be a threshold in this relationship? We can ask, is there sufficient evidence to assert that risk effectively truncates to zero below some value of dose or dose rate?

This paper examines some of the epidemiological evidence that is often taken as bearing on this question and also looks at the implications on this question of the current understanding of genetic variability of radiosensitivity in populations.

2. EPIDEMIOLOGICAL STUDIES OF LOW LEVEL RADIATION ("LLR")

There is no study of persons exposed to low dose and/or low dose-rates ("LLR") which is able to prove that the overall radiation risks for all individuals are less than the nominal risk coefficient imply. Despite claims to the contrary, most low dose studies are not "proof of no effect" but rather "no proof of effect". It is misleading to suggest that a coherent body of data suggests otherwise.

The results from comparisons of cancer incidence in inhabitants of high compared to control 'low' natural radiation background areas are a case in point. This sort of comparison has been performed for groups in the UK, USA, China, Sweden, France and Japan. The conclusion is that "None, including the largest, that in China (for details about the study in China, see reference [2], Table 41), has produced statistically significant associations" [3]. While within studies slight differences in site-specific cancer mortality rates do exist between the high- and low- radiation-background areas, overall the differences are not significant statistically, and hence no results to date provide clear evidence for either the presence or absence of detriment due to LLR.

The second case in point relates to using SMR's for cancer in occupationally exposed persons to bolster a claim that they show less risk from cancer as a result of their occupation. Such a claim seems unsustainable. Results from studying groups of nuclear industry workers tend to be somewhat equivocal. A standardized mortality ratio of <1 for a worker population ([3], Table 33),

by itself, proves nothing other than that the risk is not huge. In the table quoted, for twelve cohorts of nuclear energy workers the arithmetic and geometric means of the SMR's for deaths due to "all causes" are 0.84 and 0.83; for "all malignant neoplasms" the values are 0.89 and 0.88. In studies where risk has been assessed as a function of dose categories, a wide range of risk values exists ([3], Table 34). The majority have confidence intervals so wide that they prove or disprove very little. Not only can they not reject the ICRP coefficient, they are consistent (at their upper confidence limit) with a nominal probability coefficient which is much higher than ICRP's; at the lower confidence limit, some studies are consistent with the possibility of their being no radiation risk at all.

There is a statistically significant decreased SMR for "all causes of death" in nuclear shipyard workers compared to non-nuclear shipyard workers [2, 4], but this resulted primarily from non-nuclear workers having a higher incidence of deaths from disease other than cancer. Both groups had lower death rates than the general US population for leukemia, and for lymphatic and haemopoietic cancers. (This "healthy worker effect" [HWE] certainly makes it more difficult to interpret SMR's, which is partly why many studies do an internal analysis, where they look for a trend in risk with increasing dose—i.e., the lesser-exposed persons serve as controls.) In fact, this naval shipyard worker group has SMR = 0.99 for "all malignant neoplasms" ([3], Table 33), a value sufficiently far above the "all causes" SMR of 0.76 that a case could credibly be argued that the HWE could be masking occupationally-related cancer in the naval shipyard nuclear workers.

The issue for radiation protection therefore becomes whether there exists any consonant set of data that suggests that the two-fold lower (that is, by the DDREF factor) coefficient for LLR demonstrably over-estimates risk. Even consolidated studies organized for the purpose of garnering increased statistical power are unable to demonstrate this. For example, the International Agency for Research on Cancer (IARC) study of cancer mortality rates among nuclear industry workers in the UK, USA and Canada [5] was a high-visibility attempt to address this question in occupationally exposed persons. This study involved data on 95,673 workers (85% males) employed for six months or more and who had been monitored for external exposure to ionizing radiation. The excess relative risk for leukemia (excluding chronic lymphocytic leukemia) was 2.18 per Sv, with 90% confidence intervals (CI) of 0.1 and 5.7. This is the only statistically significant result. When the A-bomb survivor cohort was analyzed in a strictly comparable way, the resultant value of ERR/Sv was 3.67 (90% CI: 2.0, 6.5), thus implying an effective DDREF value of 1.7 for leukemias. The apparent congruity with the DDREF value led to the assertion that "These estimates are the most comprehensive and direct estimates of cancer risk associated with low dose protracted exposures obtained to date", and "Overall, the results of this study do not suggest that the current radiation risk estimates for cancer at low levels of exposure are appreciably in error". Yet the leukemia conclusion rested on a total of only 119 fatal cases, and what gave statistical significance was the 6 cases (compared to 2.3 expected) in the highest dose category (> 400 mSv).

For "all cancers excluding leukemia", the ERR in the IARC study was -0.07 per Sv (90% CI: -0.4, 0.3). Unfortunately, while providing no proof that there was an increased risk of solid cancers, the result also lacked sufficient statistical power to prove that the risk for solid cancers was in any whit lower than the estimate from the A-bomb survivor data (an ERR/Sv of 0.24, calculated in a corresponding manner); worse, the IARC result was unable even to exclude that the true risk might be even higher.

Data certainly do exist from which one could credibly argue that risk may be appreciably lower in particular situations for certain individual sites of cancer: for example, the risk of lung cancer in tuberculosis patients given highly fractionated exposures from fluoroscopic examinations [6] is clearly inconsistent with the ICRP-recommended coefficient. This is a statistically powerful result: radiogenic lung cancer risk is at a minimum (i.e., the upper 95% confidence interval) five-fold less

than the ICRP nominal probability coefficient, even though the total doses were quite high and the individual dose fractions quite large compared to the typical occupational situation. But this is only for one target organ. In the same series breast cancer risk showed a linear dose-response [7]. So we can't assert that all solid cancer risk diminishes to zero with fractionation.

In evaluating the risk that may attach to occupational exposure, we need not look as low in dose as we have, since radiobiological studies indicate that the dose rate range where decrease of dose rate makes most of its impact is still well above dose rates encountered occupationally. We suggest that it may well be time to stop looking "under the streetlight" at persons exposed to the same sort of low levels whose risk we want to assess, and look to higher dose scenarios with greater statistical power.

3. RADIATION- AND CANCER-SENSITIVE PERSONS

A large number of genes are known which are associated with propensity to cancer. The proportion of the 'natural' incidence of human cancer which is due to the aggregate of such genes is likely large. It is highly likely that both 'natural' and radiogenic cancer risk is distributed unequally; the estimates based on whole populations yield hypothetical average risks for a "population-average" person who may not exist in reality. What we wish to discuss here is how this information affects the debate about whether the LNT hypothesis is apt or not.

Cells in tissues of people who have one or more of these genes may already be some steps along the multistep path to cancer, reflected in such people having a higher risk per unit radiation dose than the nominal ICRP probability coefficients imply, and no practical threshold that might otherwise arise because of the slow progress through initial steps. The gene-screening approaches empowered by the Human Genome Project will furnish ability to ascertain this. The shortened chain of radiocarcinogenesis means fewer rate-limiting steps are interposed between the damage event and the appearance of the cancer outcome; cancer appears earlier [8]. A simple monotonic relationship may be more likely for radiogenic cancer in susceptible persons.

The difficulty is that we have probably underestimated the size of the subset(s), because of an emphasis on high penetrance cancer-susceptibility disorders where the gene-related condition is "necessary and sufficient" for cancer to appear. There may be many more disorders of lower penetrance which are "necessary but not sufficient" and require an environmental exposure for cancer to be elicited (see, *e.g.*, [9]). This class may have a large impact on radiation risk, and we are only now developing the tools that will allow us to obtain an answer.

We conclude therefore that even if the overall risk might decrease to zero in some persons at low doses and/or low dose-rates, this is unlikely to be the case for all persons. That is, there likely will always be some individuals at enhanced risk, however low the dose. (A caveat is that if there are many such genes, and if many persons possess at least one, such pervasiveness could lead to another form of spreading out of risk.)

4. CONCLUSION

We conclude that even if risk might decrease to zero in some persons (or even in a majority of persons) at low doses and/or dose rates, it is unlikely to be the case for all persons, and it may well not be the case for the subset of persons who may give rise to most cancers—whether natural or radiogenic. That is, there likely will always be some individuals at enhanced risk, however low the dose.

The "problems with LNT theory" relate to what are seen as excessive costs for protection against radiation versus other risks to human health. The issue as we see it is that the attention given to

low doses of radiation is excessively high even if the LNT-based risk coefficients were to be totally correct. This is the issue we have to continue to address and rectify. Part of this will be to narrow the band within which estimates of any risk at low dose and low dose rates must lie. Untenable generalizations will not help.

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Problem of Correct Assessment of Cytogenetic Effect Induced by Low Doses of Ionising Radiation

S.A.Geraskin, V.G.Dikarev, A.A.Oudalova and R.M.Alexakhin,
Russian Institute of Agricultural Radiology and Agroecology, 249020 Obninsk, Russia

ABSTRACT

On the basis of analysis of cell's reactions observed experimentally it was shown that the yield of cytogenetical disturbances in the range of low doses is clearly non-linear and universal in nature. Genetical effects observed within the range of low doses are caused by peculiar features of realisation of cellular response to weak exposure rather than by damaging effect of ionising radiation or other factors of physical or chemical nature.

The experience gained after the Chernobyl accident has shown that today scientific knowledge about mechanisms of biological effect of radiation at low doses are incomplete and self-contradictory in many key aspects. Analysis of causes for substantial differences in assessments of accident consequences obtained in independent investigations by various scientific groups has shown [1] that they should not be a result of respectively small variations in estimations of expected collective dose but are mainly due to different estimations of genetic and carcinogenous damage yields per unit dose in the range of low exposure. Therefore, an estimation of genetic consequences of large radiation accidents, in particular, of the Chernobyl accident, depends significantly on a concept of genetic disturbance induction by low doses which the author holds on.

A low significance of results obtained in radiobiological experiments and of epidemiological data concerning genetic effects of low dose radiation allow to make their convenient description by principally different mathematical models [2]. It makes doubtfully a use of any of these models for genetic risk estimation. Even if the information available enables a choice on behalf of one of these functions, to substantiate a legality of its use for purpose of extrapolation of observed frequencies to zero dose an additional (unempirical) data will be required. Therefore, a correct and scientifically justified assessment of danger from low level radiation could not be obtained only on the basis of empirical data. The problem of genetical risk estimation at low doses is of non-empirical character and can be based only on scientifically substantiated and intrinsically non-contradictory concept of biological effect of low dose ionising radiation. Such concept must being able to describe all available data about genetic effect of radiation in whole dose range from a unified viewpoint.

At present, there is not a unified generally recognised concept of biological effects of low-dose ionising radiation. The most common one is the linear non-threshold concept which states an absolute danger of any irradiation levels among which are levels underlying natural radiation background. However, a linear relationship, valid for the induction of potential damages in DNA molecules, must not necessarily result in similar dependence in terms of the yield of genetic disturbances. A cell is a living, complexly organised system. Therefore, its response to external radiation exposure within the range of sublethal doses may be of non-linear nature.

Actually, a lot of facts have been accumulated by now which are suggesting a non-linear shape of dose dependence. The most complete data available are those on chromosome aberrations. The analysis of numerous investigations by different authors carried out primarily on human peripheral blood lymphocytes has made it possible to identify two sites within which dose dependence deviates from the expected linear one. Significant deviations were revealed within the dose range below 5 cGy. The most careful studies of dose dependencies in this range have been conducted by research groups of J.Pohl-Ruling [3] and D.Lloyd [4]. Analysis of the results obtained in these studies has shown that at doses up to 2 cGy the frequency of dicentrics occurrence does not exceed the control level. Moreover, all the six points within the range of up to 1 cGy, obtained in three independent experiments, lie below (sometimes statistically significant [3]) the corresponding control.

The second interval which shows considerable changes in dose dependence slope varies in different authors' studies within the range of 10-50 cGy. Work [5] presents data of different researches on aberrations in human peripheral blood lymphocytes induced by low-dose ionising radiation. It follows

from these results that frequency of dicentrics observed in this range is virtually independent on dose value, i.e. there is the dose independent region (plateau). Since dependencies of the same shape are reproduced with striking constancy in independent studies of different authors, it is believed that such a behaviour of the dose effect curve is caused by qualitative features typical for the analysed experimental data rather than being determined by random fluctuations.

Similar relationships have been obtained with other objects. Thus, studies of the regularities of structural mutations induced in the root meristem of barley seeds irradiated by ionising radiation [6] have revealed the site of dose dependence within which the frequency of aberrant cells significantly exceeds the spontaneous level and is practically independent on dose value. Dose dependence of similar form (see Fig. 1, solid line) was derived in the analysis of the yield of aberrant cells in irradiated barley seedlings; this test-system is comparable in sensitivity with human lymphocytes. It should be noted that in this case the plateau range (5-30 cGy) is shifted towards considerably lower doses, corresponding to the relationship among the sensitivities of test-systems under study. We have also obtained similar

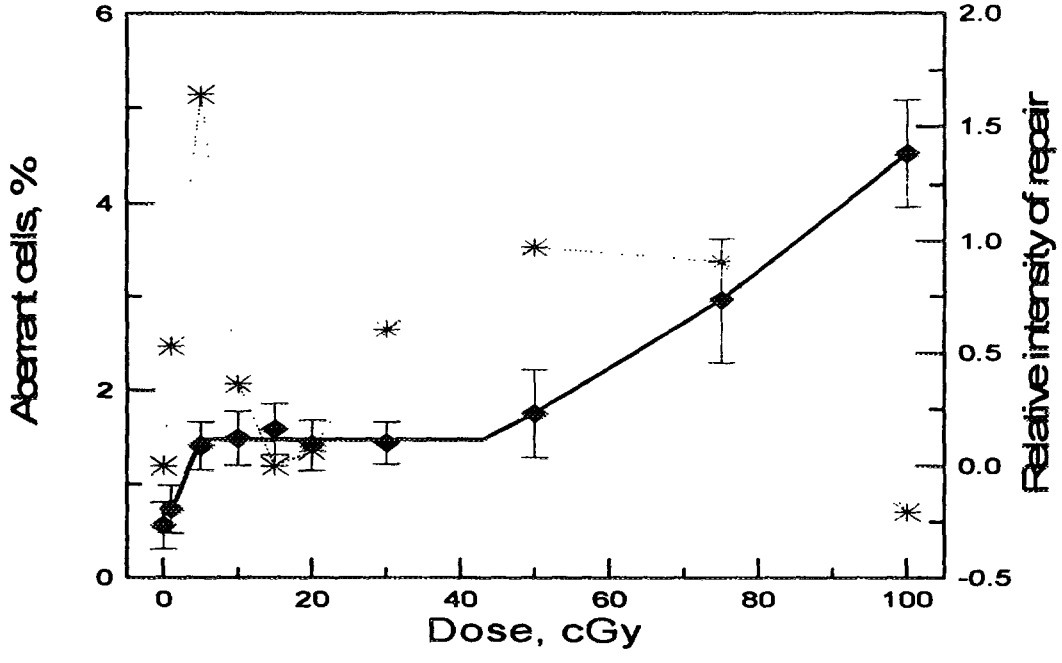

Fig. 1. Variations in the frequency of aberrant cells (solid line) and relative intensity of repair (dotted line) in the root meristem of irradiated barley seedlings versus dose.

dependencies in the course of other studies [7] which did not pursue the goal to analyse the form of dose curves.

Comparison of the form of the empirical curve, derived during these investigations, with results obtained on other objects (human lymphocytes, fibroblasts of Chinese hamster, *Vicia faba* seedlings, etc. (see review in [8])) allows the conclusion to be made that the relationship between the yield of radiation-induced cytogenetic disturbances and dose is non-linear, universal in character and varying for different objects only in dose values at which changes in the nature of the relationship occur and which are determined by objects' sensitivity to exposure. The results presented clearly demonstrate inadequacy of linear extrapolation of frequencies observed at doses above 50 cGy to zero dose. Since the relationship between the yield of genetic disturbances and dose in the range of low exposures is of a complex non-linear character, a correct estimate of the genetic risk of irradiation in this case, which is most important in terms of practical application, may be based only on the clear understanding of mechanisms governing the formation of cellular response to low-dose irradiation.

We suggest the hypothesis that the non-linear shape and the universal behaviour of dose curves within the discussed dose range are caused by peculiar features of realising a cellular response to weak exposure rather than by damaging effect of ionising radiation or other factors of physical or chemical nature. One trying to explain this part of dose curve must keep in mind that ionising radiation is capable

to induce several different repair systems in cell. Unlike systems of adaptive response and constitutive replicative repair, both of antimutagenous character, a system of SOS-response, repressed in normal state, proves a restoration of cell survival through the elevated yield of genetic disturbances. At the range of low doses, when the contribution of radiation effect into the induction of primary DNA damages is small, an initiation of mutagenic repair has to lead to an increase in the yield of genetic disturbances. The "plateau" in dose dependence registered in this dose range appears as the peculiar label of a switching cells at quite a different order of service. Here, the yield of genetic disturbances is determining by an order of cell service rather than by external impact occurring through the induction of primary cell damages by ionising particles. Because of this, we obtain in experiment the anomalous dose range within which 2-10 fold changes in dose value is not accompanied by significant increase in yield of cytogenetic injuries. One more experimental fact in a favour of the suggested hypothesis obtained in our study is that a decrease in the activity of repair systems with dose is followed by a linear increment of the potential DNA damages in the range of 5-15 cGy for barley seedlings (Fig. 1, dotted line). Similar results have been obtained by other authors [9] under study of the repair intensity in human lymphocytes at low doses. The change in activity of repair processes in this dose range was shown [9] to be followed by essential structural reorganisation of genome, indicating a change in a pattern of gene expression.

A full analysis of molecular-cellular mechanisms of cell response to low-dose radiation is beyond the scope of this paper and is presented in a special-purpose publication [10]. We would just point out here that there are two fundamentally different strategies defining the type of cellular response to external influence. A "passive" strategy is aimed at maintaining dynamic balance of cell and consists in activation of systems of adaptive response. An "active" one, along with the maintenance of homeostasis of genetic structures, provides the prerequisites for the increase in the variability pool in the exposed population of cell and consists in activation of mutagenic systems of SOS-response and duplicate transposition of mobile genetic elements. The choice between these two strategies depends on the exposure intensity.

Finally we define the features which are in our opinion the most general in cellular response to low-dose ionising radiation and to some other factors of physical, chemical and biological nature:

(a) the basis for the cellular response to low-dose irradiation and the weak influence of other external factors is fundamental evolutionary-conserved mechanisms for ensuring stability of living systems;

(b) the genetic effects observed within the range of low and adjacent doses are caused by peculiar features of realisation of cellular response to weak exposure rather than by damaging effect of ionising radiation or other factors of physical or chemical nature;

(c) in the range of low and adjacent doses the regularities in the yield of genetic disturbances show a pronounced nonlinearity and are universal in character;

(d) low-dose irradiation and weak influence of some other factors could cause an inheritable destabilisation of genetic structures appearing in particular in the increased yield of cytogenetic disturbances, a cariotypical variability and a cancer risk in offspring's of irradiated organisms;

(e) there are two fundamentally different strategies defining the type of cellular response to low-dose radiation, the choice between which depends on the intensity of exposure;

(f) in the most important in terms of practical application case of simultaneous exposure to several factors, non-linear interaction effects of synergistic or antagonistic nature are mainly observed at the range of small exposure values of harmful agents.

A non-specific character of the regularities studied and a wide spectrum of objects for which these are observed provide evidence that here we deal with a general biological phenomenon. From this point, the elevated genetic efficiency of low-level radiation has a simple and natural explanation. This is one of the manifestations of adaptation processes which take place at various stages of biological organisation as a response to stress. At the first stage this process consists in a precondition creation for the increase of a changeability pool with following selection of the most adapted forms. Just as the phenomenon of DNA molecule repair discovered by radiobiologists has gone far beyond the scope of this science and is undoubtedly of a general biological importance, the established in radiobiological studies regularities of biological effect of low-dose ionising radiation are not artefact or some exotic "anomalous" reaction but one of natural manifestation of fundamental (being a basis for life) mechanisms to ensure the resistance of living systems and the possibility of their adaptation to varying conditions of the environment.

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The French cohort of uranium miners: analysis of lung cancer risk linked to radon exposure in a population exposed to relatively low concentration over a long duration.

Margot TIRMARCHE[1], Dominique LAURIER[1], Ladislav TOMASEK[2], Jean-Marie GELAS[3]

[1] Institute for Protection and Nuclear Safety, Human Health Protection and Dosimetry Division, Risk Assessment and Management Department.
IPSN/DPHD/SEGR, BP n° 6, F 92265 Fontenay aux Roses Cedex, France.

[2] National Radiation Protection Institute, Epidemiology Unit.
Srobarova 48, 10000 Praha 10, Czech Republic.

[3] Medical Coordinator of COGEMA, BP n° 4, F 78141 Vélizy Cedex, France.

Abstract

In France, about 5,000 miners have been employed in uranium mining industry since 1946. Most of these miners have experienced relatively low annual exposures in comparison to other cohorts of miners. Consequently, the hypothesis to be tested in our study was the potential risk of cancer in a relatively low exposed population, characterised by a long period of underground work.

A first analysis of the "oldest" cohort (1,785 miners having worked underground before 1972) has been published in 1993, based on a follow-up to December 1985. Recently, this follow-up has been extended up to 1994. Compared to the first analysis, the size of the cohort has increased by 24 %, and the number of lung cancer deaths has increased by about 90 % (from 45 to 85 deaths). Mean cumulated exposure to radon is of 71.5 WLM, protracted over more than 15 years. After 1956, radon exposure is lower than 2 WLM/year for 50 % of the miners. The Standardised Mortality Ratio for lung cancer is 1.65, with confidence interval $CI_{95\%}$ = [1.3-2.0]. The Excess Relative Risk coefficient for lung cancer with cumulated exposure to radon is ERR/WLM = 0.40 % ($p = 0.05$). This estimate is very similar to the one obtained in the first analysis.

The contribution of this population to the estimation of the risk coefficient of lung cancer, in relation to low dose-rates and low cumulative exposure is far from negligible. Enlargement of the French cohort exposed after 1956 is ongoing. Moreover a European joint analysis of cohorts with low levels of exposure rates (French, Czech and German cohorts) will be performed in a near future.

1. INTRODUCTION

Most of our knowledge concerning the risk of cancer associated to radon and radon decay products exposure derives from surveys of underground miners. Eleven cohort studies of miners have been undertaken: in the USA, Canada, China, Sweden, the Czech Republic and France. These studies showed an excess risk of lung cancer in radon-exposed underground miners. A joint analysis of these eleven cohorts concluded in 1994 to a significant dose relationship between the risk of lung cancer and the cumulative exposure to radon decay products [1].

Most of the miners of these cohorts underwent high exposures to radon. In France, most of the uranium miners have experienced relatively low annual exposures in comparison to other cohorts of miners. Consequently, the hypothesis to be tested in our study was the potential risk of cancer in a relatively low exposed population, characterised by a long period of underground work. The quality of the exposure data of the French uranium miners is high, especially since 1956, when radioprotective measures have been implemented, including forced ventilation in the mines and a systematic individual survey of exposure. Since that period, we may consider that the miners are in exposure conditions, with radon decay concentrations of the same order of magnitude than those observed in some houses in France (for illustration, the annual radon exposure of French miners after 1956 is lower than 2 WLM[1] for 50 % of them, which corresponds approximately to an annual domestic exposure of 460 Bq per m^3).Therefore, the contribution of this population to the estimation of the risk coefficient of lung cancer, in relation to low dose-rates and low cumulative exposure is far from negligible, and could be of great importance when discussing the extrapolation of the risk for populations exposed in their dwellings to radon decay products [2].

2. THE FRENCH COHORT OF URANIUM MINERS

In France, uranium mining exists since 1946. A total of about 5,000 underground miners have been employed in this industry. The "oldest" cohort includes 1,785 uranium miners who began underground work between 1946 and 1972 and were exposed to radon for more than 2 years. A first analysis of this cohort has been published in 1993 [3], based on a follow-up completed to December 1985. Compared to national rates, significant excesses were observed for lung cancer (Observed = 45, Expected = 21) and for cancer of larynx (O = 17, E = 7). For lung cancer only, a linear dose response relationship was described with cumulated radon decay exposure. The Excess Relative Risk (ERR) coefficient was relatively low (ERR/WLM = 0.35%) in comparison to other studies, but the number of lung cancer cases was low (n = 45) and the confidence interval limits of this coefficient included most of the values of the other studies or estimates from international committees.

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[1] *WLM (Working Level Month) is a unit of exposure multiplying a concentration of radon decay products by the duration of exposure. A yearly exposure to 11 WLM corresponds roughly to a monthly exposure to 1 WL, the monthly exposure being defined as 170 working hours. 1 WL is equivalent to any combination of radon decay products in 1 liter of air, that results in the emission of 130,000 MeV of energy of α particles*

To increase the power of our study, follow-up of this cohort has been extended up to 1994. Causes of death were obtained from the National Mortality Database. Compared to the first analysis, the number of person-years has increased by 24 %, and the number of deaths has increased by more than 70 %. Individual dosimetric records have been validated up to 1994, and the mean duration of exposure is now of more than 15 years (Table I).

Table I: Characteristics of the French cohort of uranium miners, at the time of the first analysis, and after extension of the follow-up.

	Follow-up to 1985 [3]	Follow-up to 1994	Difference
Number of miners	1,785	1,785	
Person-years	45,000	55,600	+ 24 %
Mean duration of follow-up (years)	25.2	31.4	+ 25 %
Number of deaths	352	611	+ 74 %
Number of lung-cancers	45	85	+ 89 %
Mean cumulative exposure to radon (WLM)	70.4	71.5	+ 1 %
Mean duration of exposure (years)	14.5	15.3	+ 5 %

3. RESULTS FROM THE EXTENDED COHORT

Based on data from this extended cohort, the Standardised Mortality Ratio for lung cancer is lower than in the previous analysis: SMR = 1.65 (O = 85, E = 51.6, $IC_{95\%}$ = [1.3-2.0]). The Excess Relative Risk coefficient for lung cancer, estimated from the slope of the linear dose-relationship is: ERR/WLM = 0.40 % (Confidence Interval $CI_{95\%}$ =[-0.07 ; 0.88], p = 0.05 by one sided test). This estimate is very similar to the one obtained in the first analysis. The same result is obtained when using external reference rates or internal Poisson regression. Again, even if statistically significant, the confidence interval is large, and this estimation is in agreement with most of the values from the other studies.

For cancer of larynx, the excess risk that was noted in 1993 [3] has not been confirmed after extension of the follow-up.

4. PERSPECTIVES

This approach is of course only a small part of the research that is needed to explain the effect of low dose and low dose rate exposures on the risk of lung cancer due to radon.

Levels of exposure were strikingly reduced in French mines after 1956, and precision of exposure measurement was largely improved (systematic individual recording of cumulated dose). A separate analysis of this population will gave some more insight on the risk of cancer associated to low exposure to radon, with rates of exposure similar to what can be encountered in some houses. Among the old French cohort, the number of lung cancers death among miners exposed after 1956 is too low to allow for an accurate estimation of the ERR/WLM. Consequently, our main efforts concern now the analysis of a complementary cohort of miners having begun work since 1973, and followed up to 1994. It will soon be completed. The merging of these two cohorts of miners will give a better power to this study, including a population of about 2,500 miners, for the analysis of the risk of lung cancer among underground miners with very low rates of exposure to radon.

A complementary approach consists in an international joint analysis of cohorts with low levels of exposure rates. IPSN coordinate a European project (DG XII), with the aim to focus mainly on the dose-rate effect. The objective is a common study of the French and the Czech uranium miners cohort, which had a well registered annual exposure over long working periods [5]. Indeed, both cohorts are characterised by a long duration of underground work, on average 10 years, which distinguish them from most of the US or Canadian cohort studies. In the Czech cohort, the younger group received low exposures around 1 WLM per year. In a new study in Germany on Wismuth miners, the most recent subcohort has also experienced low annual exposures. The results from the German cohort, with a high number of miners, will bring an important contribution to radon and cancer risk assessment in the future. This collaborative work is planned for the period 1996-1999.

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