FROM RESEARCH TO REGULATIONS

When nuclear energy came into use it was recognized at the outset that we would need to keep constantly abreast of the latest advances in knowledge in order to give the soundest possible scientific basis to the regulations designed to protect operatives and the general public from the potentially harmful effects of ionizing radiation. In the years to come the experts will have at their disposal many new findings through the advent of ultra-precise techniques of experimental radiation and global approaches to the genome. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) plays a vital role in the analysis and synthesis of the most recent research results for the purpose of evaluating these effects more accurately, especially for low radiation doses.

The village of Borovaia Glinka (Belarus) in 1994, contaminated after the nuclear disaster at Chernobyl (Ukraine) in 1986.

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"Exploding" research results

Experts working to provide the authorities with the best possible scientific basis for regulating exposure to **ionizing radiation** are expecting an «explosion» in available radiobiological data in the years to come. This new wealth of results will owe much to technical developments in irradiation methods, which will make it possible to cause single targeted **DNA** lesions within a cell, and to global approaches to the genome and cell function through the study of the transcriptome and the proteome(1). Thus it should be possible to measure the modifications induced by a single radio-induced lesion, and to analyze the influence of the genetic context and the tissue environment on the response.

At present the main source of information for radioprotection is epidemiology, especially the study of the survivors of Hiroshima and Nagasaki (Japan), despite some dosimetric uncertainties. Although the experimental models are more and more thoroughly documented, and the knowledge of mechanisms and dose rate effects more and more extensive, the synthesis of radiobiological research findings comes up against a number of difficulties. The results that have accumulated over the last decades, as regards damage repair mechanisms, **cell** response, genetic instability and cell transformation (see *Chromosomal Instability and Radio-induced Cancer*), give insight into the parameters that govern certain steps in the processes of **mutagenesis** and (or) **carcinogenesis**. Even so, these mechanisms are still insufficiently well-known to permit a general description according to radiation type, **dose**, **dose rate** and associations with other agents. The direct investigation of low doses (box 1) has till now been held back by the insufficient sensitivity of the detection methods and number of parameters that could be studied simultaneously.

The role of UNSCEAR

These radiobiology research results have to be rapidly integrated by the international bodies that ensure the scientific basis on which the relevant authorities can draft regulations. Every five to seven years UNSCEAR(2), a body belonging to the United Nations Organization (UNO), draws up scientific documentation that analyzes and reviews all the available data in the fields of radiobiology, radiopathology and radiation exposure and its effects (box 2). These periodical updates also include a review of the sources of exposure, which will not concern us here, and the biological effects of ionizing radiation, a radiobiology research topic dealt with elsewhere in this issue. The interest elicited by these effects is justified by their mechanisms of action, which apply to all types of cell, and which mostly prove to be relevant to other contexts, and also by the absence of any apparent specificity of the cancers or hereditary effects induced by radiation.

The understanding of mechanisms has become increasingly important relative to the descriptive study of the observed effects. Thus in the course of the last ten years research has focused on the mechanisms of radio-induced carcinogenesis, the influence of dose rate on these effects, adaptive reactions, effects on the environment (reviews published between 1993 and 1996), mechanisms of DNA repair and mutagenesis, and the effects of low doses (forthcoming). These documents attest the advances in knowledge in this area. Their purpose is also to present, on a sound scientific basis, all the recent data to help arrive at an estimate of the risks of **stochastic** effects, whether harmful or beneficial, and to pinpoint uncertainties or misconceptions that further research ought to address.

1 Low doses

Low doses are defined as doses for which no biological or health effect can be observed. This level depends on:

- The **diagnostic means** available to identify specific damage due to the action of ionizing radiation.
- The **exposure conditions**, the lower limit corresponding to acute irradiation.
- The **sensitivity of the organism**, the lowest harmful levels being found in the fetus and infant.
- The **sensitivity of the target organ**, e.g., the thyroid in children. In adults acute doses below 200 mSv are considered as low doses. But in children cancers of the thyroid are observed above 100 mSv delivered to that organ. In the fetus the results are controversial, but there may be a risk of cancer above 10 to 20 mSv.

(1) The **proteome** defines the translation, under given conditions, of genes into proteins from messenger RNA transcription, the **transcriptome** being the expressed part of the genome of a cell under these same conditions.
(2) United Nations Scientific Committee on the Effects of Atomic Radiation.

AFP

A former worker at the Bayard factory at St-Nicolas-d'Aliermont (Seine-Maritime, France) shows an alarm clock the manufacture of which entailed significant exposure to radium.

New research directions

Cells models, ***in vivo*** experimental models and **epidemiology** have long contented in terms of relative efficiency in the measurement of the effects of different types of radiation, e.g., nature and levels of DNA breaks, **chromosomal** modifications, cell death, **mutations**, transformations and excess prevalence of cancer. But with the development of more powerful techniques, the study of radiation mechanisms in the strict sense and the understanding of the corresponding physiological behavior at the cell level have become increasingly intermeshed. Areas of overlap concern in particular the **cell cycle**, proliferation and **differentiation**, **apoptosis**, DNA repair, **replication** and recombination, conditions for **gene** induction, genetic instability, etc. Outside physiology the common objective of radiobiology and cell biology is to understand the mechanisms of response to different types of stress (oxidative, thermal, radiation, etc.) and to analyze the factors that influence the return to equilibrium. The frontier between these two fields of study has become blurred, as we can see in the contributions to this issue.

This common direction hinges without a doubt on DNA. The UNSCEAR overview on repair and mutagenesis gives prominence to those elements that have recently evolved. Only a few examples will be cited here.

The numbers and distribution of initially induced lesions must thus be looked at again using more sensitive and more specific tools (see *Radiation-induced Damage to Nucleic Acids*). However, it does seem that complex damage is probably much more typical of the action of radiation than of other mutagens.

2 The raw material of UNSCEAR: all the facts and nothing but the facts

UNSCEAR[2]) brings together scientists from twenty-one different nations. It was set up in 1955 by UNO to gather as much data as possible on levels of exposure due to various sources of ionizing radiation and their biological, health and environmental consequences. This exhaustive factual review is accompanied by an analysis of the underlying biological mechanisms to help explain the observed effects and provide a basis for an extrapolation to doses at which effects can be considered nil or too weak to be observable.

The list of documents currently being discussed by UNSCEAR and which are to be published in 2000 illustrates the extent of this work, which covers two important areas:

- **Exposure sources**. UNSCEAR issues a regular report on the current situation supported by data from all countries. These periodically published reviews form an irreplaceable sum of information on how the exposure of populations is evolving according to the source of radiation (natural, ionizing radiation of human origin, medical and professional exposure, etc.).
- **Impact assessment**. UNSCEAR scrutinizes experimental evidence, dose estimates, human data, models and extrapolation methods. In this area it issues documentation covering the following: methods of dose estimation, epidemiological evaluation of radio-induced cancer, DNA repair and mutagenesis, hereditary effects of ionizing radiation, combined effects of irradiation and other agents, biological effects of low doses (models, mechanisms and uncertainties), and exposure and effects of the Chernobyl nuclear reactor accident.

However, it is not possible to predict the average incidence of mutations for a particular dose, in particular because misrepair of DNA can itself be mutagenic.

Methodologically, the conservation of mechanisms during evolution permits the use of simplified models such as **yeasts** (see *The Caretakers of the Genome, Effects of Radiation on the Cell Cycle*) to help identify, in mammals, the many genes implicated in the early effects of radiation, from initial lesions to mutagenesis. In cancer cells the pathways controlled by these genes (cell division, apoptosis) are often defective.

The study of radiosensitivity draws benefit from available knowledge concerning genetic disorders of the repair mechanisms (*ataxia telangiectasia*, Fanconi's anemia, etc.) that are accompanied by an increased sensitivity to radiation and a high risk of certain types of cancer. Their analysis has confirmed the intricacy, complexity and sometimes the redundancy of the repair systems that intervene in the early cell response (repair and recombination, cell division cycle, apoptosis) and in deferred instability (see *Chromosomal Instability*). Moreover, the study of the complex systems brought into play during repair has shown the multiplicity of the functions of the genes involved in the recognition and signaling of damage and in the blockage of the cell division cycle. It has also demonstrated the cooperation of the different molecular pathways in maintaining the stability of the **genome** and cell survival, the genes assigned to double-strand breaks repair also operating in immune function. Hence human radiosensitivity may be linked to a much greater number of genes than was initially estimated.

Weakly specific mechanisms

Finding a lesion or a mechanism that is specific to radiation is becoming increasingly complex, at least for low levels of exposure. Some of the mechanisms described in this issue are also brought into play in the course of physiological processes, such as apoptosis during embryogenesis or genetic instability in aging, as a response to stress from various sources, and during pathological processes such as carcinogenesis. Even as regards initial damage the range of radio-induced lesions, although distinct from that of spontaneous lesions, overlaps it to a very large extent. A large amount of data indicates that the mechanism of formation of lesions and of DNA repair may not be the same at high and low dose rates, and that at least some of the mechanisms involved may be induced by prior exposure to radiation or other toxic agents that accordingly modify the dose-effect relation.

Research areas ripe for development

Concerning hereditary effects research has so far focused on the analysis of **dominant** mutations. However, the study of mechanisms of transmission of **recessive** mutations and their consequences on subsequent generations seems bound to expand (see *Radio-induced Genetic Risk Estimated*).

Alongside research into the consequences of DNA damage, studies of the influence of epigenetic factors(3) show that these are liable to modulate or even change response to radiation, especially at low exposure levels. This is the case for intercellular communication, secretion of mediators, the «bystander effect», i.e., the occurrence of lesions in a cell that has not been directly irradiated, and the role of cells of the immune system, in particular polynuclear cells. However, little is known at present about the respective roles of mutations and epigenetic events, which cannot be predicted from effects observed at high doses.

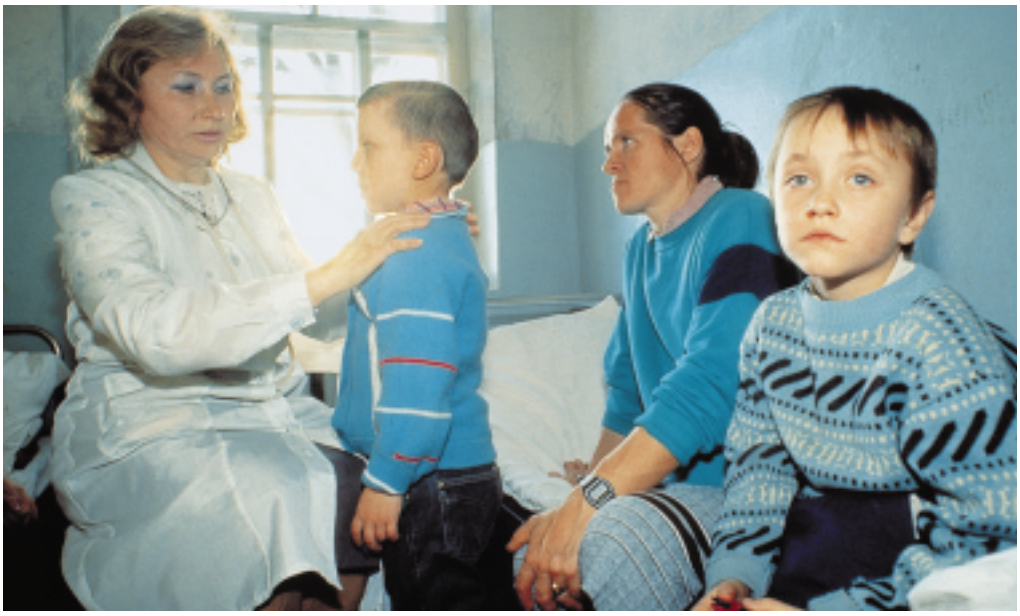
Low doses: toward specific regulations for protection

Radioprotection measurements made in the course of the last seventy years have eliminated from the work place the pathologies induced by high doses, and have reduced the risk of adverse effects possibly attributable to low level exposure. The contribution of radiobiology to radioprotection is threefold: (i) identification and characterization of effects and risks of low level exposure, (ii) determination of major hazards according to the characteristics of both the source and the subject, and (iii) proposal of dose-effect relations on the basis of experimental results and knowledge of mechanisms. The ultimate objective is to establish rules for protection from low level radiation directly, without extrapolation.

What are the predominant effects and risks at low doses? Until now the purpose of radioprotection was to protect persons from the consequences of mutagenic effects, i.e., cancers and hereditary effects. Insofar as no hereditary effects have yet been found in man, efforts have been concentrated on the mechanisms of carcinogenesis. But the potential significance of recessive mutations in the occurrence of hereditary effects (see *Radio-induced Genetic Effects Estimated*), together with recent results showing the importance of epigenetic effects and the influence of irradiation on immune functions and aging(4), may challenge the relative importance attached till now to the carcinogenic hazard.

How can a hazard be estimated through integration of scientific data? Radiobiology provides qualitative and quantitative results. Qualitatively, the study of the effects of ionizing radiation focuses on the identification of molecular and cellular mechanisms, both to understand the processes by which these effects appear and to know more about the factors that modulate them, such as genetic predisposition, age-related sensitivity, and the behavior of irradiated

(3) These factors intervene in the responses of the cell, tissue and whole organism to ionizing radiation. They result in a modification, most often transient, of the expression of genes and proteins without modification of the genome itself.
(4) These results are supported by the last report on the monitoring of the survivors of Hiroshima and Nagasaki, which shows an excess death rate from non-cancer-related causes such as heart, cerebrovascular and lung disorders above a threshold of 0.5 to 1 Gy.



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Thyroid screening in children in a hospital at Gomel (Belarus), particularly affected by the nuclear disaster of Chernobyl (Ukraine).

tissue. Such knowledge can be increasingly quantified. The study of the influence of dose rate and factors linked to the subject, as a function of radiation type, has shown the importance of individual radiosensitivity, and more fundamentally of dose rate, both on early effects such as DNA repair and on the incidence of transformation or cancer prevalence. For low level exposures, there is increasing evidence that dose rate may be more relevant than cumulated dose. This raises once again the

Further work necessary

Other topics deserve further work, especially concerning the catenation of the biological processes taking place between exposure and effect, their relative importance, the influence of genetic and environmental factors on the kinetics and level of action of the mechanisms brought into play, and the reversibility of certain steps. More general questions cannot be systematically addressed at present from available research results. These concern the representativity of the results obtained at the molecular and cellular levels and biological uncertainties.

Current understanding of the mechanisms operating at low doses and dose rates, and especially the quantification of the effects, are still fragmentary, making it necessary to resort to models extrapolating to «low doses» the effects observed at high doses, essentially using epidemiological data (box 1). Here, the role of UNSCEAR is not so much to propose the most relevant models, which is the job of the ICRP[5], but rather to transmit the point of view of scientists concerning the representativity of the biological phenomena and the limits of validity of the models derived from them. Indeed this is one of the topics dealt with in the document concerning low doses.

There are two schools of thought at UNSCEAR concerning the analysis of the cancer hazard. The first advocates as a general rule the biological assumption of a linear non-threshold (LNT) relation, though not unreservedly. Initiation of mutations by radiation is here considered as the main step. The second, though acknowledging LNT as a practical tool in radioprotection, does not consider non-threshold extrapolation to be a biological reality. It was first of all the attenuation of effects with decreasing dose rate that justified this point of view, followed more recently by the influence of the density of lesions on the mechanisms of DNA repair and cell response.

The conclusion - provisional - is that in the absence of a synthesis of all the mechanisms in play at low doses and of quantification of the resulting effect, linear non-threshold extrapolation remains officially recommended, with a reserve concerning the form of the dose-effect relation, which is uncertain below 100 mGy (low **lineal energy transfer**). On this point also, ever faster advances in knowledge are to be expected.

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(5) International Commission on Radiological Protection.