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Ce numéro contient les textes des exposés présentés le 18 mars 1994 lors d'une réunion organisée à Bruxelles par l'Association belge de Radioprotection consacrée à:

INHOUD

Dit nummer bevat de teksten van de uiteenzettingen gedaan in Brussel op 18 maart 1994 ter gelegenheid van van een vergadering van de Belgische Vereniging voor Stralingsbescherming gewijd aan:

HORMESIS

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L'HORMESIS : INTRODUCTION

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II est actuellement admis qu'une partie importante des conséquences que peut avoir l'exposition aux rayonnements ionisants, et notamment les effets à long terme, n'est que l'expression de la fraction des dommages initiaux subis par le matériel génétique, qui n'a pas été réparée ou qui a été mal réparée. Les travaux effectués, notamment sur des procaryotes tels que *Escherichia coli*, ont démontré qu'il existait différents mécanismes capables de réparer correctement les dommages à l'ADN, soit avant, soit pendant, soit après sa réplication. L'efficacité et les capacités de ces mécanismes ne sont évidemment pas illimitées et leur saturation explique en partie les effets de débits de dose ou du fractionnement de la dose administrée. A côté de ces mécanismes capables de restaurer l'état originel de l'ADN en existent d'autres, tels que le "SOS repair", qui vont, grâce à une inhibition des mécanismes de contrôle cellulaire, permettre à la cellule de répliquer son ADN altéré et de perpétuer, ainsi, les dommages qu'y auront produits les agents mutagènes.

Si, pendant de nombreuses années, et la chose est tout à fait normale en radioprotection, on s'est presque uniquement préoccupé des effets délétères des rayonnements ionisants, différentes études, dont certaines remontent à une trentaine d'années (Planel et al., 1965) ont démontré que l'exposition à de faibles doses de rayonnements ionisants pouvaient avoir un effet stimulant sur le comportement des cellules exposées et notamment sur leur prolifération. Le

terme "**hormesis**", qui dérive du grec "hormao" (promouvoir) a été utilisé pour désigner de manière spécifique cet effet de l'exposition aux rayonnements ionisants. Alors qu'à l'origine il ne recouvrait que cet aspect de stimulation de la prolifération cellulaire, des travaux plus récents ont démontré qu'une exposition préalable à de petites doses augmentait, en plus, la résistance cellulaire à une exposition ultérieure à des doses plus élevées. Comme nous le verrons d'ailleurs dans les exposés qui vont suivre, on s'est aperçu que d'autres agents environnementaux, des maladies, ou même des facteurs cellulaires intrinsèques pouvaient avoir les mêmes effets. On les englobe sous le terme général de "réponse au stress".

Ces effets biologiques sont évidemment liés directement à la quantité d'énergie absorbée. La mesure des doses reçues, et notamment la microdosimétrie, constitue dès lors un préalable essentiel dans l'appréhension de ces mécanismes de stimulation et de réponse adaptative. C'est pour cette raison que le programme de cette réunion comprend trois exposés:

- le premier, sur la microdosimétrie, sera donné par le Professeur H.G. Menzel de la Commission de l'Union Européenne;

- le second, par le Professeur G.B. Gerber, ancien responsable de l'Unité de Radiobiologie à la Commission des Communautés Européennes, traitera de la stimulation cellulaire produite par de faibles doses;

- mon exposé, abordera la question de la réponse adaptative.

Pour terminer, le Professeur G.B. Gerber, synthétisera les conclusions que l'on peut tirer, à l'heure actuelle, de ces effets un peu particuliers des faibles doses de rayonnements ionisants et les perspectives de recherche qui s'ouvrent dans ce domaine qui est certainement un des plus originaux qui se soit révélé en radioprotection ces dernières années.

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MICRODOSIMETRY AND LOW DOSE: CONSTRAINTS FOR THE INTERPRETATION OF RADIATION INDUCED BIOLOGICAL EFFECTS AND HORMESIS

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Abstract

In general, the yield of biological effects induced in cells and organisms by ionising radiation depends on the type and energy of the incident radiation. Research in microdosimetry is concerned with the investigation of those features of the primary physical events which are determining this biological effectiveness or radiation quality. Low dose and low dose rate effects are characterised by energy deposition events due to **single** primary particles. Microdosimetry provides data on the frequency of energy deposition events in cells or subcellular structures for a given absorbed dose as well as descriptions of physical track properties for different radiation qualities. These data represent constraints for the interpretation of low dose and low dose rate effects, and thus, also for hormesis.

Radiation medicine, radiation protection and radiation biology need a quantity which can be used to specify the "amount" of ionising radiation delivered to organs, tissues or cells and which is quantitatively related to the induced biological effects or the expected risk. Ideally, a single physical quantity based on the interactions of the radiation with matter would quantitatively predict biological effects for all types of ionising radiations. However, such a parameter does not exist, and, in practice, pragmatic and empirical approaches are used. The basic quantity used in radiation dosimetry is absorbed dose. It is defined as the energy imparted to the matter in a small volume divided by the mass of the matter (Unit: joule per kilogramme: gray (Gy)). Although it is defined as a point quantity, in practice it is mostly used for extended volumes such as organs, which implies that appropriate averaging over the entire volume

is possible. In general, the yield of induced biological effects per unit absorbed dose depends on the type and energy (spectrum) of the incident radiation. For example, more densely ionising particles (alpha particles, charged particles released in neutron interactions) can be up to factors of 50-100 more effective than sparsely ionising particles (electrons from photon interactions). In radiation protection, this fact is accounted for by introducing a weighted dose quantity called "equivalent dose", which is defined as the product of absorbed dose, and the quality factor or the radiation weighting factor which have been specified for different radiations based on an evaluation of results of epidemiological studies and radiobiological studies by international committees.

The basic objective of microdosimetry is to understand the relation between primary physical interaction events and the biological consequences of these events and to identify those features of the primary physical events which are determining the biological effectiveness. The motivation for research in this area is not only the search for a sound dosimetric concept for practical purposes, but the expectation that insight will be gained into the chemical and molecular processes leading to the biological effect and, as a consequence, to be able to quantify biological effects induced in humans at the low doses of exposure relevant to radiation protection.

As the nature of the primary products of radiation interactions, predominantly ionisations and excitations, is the same for all types of ionising radiations, the sometimes large differences in the biological consequences cannot be due to the individual physical interactions, but must be intimately related to the spatial (and temporal) relationships of these initial physical events on the molecular and cellular scale. The stochastic nature of the radiation interactions causes a highly structured and thus, on a cellular or molecular level, strongly inhomogeneous pattern of energy depositions along the track of charged particles. Microdosimetry is concerned with the determination of the characteristics of the microscopic topology of interactions and energy depositions of different radiations.

Various experimental and computational microdosimetric methods have been developed to investigate energy deposition by charged particles on a cellular and molecular level. In principle, two approaches can be distinguished. One uses the path of the charged particles as the base for describing the structure of the track produced in the interactions with atoms and nuclei. Monte-Carlo calculations of charged particle tracks use basic atomic and nuclear cross-sections for interactions with materials of biological relevance. Due to considerable limitations in the availability of relevant input data, most of these calculations were initially carried out for water vapour, but currently progress is being made in employing data for condensed phase matter and increasingly

complex structures of the biological object simulated. Moreover, the calculations of the initial physical stage are being complemented by including the modelling of subsequent chemical and molecular processes. This approach is aimed at a mechanistic understanding of those processes involved in the manifestation of biological effects of interest. It requires an interdisciplinary cooperation between physics, radiation, chemistry, molecular and cellular biology.

The identification of processes and track structure features critical for the subsequent biological effects is necessary for quantitative understanding, but is also required in order to reduce the enormous complexity of modelling the target and track structures to manageable size. The long-term goal is to be able to quantitatively predict biological effects, and ultimately cancer induction, for the low doses (and low dose rates) relevant in radiation protection. The extrapolation of data obtained from epidemiological studies, to these low doses is associated with large uncertainties which can only be reduced when a quantitative, mechanistic understanding of the processes involved becomes available.

The other microdosimetric approach is based on the energy deposition of single charged particles in finite size volumes, usually with diameters to the order of 1 micron. An experimental method to measure such energy deposition spectra using low pressure proportional counters made of tissue equivalent material was developed more than 30 years ago by H.H. Rossi. The technique can be applied to any penetrating radiation. It is limited, in general, to volumes with simulated diameters above a few tenths of a micrometer, and there are other limitations to the simulation of a microscopic tissue site. However, there is increasing evidence that this technique can be used for various practical applications. The measured spectra reveal the large variations in energy depositions by single primary particles. In the

case of photons, event sizes range over three orders of magnitude (few tens of eV/μm to about 20 keV/μm) for fast neutrons over more than five (few tens of eV/μm to more than 1000 keV/μm). They can be used to evaluate absorbed dose contributions by different primary (photons and neutrons) or different secondary particles (electrons, protons, alpha particles, heavier ions).

Experimentally determined microdosimetric distributions and derived parameters are also being used as the basis of phenomenological models describing biological responses and some models have been successful in analyzing radiobiological results.
Radiation protection, in particular for mixed field radiation fields and high-LET radiation therapy, are increasingly benefiting from the use of such phenomenological approaches based on experimental microdosimetry. It is this phenomenological use of microdosimetric data and information which provides implications and, in fact, constraints for the interpretation of low-dose and low dose rate effects and, thus, hormesis.

The public and workers are, in general, exposed to low doses and low dose rates. As a consequence, it is very unlikely that individual cells in a human body will receive more than one energy deposition by a single track and the average period of time between two potential subsequent events is of the order of months or years. The relevant processes within cells, including repair processes, have time constants of the order of minutes to days, so that any observable change to a cell must arise from a single primary track. Microdosimetry provides data and information on the frequency of events in cells for given absorbed doses and different radiation qualities as well as descriptions of physical track properties. Here, only some considerations on event frequencies are presented. More comprehensive overviews on the role of microdosimetry for the understanding of low dose effects can be found in the published literature [1-5].

For a given absorbed dose and type of radiation, the frequency of energy depositions in microscopic sites depends on the size of the site. Following a suggestion of Feinendegen et al. [3], here microdosimetric results for spherical volumes of 8 μm diameter are used because this is a size reasonably typical for many cell nuclei or entire cells. Approximate frequency data for other volume sizes can be obtained by assuming an inverse proportionality to the square of the sphere radius. Table 1 gives absorbed doses for different radiations for which the average

number of tracks per cell (nucleus) is 1. The data are based on microdosimetric measurements and calculations and on the assumption that the frequency distribution for the cells is described by a Poisson-distribution.

Table 1: Doses giving average of 1 track per cell nucleus (or cell)* from [1]

Radiation	Dose (mGy)
γ-rays (~ 1 MeV)	1
Neutrons alone (~ 1 MeV)	100
Neutrons + 10% γ-rays	9
α-particles (5.5 MeV)	370

*Assumed to be 8 μm diameter spheres for these examples

The table documents that the event frequencies are strongly dependent on radiation quality and that there is a variation of more than two orders of magnitude.

In Table 2 similar information is presented. Here the typical annual doses and exposure limits are correlated with the average number of tracks per cell (nucleus) for various radiations.

Table 2: Typical annual doses and tracks in human exposures (from [1])

Condition	Radiation LET	Absorbed Dose (mGy)	Q	Dose Equivalent (mSv)	Ave. tracks per cell nucleus
Average Public					
Whole-body	Low	1	1	1	1
Lung	High (α)	0.4	20	8	~ 0.001
Worker Limits[a]	Low	< 20	1		< 20
(whole body)	Neutrons[b]	< 1	10	20	< 0.01[b]
	High (α)	< 1	20		< 0.003

[a]ICRP Report 60 (1991)

[b]Assuming pure 1 MeV neutrons (and no associated γ-rays)

It can be seen that natural, low LET background leads to one track per cell per year. The average annual exposure of the lung to radon and radon daughters expressed as absorbed dose is only 40% of that of external whole-body exposure; however, expressed as dose equivalent it is the main contribution to the exposure of the population. This is to be correlated with the fact that only 0.001 or 0.1% of the lung cells will experience per year any dose at all. The low frequency is obviously correlated with a correspondingly high absorbed dose in the "bit" cells due to the high ionisation density in alpha particle tracks. This large inhomogeneity of absorbed dose on a cellular level is basically the reason for the high biological effectiveness of alpha particles. The dose limits for occupational exposure correspond to higher event frequencies. Nevertheless, the average number of tracks per cell nucleus is still much less than 1 for neutrons and alpha particles.

The same type of microdosimetric analysis can be applied to assess the average time between two consecutive tracks from different primary particles for a given absorbed dose rate. In Table 3, examples are given for 100 kV X-rays. Examples for other radiations can be deduced from Tables 1 and 2. The phenomenological information in Table 3 can be correlated with observed dose rate effects. If the time constant of biological processes, in particular repair processes, become comparable or larger than the time interval between two consecutive events, interaction between the two events is possible, which may have an influence on the overall outcome.

Table 3: Influence of Dose Rate (from [3])

100 KV X-Rays

Dose Rate	**Average time between 2 hits**[a]
0.10 cGy (100 mrad)/d	3 days
0.30 cGy (300 mrad)/d	1 day
0.01 Gy (1 rad)/d	8 hours
0.10 Gy (10 rad)/d	50 minutes
1.00 Gy (100 rad)/d	5 minutes

[a]Assuming 8 microns diameter spheres

Concluding Remarks:

Quantitative observations of biological effects after exposure to low doses and dose rates of ionising radiation are of great relevance for radiation protection, and thus for any practice or industry which involves ionising radiation. The quantitative understanding of low dose effects is still limited due to the large uncertainties inherent to low dose experiments and observations. Microdosimetry is aiming at improving this understanding through its contribution towards a mechanistic understanding of low dose effects. Although this is a long-term goal which may not be reached for years to come, existing microdosimetric data provide already relevant constraints to phenomenological explanations and interpretations of observed effects, including hormesis. For example, any interpretations which require the occurrence of more than one track in a microscopic volume of interest such as a cell, cell nucleus or smaller structures must be tested against the likelihood of the required frequencies. Microdosimetric data are available for practically all radiations of interest.

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Résumé

En général, la génération d'effets biologiques dans des cellules et des organismes par les radiations ionisantes dépend de la nature et de l'énergie de ces radiations. La recherche en microdosimétrie est orientée vers l'investigation des caractéristiques des effets physiques primaires déterminant l'efficacité biologique ou qualité des radiations.

Les effets de faibles doses et de faibles débits de doses sont caractérisés par des dépôts d'énergie dus à des particules primaires isolées. La microdosimétrie fournit des informations sur la fréquence des dépôts d'énergie primaire dans les cellules ou structures subcellulaires pour une dose absorbée déterminée ainsi que la description des propriétés du parcours physique pour des radiations de qualité différente. Ces données représentent des contraintes dans l'interprétation des effets faibles doses et des faibles débits de doses et par conséquent pour l'hormesis.

Samenvatting

In het algemeen is het ontstaan van biologische effecten in cellen en organismen na blootstelling aan ioniserende stralen afhankelijk van het type en energie van de stralen. Het onderzoek in de microdosimetrie is gericht naar de caracteristieken van de primaire fysische verschijnselen, verschijnselen die de biologische doeltreffendheid of stralenkwaliteit bepalen. Lage dosissen en lage dosisdebieten zijn gekenmerkt door energie deposities van uit enkelvoudige primaire deeltjes. Microdosimetrie levert informaties over de frequentie van de energiedepositieverschijnselen in cellen of subcellulaire structuren voor een bepaalde geabsorbeerde dosis zowel als bepalingen van het fysisch verloop voor verschillende stralenkwaliteiten. Deze data vertegenwoordigen parameters in de interpretatie van effecten van lage dosissen en lage dosisdebieten en dus eveneens in hormesis.

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HORMESIS: FACTS AND FICTION

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Abstract

Stimulating effects (hormesis) due to an exposure to ionising radiation represent a topic of substantial interest from a theoretical point of view and are sometimes adduced as an argument in regulating radiation protection at exposures at low doses/low dose rates.
Presence of hormesis is characterised by an inverted dose effect relationship. Stimulation of an effect by small doses of ionising radiation does not necessarily imply a beneficial effect; it can be deleterious as well or without consequence for the organism. A substantial amount has been published on hormesis, but often experimental design was deficient without proper controls, repetition of experiments and/or statistics; also material and methods were often poorly standardized. Data on stimulation appear trustworthy for growth and division of bacteria, algae and protozoa, nervous and sensory excitation, immunogical reactions and the adaptive response. Data on stimulation of germination, growth and productivity of plants growth and survival of insects and rodents, lifespan and lower cancer rate in man remain doubtful.
Application of low doses for the treatment of various of various diseases (infections arthrosis etc) by external radiation or spas should be reexamined with respect to risks and benefits. In view of the paucity of means and man power in radiobiology, future research should concentrate on the adaptive response and the immune reaction focusing on mechanisms of action and consequences to the organism. Hormesis is presently not suitable argument against a reduction of dose limits or for sanctioning a de minimis dose. Scientific data are still insufficient for a claim that hormesis can reduce those deleterious effects (ie cancer and damage to the progeny) against which one wants to protect the population. Moreover, under present circumstances of

public and political feeling, adducing the hormesis argument might be rather counterproductive.

Introduction:

Few topics in radiation protection are as controversial as hormesis, opinions ranging from fanatic prophets to almost as fanatic opponents. Indeed, stimulating effects due to exposure to ionising radiation (often called hormesis from ο ρ μ α ω to set in motion to stimulate, also to consider) represent a topic of substantial interest from a theoretical point of view and are sometimes adduced as an argument in regulating radiation protection at exposures at low doses/ low dose rates.

Presence of hormesis is characterised by an dose effect relationship descending below background levels at low doses and has to be clearly distinguished from a "no effect" at low doses. Even when statistics leaves the decision open, "lack of evidence for a toxic effect and the presence of evidence for a beneficial effect" are not the same (26). Stimulation of an effect by small doses of ionising radiation does not necessarily imply a beneficial effect; it can be deleterious as well as without consequence for the organism. Even if the effect is beneficial in some way, it may not necessarily counteract those harmful consequences against which we want to protect man. For example, should one assume that an accelerated growth and maturation or a better immune response due to a reduction of immune suppressor cells are beneficial? Thus, the role of hormesis for life in general is controversial. Luckey (24, 25) claims that small radiation doses are essential to maintain life and have played an important part in its evolution. He proposes a dose effect relationship (Fig 1) where the optimum for life is situated somewhere above the natural radiation background and where detrimental effects are expected for higher as well as lower doses. Prof Léonard's and, less so, this presentation will show that small radiation doses can indeed improve the response to harmful agents; yet Luckey's claim is certainly not supported by the facts in general. In fact, hormesis is often defended with a zeal which seems to originate from the old human belief that what is bad in large amounts must be good in small ones. We can trace this idea in human history from Aristoteles to Paracelsus and the homeopathy.

Literature on the subject of stimulating effect is abundant and confusing (reviews 3, 24, 26, 34, 36, 37); it is certainly not true that this subject has been relegated to a second rank as some proponents of hormesis profess, but it is also true that many scientists feel not very comfortable about hormesis. In this area,

fact is difficult to separate from fiction. Many experimental designs were deficient in controls and/or statistics, the experimental material and methods were often poorly standardized and described, and, frequently, experiments could not be reproduced in another laboratory or even in the same one at a different occasion. Thus, it is not surprising that many observations made exclusively by one research group fell in oblivion once the principal investigator had departed. On the other hand, one should also admit that, although the approaches may sometimes have been deficient and/or biased, many scientists working on hormesis have a solid scientific reputation proven by excellent research and appear much more trustworthy than some who reported deleterious effects after very small doses. In any case, one should insist that no claim for beneficial or deleterious effects of small radiation doses be accepted unless it has been confirmed in repeated experiments in another laboratory and unless a rational explanation can be given on microdosimetric (4, 9, 11) as well as on biological grounds.

Next, we shall briefly review the observations made in different systems which relate to

- growth and division of bacteria, algae and protozoa,
- germination, growth and productivity of plants,
- metabolism and division of mammalian cells,
- reduction of damage to DNA by previous small exposures from a subsequent exposure to radiation and mutagens (adaptive Response),
- growth and survival of insects and rodents,
- fertility in fishes and male rodents,
- stimulation of nerve and sensory cells,
- improved immunological responses including also those against tumour development,
- lifespan and cancer in human populations,
- treatment of various diseases (infections arthrosis etc) by external radiation or spas.

However, the adaptive response is certainly the most interesting and important aspect of hormesis and will therefore be treated in the following lecture by Prof. Léonard.

Observation on Hormesis in different biological Systems

Microorganisms

A substantial number of observations exist on stimulation of growth, cell division and biochemical alterations in bacteria, yeast, algae and protozoa after

very small doses. Thus the cyanobacteria Synechoccus lividus shows a reduction in growth when natural radiation was reduced from ≈ 5 μGy/d to below 1 μGy/d by shielding with 5-10 cm of lead (Fig. 2a) and this organism grows more rapidly when given additional exposure with an optimum at ≈ 100 μGy/d (31, 32). These doses are so small that a bacterium would not be directly hit by an absorption event even when exposed during a whole year. Consequently, the activating factor must come from radicals formed in the culture medium. This is confirmed by the observation that non-irradiated bacteria are also stimulated by irradiated medium and that the effect can be abolished by destroying radiation-induced hydrogen peroxide with the enzyme catalase. It should also be mentioned that the stimulating effect depends on the growth phase of the bacteria and is most notable when the bacteria must adapt to a different environment. Very similar results have also been obtained in the protozoa Amoeba tetraaurelia (Fig. 2b) (6).

In conclusion, the data on a stimulation of microorganisms by very small doses are reproducible and of interest for understanding the general mechanisms of action. They can, however, not be used as an argument for hormesis in higher organisms because mammalian cells are in close contact with each other so that an attack from radicals formed at some distance is not possible. Work on hormesis of microorganism was never very intensive and today is almost abandoned except for the group in Toulouse.

Plants

Stimulation of growth of plants by X-rays was reported already in 1898 and since almost 1000 publications have appeared on this subject, many of them in the former Soviet Union where it was hoped to increase agricultural production in this way. In contrast to the very low doses acting on microorganisms, stimulation of plants was seen after doses in the order of Sv and even several tens of Sv. During recent years, interest has faded since results were not very reproducible. Miller and Miller (28) examining 208 reports of which 147 claimed a stimulation, found only 35 which were internally replicated and, of those, only 21 were statistically evaluated. None of the scoring was done blindly. The average stimulation in these 21 reports was of the order of 10%. Sax (39, 40) reviewing the USSR paper observed that many of the marked effects claimed in Russian papers could not be substantiated in the USA. Seeds irradiated with doses in the order of a few Sv often displayed earlier germination and growth and, sometimes, an improved crop yield (41) (Fig.3a). However, results have been variable, and many factors affect the hormetic response e.g., humidity of seeds, time of storage; thus, an application for agriculture is not feasible. Irradiation of growing plants yielded stronger branching, more flowers and fruits. An example for stimulation of the aquatic

plant Lemnia is shown in Fig.3b (10).

In conclusion, hormesis in plants, where it exists at all, occurs only at doses close to those causing damage. One may explain the stimulation of seeds by a better transfer of water; the stimulation of plants may be due to damage to the meristem in a similar way as the gardener pinches buds to get more branching and flowering.

Eukaryotic cells

Data on hormesis of isolated cells are not very impressive except, of course, for the adaptive response discussed elsewhere. A response of a different type, but perhaps ultimately also related to an induction of repair processes by radiation, has been observed in haemopoietic cells by the group of Feinendegen. Following a whole body exposure of mice to as little as 10 mGy, thymidine kinase is depressed and iododeoxyuridine incorporation into DNA is increased after about 4 hours with recovery after about 6 hours and a refractory phase thereafter. This effect is already fully present at about 10 mGy and does not further increase at 1 Gy. The response can be modified by several factors; results indicate that radical detoxication is involved in the mechanism (8).

Growth and lifespan

During the years 1920-1970, several studies reported a longer lifespan of lower animals insects, worms, etc., exposed from a few to tens of Gy (Fig.4a) (7). Although these experiments were not all carried out under optimal conditions, the results appear valid and could be explained by the fact that these animals normally replace their cells rarely unless stimulated by tissue loss. Radiation-induced cell death would thus cause a regenerative response resulting in rejuvenated cells which could make the animal survive longer.

A longer life span has also been observed in continuously irradiated mice (about 1 mSv/d) carried out by Lorenz (23) and coworkers at the Argonne National Laboratory in 1947 (Fig 4c) (5, 45). These mice had fewer inflammatory changes but more ovarian, lung, mammary and lymphatic tumours and, especially the males, gained more weight, mainly as abdominal fat (Fig.4b). Similar observations were made elsewhere and in other species. Very careful Japanese studies (38) showed, however, that survival is reduced in female mice already at 29 mSv/d and in males at 85 mSv/d. Thus, even if this effect were to exist- one may doubt in view of the less than optimal animal care during these earlier experiments - it would be limited to a very small dose range and over a limited period of time. It should be recalled in this context that not all tumours increase after irradiation, some types, with a high natural incidence,

are actually reduced at doses in the order of 1-3 Gy. In conclusion, the studies on longevity, although potentially valid, have only limited value for proving hormesis.

Several investigations in the years 1950-1960 found a higher LD 50 for acute radiation damage after a challening radiation dose, especially in younger animals. Recent Japanese studies (43) using a challenging dose of 50 or 100 mSv observed a substantial increase in survival of mice after 7.75 Gy. This is probably due to an overshoot repair as shown by the increased number of colony forming cells in the spleen of these animals.

Fecundity

A substantial number of earlier observations suggested that irradiation promotes fertility in lower animals. Irradiation of trout sperms with 250 and 500 mGy (30) produces more embryos, reduces embryo mortality and might even result in a higher fertility of descendants (Fig.5a). These data have been confirmed. One may speculate that irradiation of the sperms induces an adaptive response which allows more embryos to pass the difficult early phase of embryonic development; alternatively the more vital surviving sperms might engender the more resistant descendants.

Female mice exposed, under hypoxia, to doses of a few tens mSv (20) show a short-term increase in fertility due to a more rapid maturation of surviving oocytes before becoming ultimately sterile as do those exposed to higher doses. On the other hand, male mice kept in an area of high natural radioactivity engender a greater number of offsprings (Fig.5b)(19). The latter observation might be related to a stimulation of vitality which man also seems to experience in radioactive spas.

Immunology

Already in 1909, a greater resistance of irradiated mice toward bacterial disease was reported (35) followed by observations on more rapid healing and cicatrising of wounds, better repair of fractures, a delay in the growth of spontaneous or chemically-induced tumours (Fig.7a) (22), etc. These effects were usually seen after doses in the order of 1 Gy, and encouraged and seconded clinical observations. Many of these earlier observations are difficult to evaluate retrospectively with regard to experimental criteria and conditions of exposure. Recently, attention to this topic has resurged and given rise to highly interesting results based on modern immunological methods. Careful studies have confirmed the earlier observations on an activation of the immune response by small doses (reviews 1, 33) and have also shown that the

autoimmune response may be down regulated by irradiation (14, 16). In judging these different results, which we cannot review in detail, one must remember that the immune system depends on a finely tuned interplay of different cellular and humoral factors. Antibodies or foreign cells must be recognized, the signal be transmitted to the immune effector cells and these cells must be activated and/or stimulated for cell division. At each step, activating as well as inhibiting factors maintain the immune response at optimal conditions. Factors which could play a role after radiation are the greater radiosensitivity of those cells which restrains the immune response (the suppressor T cells) compared to those (the helper cells) which promote it (Fig 6b) (27). Other mechanisms could be a stimulation of the cell division of immune cells, the mitogenic response (Fig. 6a) (15) or an activation or increased expression of genes.

In conclusion, small doses of radiation do not damage the immune response, as some have pretended after the Chernobyl accident, and can be beneficial under certain circumstances. Of course, damage to the immune system at doses above 1-2 Gy is an important deleterious factor in the radiation syndrome.

Effects on Sensory Organs and Nervous Tissue.

Sensory and nerve cells are most responsive to ionizing radiation reacting via still poorly understood mechanisms which are almost certainly not related to an action on DNA. Most likely, these reactions are neither beneficial nor harmful. They are all characterized by the fact that it is the dose rate rather than the total dose which determines whether a reaction will ensue. That X-rays can be "seen" has been reported already in 1896 soon after the discovery of Roentgen and has been confirmed in many species when dose rates in the order of some tens of mSv/sec were given for less than 100 msec (ie doses of less than 1 mSv) (21). Other radiosensitive nervous functions are (reviews 17, 18): snails retract their antennas 5-15 sec after being exposed to a dose rate of 1.5-2 r/sec (13); moths start to beat their wings less than 1 sec after exposure to 0.01-1.5 r/sec; planaria move away from the radiation field at levels of 1.5-9 times background radiation; daphnia swim downward at an exposure of 3 r/sec. Similar observations exist for higher animals: rats develop an aversion towards saccharin - which they normally relish - when it is given at 30 R or more gamma-irradiation or are aroused when exposed to 0.25 r/sec for less than 1 sec. Other observations, many of them from Soviet scientists, deal with conditional reflexes. It is regrettable that this research area has been altogether abandoned in recent years since it would be important to characterize these unknown cellular target structures which respond so readily to radiation, ie when, on the average, less than one absorption event occurs in a cell.

Human Epidemiology

Human populations have been investigated for longevity and cancer incidence in several areas where natural background radiation is elevated, ie, the Guangdong province in China (≈80.000 persons with a threefold excess of natural exposure compared to a control province) (43), the Kerala region in India (500.000 persons with an average of 7 mSv/y and some as much as 15 mSv/y) (29) and are now under way in several areas of Europe and the USA. Most of these data have not revealed any difference compared to controls; some indicated a slight increase in lung cancer and none displayed a clear reduction of mortality when confounding factors were eliminated. Mention should be made of an earlier investigation on mortality in different areas of the USA (12) with higher mortalities in the Eastern States than in Colorado which has a high natural background. Obviously, social factors and pollution play an important role in this case.

Studies on workers in the nuclear industry showed rarely a slight increase in some cancers - not always the same and in a consistent manner - but also indicated consistently that these workers live longer than the population as a whole. A higher social status and better disease prevention could explain these results rather than recourse to unknown factors of hormesis. The most extensive and carefully collected data on man from the survivors of the atomic bomb explosions in Japan show a monotonic increase at low doses for all cancers except leukaemia where a non-significant trend towards a relative risk of less than one exists at about 100 mSv. This may be due to the difficulty of using appropriate controls in a population where leukaemia incidence and detectibility was increasing since World War II.

Clinical observations:

Radon spas, such as Wiesbaden, Bad Gastein etc, still have considerable appeal to patients suffering from a variety of degenerative diseases. Thus in the 1970ties about 25.000 radium bath applications were made daily in the Soviet Union (2). I must admit, that I had been extremely sceptical about the validity of these observations since many factors, beside radon, play a role when a person comes to the calm atmosphere of a spa, feels himself taken seriously for all his major and minors illnesses and respires the dry atmosphere in a mine. Recently, however, I talked to some serious physicians who perform these treatments and must admit that there may be something - but not much - to it (Deetjen in 3). On the other hand, although the additional doses to the patient are very small radioprotection of the paramedical personal working in such Spas should not be neglected.

In the past and, to a smaller degree, even today, small radiation doses are used to treat several non-malignant diseases, such as eczema, degenerative disease and local, chronic infection (42 and in 3). Small doses of whole body irradiation have also been employed to retard the spread of metastatizing cancer, and this application seems to find increased favour now.

In conclusion, small doses of ionizing radiation are still employed with success for certain diseases although much less often than previously. One may speculate that the possible benefice of this treatment are due to a promotion of the immune reaction or an adaptive response. Without promoting an indiscriminate use of small radiation doses in medicine, there are certainly diseases which can be treated with success and relatively little risk. Nevertheless, care must be exercised until the benefits are definitely proven by statistical analysis and the risks (including cancer and immune damage) have been carefully evaluated.

This review will have left the impression that there is more wind than rain to hormesis and I would fully concur with this assessment. However, there is one area which merits very serious consideration, namely the adaptive response, about which Prof. Leonard will now speak.

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Low Doses Necessary for Life?

The Idea of Prof. Luckey

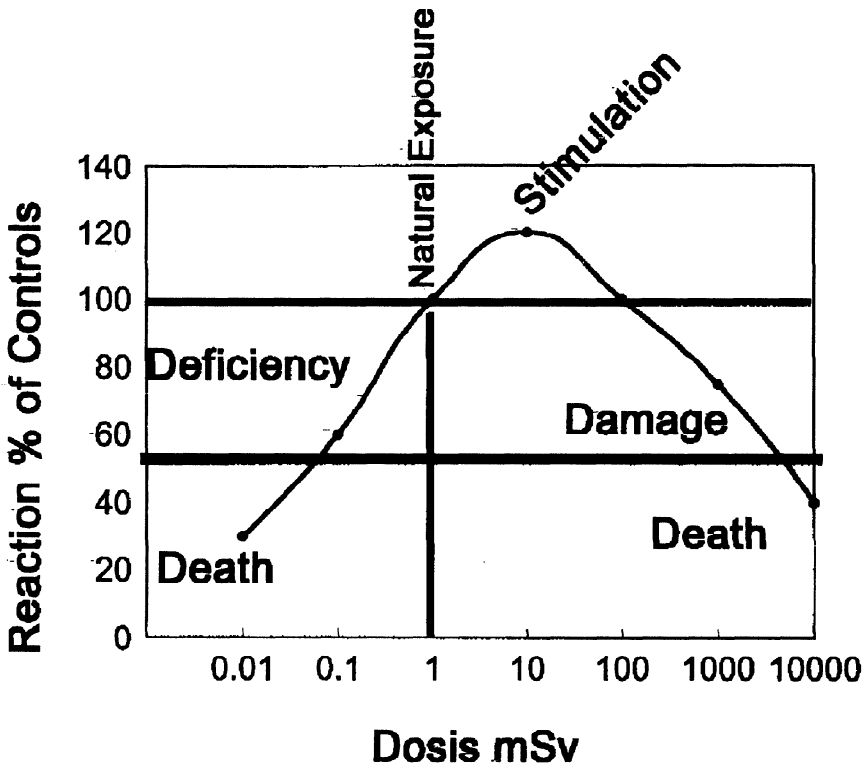


Figure 1

Hormesis in Microrganisms

Studies by Planel and Coworkers (Toulouse)

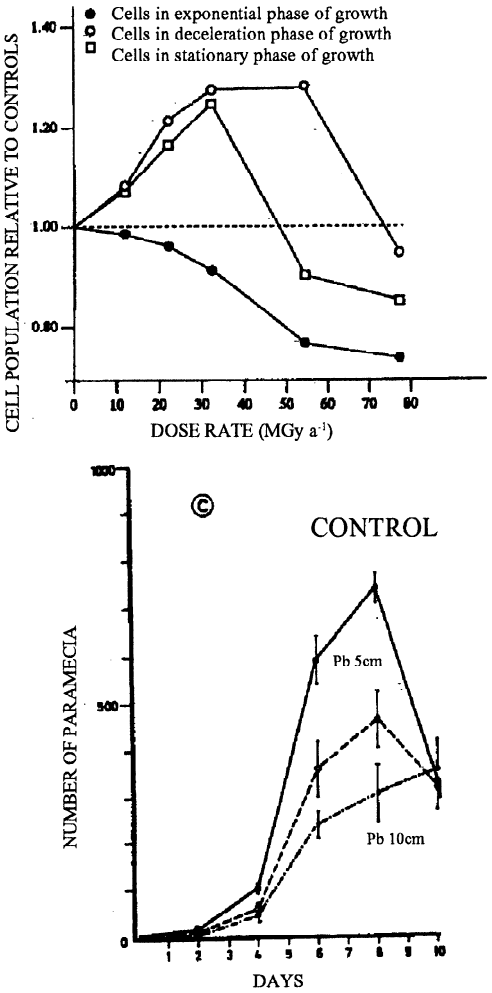
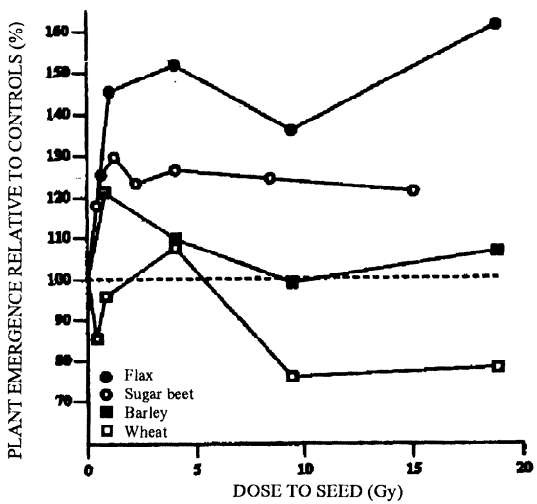


Figure 2

Hormesis and Plants

Irradiation of Seeds (Sheppard)



Irradiation of an Aquatic Plant (Feldmann)

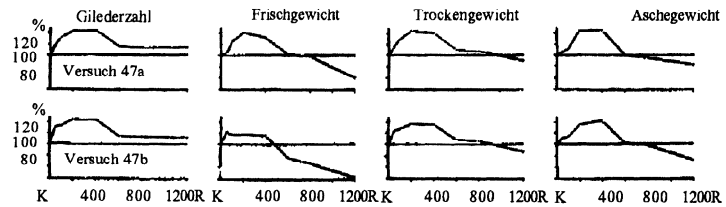
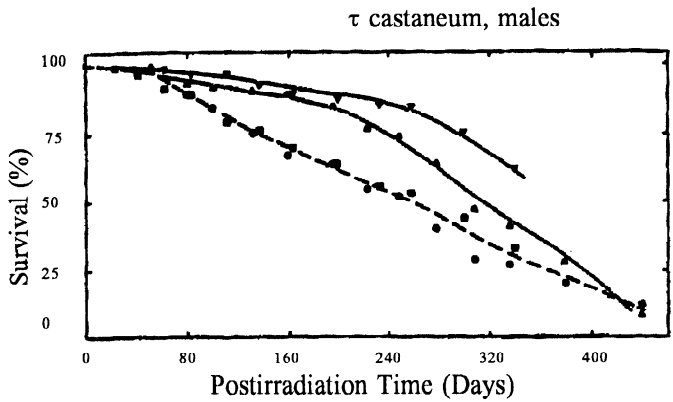


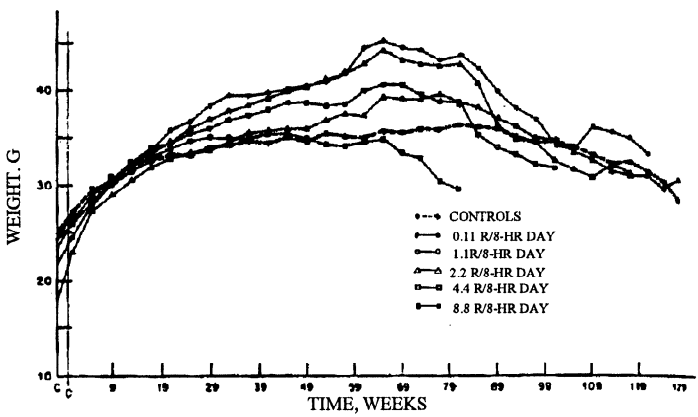
Figure 3

Hormesis and Growth

Survival Insects (Ducoff)



Growth LAF1 Mouse (Zirkle)

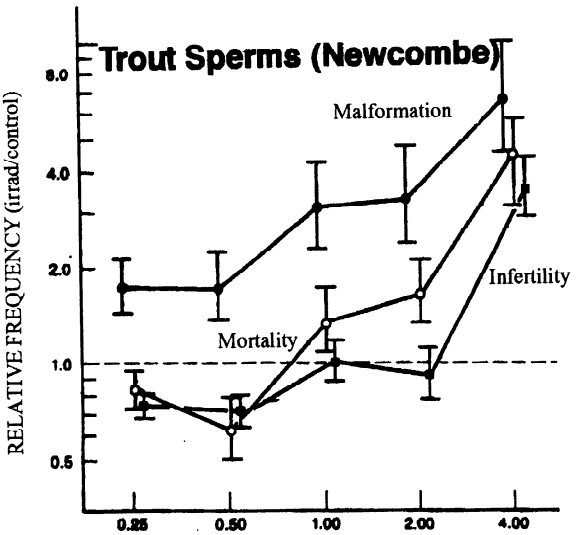


Mouse Survival (Lorenz)

Dose R/d	Sex	Mean Survival Days
0	male	683±14
0	female	803±16
0.11	male	783±14
0.11	female	820±18

Figure 4

Hormesis and Fertility



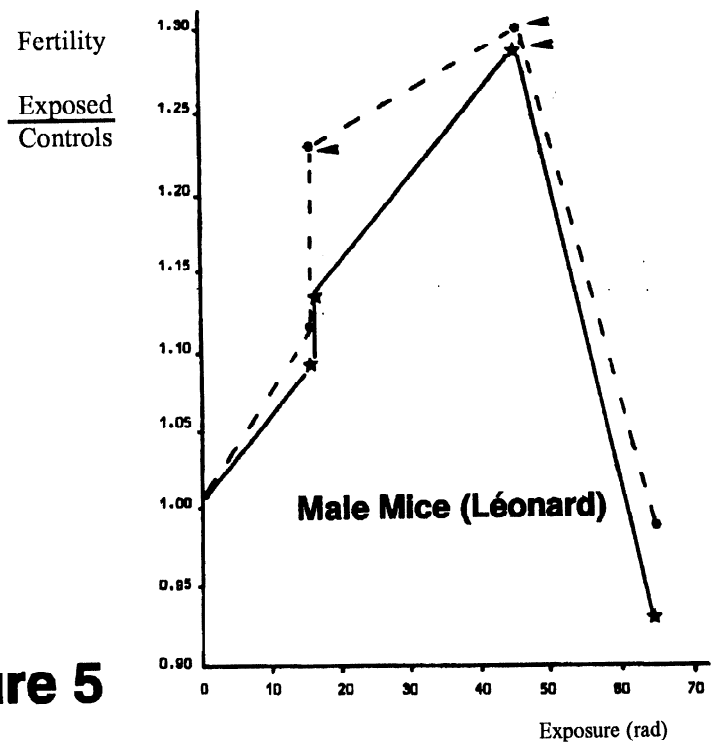
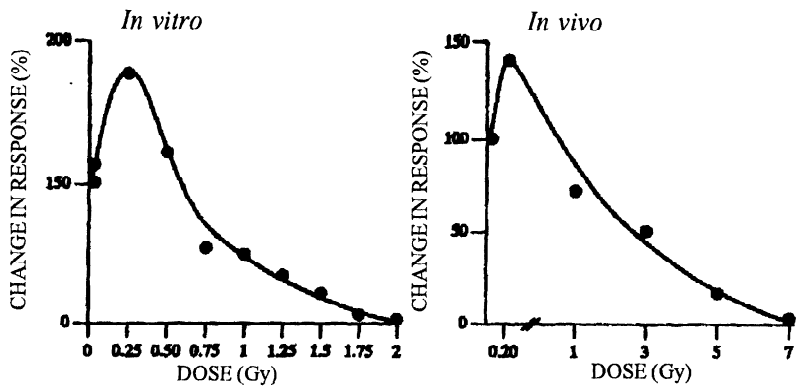


Figure 5

Hormesis and Immunology

Proliferation of Spleen Cells (Makinodan)



Ratio Helper/Supressor Cells (Kamisaku)

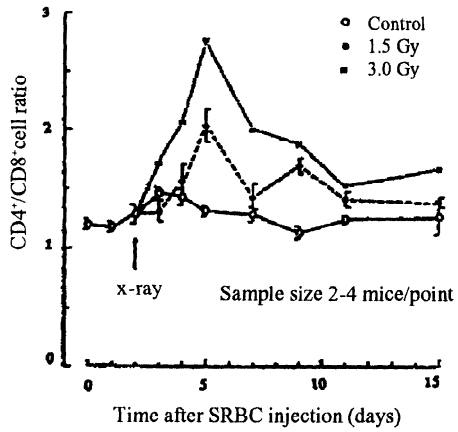
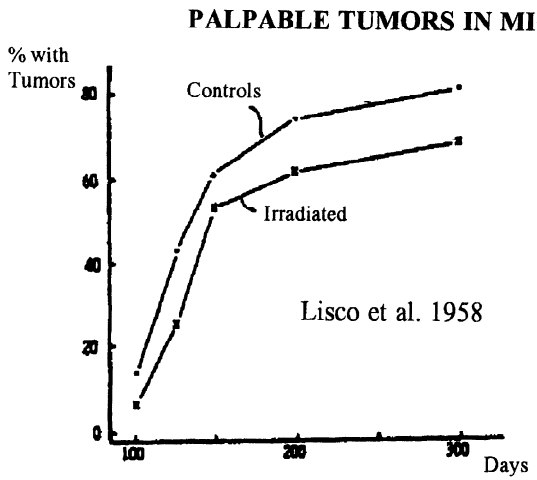


Figure 6

Hormesis and Carcinogenesis

Palpable Tumors after Methylcholanthren Administration in mice surviving 500 R (Lisco)



Cancer Frequency in States of the USA with different rates of natural exposure (Frigerio)

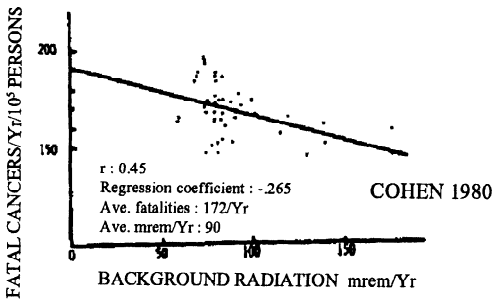


Figure 7

Résumé

Les effets stimulants (hormesis) dus à une exposition aux rayons ionisants représentent un sujet de grand intérêt du point de vue théorique et sont parfois cités comme argument dans la réglementation de la radioprotection pour des expositions à des faibles doses/débits de doses.
La présence d'hormesis est caractérisée par une relation dose effet inversée. La stimulation d'un effet par de faibles doses de rayonnements ionisants n'implique pas nécessairement un effet bénéfique. L'effet peut être délétère ou simplement sans conséquence pour l'organisme. On a beaucoup publié sur l'hormesis, mais souvent le schéma expérimental était déficient, sans contrôles adéquats, répétition desexpériences et/ou statistiques; de plus, le matériel et les méthodes étaient peu standardisés.
Les données sur la stimulation semblent mériter l'attention dans les cas de croissance et de division de bactéries, algues et protozoaires, l'excitation nerveuse et sensorielle, les réactions immunologiques et les réponses adaptatives.
Les données sur la stimulation de la germination, la croissance et la productivité des plantes, la croissance et la survie des insectes et rongeurs, la durée de vie et la prévalence du cancer chez l'homme restent à démontrer.
L'application de faibles doses dans le traitement de diverses maladies (arthrose inflammatoire, etc) sous forme de rayonnements externes ou spas devrait être réexaminée sous l'angle des risques et bénéfices. Au vu des moyens restreints en matériel et personnel en radiobiologie, la recherche devrait se concentrer à l'avenir sur la réponse adaptative et la réaction immunitaire, orientée sur les mécanismes d'action et les conséquences pour l'organisme. L'hormesis n'est pas à l'heure actuelle un argument suffisant contre une réduction des limites de doses ou pour sanctionner une dose de minimis. Les données scientifiques sont insuffisantes pour prétendre que l'hormesis peut diminuer les effets délétères (cancer et dégâts dans la descendance) contre lesquels on souhaite protéger la population. De plus, dans les circonstances actuelles de sensibilité publique et politique, insister sur l'hormesis pourrait engendrer un effet contraire.

Samenvatting

Stimulerende effecten (hormesis) veroorzaakt door blootstelling aan ioniserende stralen zijn een onderwerp van groot belang op theoretisch vlak en worden soms aangehaald als argument bij het reglementeren van de stralingsbescherming bij de blootstelling aan lage dosissen/lage dosisdebieten.
Hormesis wordt gekenmerkt door een omgekeerde dosis-effect relatie.
Stimulatie van een effect door kleine dosissen ioniserende stralen impliceert niet noodzakelijk een gunstig effect, dit kan schadelijk zijn ofwel zonder

gevolg voor het organisme. Heel wat werd gepubliceerd over hormesis maar dikwijls was de experimentele opzet deficiënt, zonder passende controles, herhaling van proefnemingen en/of statistieken. Materiaal en methodes waren dikwijls weinig gestandaardiseerd.
Gegevens i.v.m. stimulatie blijken betrouwbaar v.w.b. stimulatie van groei en deling van bacteriën, algen en protozoa, zenuw en sensiebele excitatie, immunologische reacties en adaptatieve antwoorden.
Gegevens over stimulatie van het ontkieming, de groei en de produktiviteit van planten, groei en overleving van insecten en knaagdieren, levensduur en kankermorbiditeit van de mens blijven twijfelachtig. Toepassing van lage dosissen in de behandeling van verschillende ziekten (infectieuse arthrose) uitwendig of langs spa zou moeten herzien worden in functie van de risk-benefit. Aangezien de geringe middelen in mankracht en materiaal, zou de research in de radiobiologie best georiënteerd worden naar de actie mechanismen en de gevolgen voor het organisme. Hormesis is geen voldoende argument tegen de mindering van de dosislimieten of om de deminimis te bevestigen. Wetenschappelijke data zijn nog geen passend argument om te beweren dat hormesis de schadelijke effecten kan minderen (kanker en schade aan de afstammelingen) tegen dewelke men de populatie wenst te beschermen. Daarboven, in de huidige omstandigheden van publiek en politieke gevoeligheid zou het verkeerd zijn het hormesis argument aan te halen.

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LA RÉPONSE ADAPTATIVE AUX RAYONNEMENTS IONISANTS

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Résumé

L'exposition in vitro de lymphocytes humains à des doses de 0,5 cGy à 1cGy de rayonnements ionisants de TEL faible réduit fortement les effets que peut avoir l'exposition ultérieure de ces cellules à des doses plus élevées. Cette réponse adaptative a été mise en évidence pour d'autres types cellulaires et existe également en cas d'exposition in vivo. Elle se traduit, notamment, par une diminution du taux de dommages chromosomiques produit par la seconde dose mais aussi par une diminution des mutations géniques et un accroissement de la survie cellulaire. Elle n'est pas spécifique aux rayonnements ionisants et on a démontré qu'elle pouvait être induite par toute une série d'agents environnementaux, des maladies ou des facteurs cellulaires intrinsèques. Cette réponse adaptative s'accompagne de la synthèse de protéines qui interviennent probablement dans la réparation des dommages produits à l'ADN et aux protéines cellulaires.

Pendant de nombreuses années, les travaux de Planel (1965) sur Paramecium ont été considérés avec une certaine condescendance et n'ont suscité qu'un intérêt amusé. Ce protozoaire paraissait, en effet, tellement éloigné des eucaryotes en général, et de l'Homme en particulier, qu'il paraissait abusif que l'on puisse leur extrapoler à eux, les effets bénéfiques que les études de ce chercheur avait mis en évidence. Ce n'est que lorsque ces observations ont été confirmées pour des organismes supérieurs tels que les plantes et surtout les mammifères qu'on a réellement pris conscience de la réalité de ces effets. L'importance que l'on accorde à ces effets positifs d'une exposition à de faibles doses de rayonnements s'est d'ailleurs concrétisée par l'organisation de 3 réunions internationales à Oakland en 1985, à Francfort en 1987 et à Kyoto en 1991.

1. Caractéristiques générales de la réponse adaptative

Comme cela a été indiqué dans l'introduction, et même si nous nous occupons principalement de radioprotection, il est bon de rappeler que l'effet stimulant d'une exposition aux radiations ionisantes n'a rien de spécifique. Parmi les facteurs susceptibles de produire des effets tout à fait comparables, citons:

. Des agents environnementaux
- choc thermique
- métaux lourds
- inhibiteurs du métabolisme énergétique
- analogues des acides aminés
- substances thérapeutiques (p.ex.cytostatiques)
- rayonnements électromagnétiques ionisants ou pas

. Des maladies
- infections virales
- fièvre
- inflammation
- ischémie
- hypertrophie
- dommage oxydatif
- cancers

. Des facteurs cellulaires intrinsèques
- cycle cellulaire
- facteurs de croissance
- développement et différenciation

Chez les procaryotes, les nombreuses études, réalisées principalement chez *Escherichia coli* et *Bacillus subtilis* , ont avant tout porté sur la réponse adaptative résultant d'une exposition à de faibles doses d'agents méthylants ou de radicaux oxydants. Il est bon de rappeler que ces derniers peuvent être produits non seulement par certaines substances chimiques mais également par les radiations ionisantes. On a conclu que la réponse adaptative observée résultait avant tout d'une stimulation des systèmes de réparation qui peuvent être très divers, comme nous l'avons déjà souligné, dans le cas d'une exposition à des substances chimiques susceptibles d'altérer l'ADN de multiples façons. Les

effets bénéfiques d'une première exposition à des doses faibles de ces agents peut perdurer un certain temps n'excédant cependant généralement pas quelques heures.

Pour être complet signalons, parmi les autres explications proposées à la réponse adaptative, la possibilité de changements dans les processus métaboliques producteurs d'énergie (glycolyse, respiration aérobique, photosynthèse) qui produiraient de l'oxygène qui se fixerait sur les radicaux libres, les superoxydes produits par les électrons non-appariés des radicaux étant détruits par la superoxyde dismutase.

Chez les plantes (*Vicia faba, Allium cepa*) une réponse adaptative, évaluée par le taux d'anomalies chromosomiques produites in vitro dans les cellules de méristème a été mise en évidence aussi bien pour les agents S-dépendants (UV, agents alkylants, etc.) que pour les agents S-indépendants (radiations ionisantes, bléomycine, etc.). Le mécanisme est sensible à la température, ce qui démontre sa liaison au métabolisme cellulaire.

C'est cependant sur les cellules de mammifères que les études ont été les plus nombreuses. Parmi les cellules utilisées nous trouvons (Tableau I) des cellules humaines, des cellules murines, des cellules de Hamster et des cellules de Rat.

Tableau I

Cellules de mammifères utilisées dans les études sur la réponse adaptative

Cellules humaines	**Cellules murines**
. lymphocytes	. spermatocytes
. fibroblastes embryonnaires	. ovocytes
. lymphoblastes	. embryons préimplantés
. fibroblastes de la peau	. lymphomes
. kératinocytes	. carcinomes
Cellules de Hamster	. cellules de moelle
. fibroblastes embryonnaires	. thymocytes
. fibroblastes ovariens	. splénocytes
Cellules de Rat	
. thymocytes	
. splénocytes	

Les agents pour lesquels on a pu mettre en évidence une réponse adaptative sont:

- les rayonnements ionisants
- la chaleur
- les UV
- des mutagènes chimiques
- des anesthésiques locaux (procaïne, lignocaïne)
- des métaux lourds (mercure, cadmium)
- le manque d'oxygène
- la privation de glucose

En ce qui concerne les lymphocytes humains, qui nous intéressent évidemment plus particulièrement, cette réponse adaptative se traduit notamment par une augmentation de la survie cellulaire et par une diminution des dommages produits au matériel génétique (mutations géniques, anomalies chromosomiques, micronoyaux, échanges entre chromatides soeurs).

La réponse adaptative produite par une exposition à de faibles doses de rayonnements ionisants de TEL {Transfert d'Energie Linéique) peu élevé dépend notamment de la dose initiale d'induction : la meilleure réponse est obtenue avec des doses de 0,5 cGy à 1 cGy administrées à un débit élevé. Le développement de cette réponse adaptative prend de 4 à 6 heures et dure environ 3 cycles cellulaires. Ajoutons encore qu'elle varie parfois beaucoup d'un donneur à l'autre et qu'elle sera fonction du stade cellulaire auquel elle est administrée.

Les tableaux 2 et 3 donnent des exemples de réponse adaptative des lymphocytes humains aux radiations ionisantes. Des résultats très comparables ont été rapportés après traitement des lymphocytes avec de petites doses de thymidine tritiée, de thymidine marquée au C^{14}, d'eau tritiée ou de P^{32} (Olivieri et al, 1984; Wiencke et al., 1986; Sankaranarayanan et al., 1989), c'est-à-dire après exposition, également, à des rayonnements de TEL faible.

Tableau 2

Exemple de réponse adaptative des lymphocytes humains (Wojcik et al., 1992)

Dose de conditionnement **10 cGy après 32 h de culture**
Dose de production **150 cGy après 48 h**
Colchicine **après 50 h**
Arrêt **après 54 h**

Traitement (Rx)	**Cellules anormales**	**Cassures**
Témoins	1	1
10 cGy	7	7
150 cGy	74	300
10 cGy + 150 cGy	62	23 (P<0.05)
Témoins	1	1
10 cGy	1	1
150 cGY	21	54
10 cGy + 150 cGy	13	32 (P<0,05)
Témoins	1	1
10 cGY	2	3
150 cGy	24	61
10 cGy + 150 cGy	14	37 (P<0.05)

Tableau 3

Exemple de réponse adaptative des lymphocytes humains (Shadiey et Dai, 1992)
Dose de conditionnement 5 cGy après 12 h
Dose de production 200 ou 400 cGy après 18 h
Arrêt après 48 h

Traitement	**Dicentriques et anneaux**	**Délétions**
Témoins	0	0
5 cGy	2	0
200 cGy	61	23
5 cGy + 200 cGy	49	14
400 cGy	140	51
5 cGy + 400 cGy	102	37

On s'intéresse, depuis quelques années, au rôle que pourrait jouer le radon dans les cancers des voies respiratoires (Harley et Harley, 1990): on a été jusqu'à attribuer 10 % des cancers du poumon aux particules alpha de TEL élevé qu'il émet et au dépôt de ses produits de dégradation. Parmi les arguments qui ont été avancés à l'appui de cette théorie figure la faible réparation des dommages produits au matériel génétique par des rayonnements d'EBR élevée. Les résultats obtenus récemment par Wolff et al. (1991), et qui illustrent le tableau 4, sont dès lors particulièrement intéressants puisqu'ils démontrent qu'une faible dose (2 cGy) de rayons X diminue de façon spectaculaire le taux d'anomalies de structure produite par une exposition ultérieure à une dose de 15 cGy de rayonnements alpha. Dans cette expérience, les cellules ont reçu 2 cGy de rayons X après 48 heures de culture et ont été exposées au radon 24 heures plus tard, la fixation intervenant 8, 11 ou 14 heures après l'exposition au radon. Les résultats de Wolff et al. (1991) démontrent donc qu'une faible dose de rayons X peut engendrer une réponse adaptative aux particules alpha émises par le radon.

Tableau 4

Réponse adaptative des lymphocytes humains aux rayonnements alpha émis par le radon (Wolf et al., 1991)

Traitement cellules	Fixations (h après exposition au radon)	Nombre d'aberrations/400	
		Observées	Attendues
Témoins		4	
2 cGy Rx		10	
Radon, 16.4 cGy	8	138	
Rx + radon, 15.3 cGy	8	72	
			138.8
Radon, 16.4 cGy	11	263	
Rx + radon, 15.3 cGy	11	182	
			255.4
Radon, 16.4 cGy	14	445	
Rx + radon, 15.3 cGy	14	218	
			425.2

2. Aperçu des mécanismes de la réponse adaptative

En ce qui concerne les mécanismes de la réponse adaptative, nous devons distinguer les résultats proprement dit, des diverses hypothèses qui ont été émises pour expliquer le fonctionnement.

2.1. Résultats des expériences

. La réponse adaptative demande un certain laps de temps pour devenir complètement opérationnelle. Après une exposition des lymphocytes à une dose d'induction de 1 cGy elle atteint son maximum 6 heures plus tard. Ceci est compatible avec l'induction d'enzymes qui répareraient les lésions produites à

l'ADN avant qu'elles ne traduisent par des anomalies chromosomiques.

. La réponse adaptative aux radiations ionisantes peut être supprimée par diverses substances inhibitrices de la synthèse des protéines (p.ex. la cyclohexímide) ou encore la 3-aminobenzamide qui agit sur la poly (ADP-ribose) polymérase, une enzyme induite par la présence de cassures à l'ADN et impliquée dans la réparation des dommages à l'ADN.

. Des études en électrophorèse ont démontré que l'exposition à des doses d'induction entraînent la production, par les cellules, de toute une série de protéines qui pourraient être impliquées dans ce processus de réponse adaptative.

. L'induction d'une réponse adaptative n'est pas spécifique aux radiations ionisantes. Comme nous l'avons signalé elle peut être produite par toute une série d'autres agents. La réponse adaptative à un agent bien déterminé peut, dans certains cas, être induite par un autre agent et inversement ; c'est pour cette raison qu'on utilise le terme général de réponse adaptative au stress.

2.2. Hypothèses émises pour expliquer le mécanisme de la réponse adaptative

Si toute une série de protéines semblent impliquées dans cette réponse, on en est encore aux stades de décryptage de leur rôle exact.

. On a pu montrer que des protéines d'un poids moléculaire de 14-18 kDa et de 30-35 kDa, dont la production est augmentée par une dose d'induction de quelques cGy, se lient aux régions endommagées de l'ADN ce qui suggère leur implication dans les mécanismes de réparation (Wolff, 1992).

. On a démontré qu'un stress cellulaire provoqué par une température élevée, des métaux lourds, des toxines, des agents oxydants, des infections virales ou bactériennes se traduit par une synthèse élevée de "heat shock ou stress induced proteins" (pour revue Morimoto, 1993 et Welch, 1993). Ces protéines jouent un rôle essentiel dans la synthèse, le transport et l'assemblage des protéines cellulaires. En cas de stress un "Heat Shock Factor" (HSF) présent normalement sous une forme monomérique dans le noyau et le cytoplasme se lierait momentanément, sous forme trimérique, á des régions spécifiques de l'ADN,

pour accroître la production des "stress-induced proteins" que les gènes de ces régions contrôlent. Le poids moléculaire de ces hsp se situerait dans la région de 70 kDa. Certaines formes de ces hsp 70 seraient identiques á l'"immunoglobulin binding protein" (BiP).

On a identifié chez certaines bactéries des gènes (GroELet GroES) qui permettent l'assemblage correct des protéines des virus qu'elles contiennent. Des mutations de ces gènes empècheraient cet assemblage. Des protéines comparables (hsp 10 et hsp 60) aux protéines produites par les gènes GroEL et GroES auraient été identifiées chez les plantes, la levure et les cellules animales.

Conclusions

Beaucoup d'agents, comme nous l'avons vu, peuvent entraîner une réponse adaptative non seulement aux radiations ionisantes mais également à d'autres facteurs de stress. Si l'on tient compte du fait que les résultats in vitro sur cellules de mammifères ont, dans certains cas, été confirmés par des observations in vivo sur les cellules somatiques et reproductrices d'animaux de laboratoire (Cai et Liu 1990; Cai et al., 1993) il se pourrait que l'on aie parfois surestimé les effets à long terme d'une exposition à des faibles doses d'agents nocifs tels que le radon ou les rayonnements ionisants. Dans ce dernier cas, cela est d'autant plus plausible que l'appréciation des effets des faibles doses se fait toujours par extrapolation linéaire des résultats obtenus avec de fortes doses. Ceci démontre aussi les difficultés de l'extrapolation, à l'Homme, des résultats d'expériences réalisées sur animaux de laboratoire dans des conditions supprimant notamment l'exposition simultanée à d'autres agents de stress.
Si rien ne permet d'affirmer que cette réponse adaptative existe réellement in vivo pour l'Homme il est néanmoins probable que c'est le cas et qu'elle a joué un rôle dans l'évolution.

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Summary

Adaptive response to ionizing radiation
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In vitro exposure of human peripheral blood lymphocytes to 0.5 cGy - 1 cGy doses of low-LET radiation decreases the damage produced by a further exposure to a few Gy. Comparable adaptative response has been shown to exist in various other cell types and in vivo in laboratory animals. It mainly results in a decrease of chromosome aberrations and genic mutations produced by the second exposure and in an increase of cell survival. This response is not specific to low-LET radiation and can be induced by several environmental factors, viral and bacterial diseases and intrinsic cellular components.
The adaptive response probably results from the activation of genes controlling production of enzymes involved in the repair of DNA and cellular protein damage.

Samenvatting

Het in vitro blootstellen van menselijke lymphocyten aan lage ioniserende stralingen van 0,5 cGy tot 1 cGy, vermindert aanzienlijk de invloed die deze cellen kunnen hebben aan de blootstelling van een volgende hogere dosis. Deze aanpassing wordt reeds aangetoond met andere cellulaire types en bestaat reeds in geval van een expositie in vivo. Dit wordt onder andere aangetoond door een vermindering in de aantasting van de chromosomen veroorzaakt door de tweede dosis maar ook door een vermindering van de genische mutaties en een

verbetering van het in standhouden van de cel. Zij is niet specifiek aan de ioniserende stralingen en men heeft vastgesteld dat een hele reeks van andere factoren, zoals omgevingsfactoren, ziekten en innerlijke cellulaire criteria, hetzelfde resultaat geeft.
Deze adaptatie gaat gepaard met een synthese van proteïnen, die waarschijnlijk tussenkomen in het herstellen van de schade veroorzaakt aan het ADN en aan de cellulaire proteïnen.

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CONCLUSIONS AND PERSPECTIVES

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Now that the facts about the stimulating effects of small doses of ionising radiation have been presented to you, we need to consider the consequences with respect to three aspects, namely, possible mechanisms of action, future research needs and implications for radiation protection.

The **study of the mechanisms of action** of the proven stimulating effects of small radiation doses are among the most interesting topics of radiation biology today and are relevant for other aspects of cellular biology as well. For example, the adaptive response to minor DNA damage might be indispensable for the organism to keep its enzymatic repair systems fully active. Earlier, it was stated that observation on hormesis should be accepted only in so far as they make sense from a microdosimetric and biological point of view. Regarding microdosimetry, Prof Menzel explained that the distribution of tracks in space for the different types of radiation results in a situation where below a certain dose level, the number of cellular targets hit decreases with dose but the energy deposited in each affected target remains the same.

From a biological point of view, several mechanisms of hormesis are conceivable: an adaptive response can result in an improved repair of DNA damage from a subsequent insult; cells can be inactivated thus changing the relations between different populations or mobilizing dormant cells; the expression of cellular genes can be activated; certain effects on membranes or still unknown cellular targets can be affected: for example, in nervous cells.

In view of the paucity of means and man power in radiobiology, **future research** should concentrate only on the adaptive response and the immune reaction focusing on mechanisms of action and consequences to the organism. With respect to the adaptive response priority should be given to the questions:

- which relations exist between the different expressions of the adaptive response,
- which type of damage can elicit an adaptive response and what levels are needed,
- does an adaptive response occur in all tissues and cells and which factors determine its presence,
- is the induced repair also effective against malignant transformation and mutations and how accurate is this repair,
- how does the adaptive response behave when the insult is chronic,
- which are the mechanisms of the adaptive response: which products cause it, which are the secondary reactions and how does it induce DNA repair, which are the relations to the concentrations and detoxication of radicals, to the formation of stress proteins and the induction of the products of DNA repair (gadd 45).

Concerning the stimulation of immunological reactions, one should study:

- which are the mechanisms of the immunological stimulation? increased ratio CD4+/CD8+ (helper/suppressor), mitogen stimulating factors, antigen recognition, antibody synthesis, relations to adaptive response,
- how do other constituents of the immune system participate: Macrophages, cytotoxic cells, B cells, cytokinines, interleukin, kinases,
- what are the long-term consequences of the higher radiosensitivity of the suppressor cells? increased risks of auto-immune diseases, overshoot reactions...
- how can clinical research be carried out on the immune response after irradiation: in spas, whole body exposure of cancer patients with small doses, exposure against inflammations, arthrosis etc

It has been argued that **radiation protection regulations and practice** should take account of potential hormetic effects, and that hormetic effects could be used as an argument against the further reduction of dose limits and the application of the ALARA (As Low As Reasonably Achievable) principle at doses below a certain level and could also be invoked to sanction the introduction of a de minimis dose or of exemption levels. Personally, I doubt that the hormetic argument will find favour with the public or law givers because it could only be justified if the hormetic effect would counteract those effects against one wants to protect, i.e. cancer or genetic damage or if the

benefice would be so large as to offset any other possible damaging effect. The first possibility remains to be demonstrated although it cannot be excluded a priori in view of the observations of an induced DNA repair. Nevertheless, under present circumstances, it would be very difficult to convince the public and law makers that the benefit from other types of stimulating effects, such as a more rapid growth, stimulation of certain immunological functions etc, even if proven, would outweigh the potential risks of excess cancer.