SAFETY SERIES

No. 3

Safe Handling of Radioisotopes

Medical Addendum

INTERNATIONAL ATOMIC ENERGY AGENCY

VIENNA 1960

SAFETY SERIES No. 3

SAFE HANDLING OF RADIOISOTOPES

MEDICAL ADDENDUM

by

Dr. F. HERČÍK and Dr. H. JAMMET

INTERNATIONAL ATOMIC ENERGY AGENCY
Kärntner Ring, Vienna I, Austria
1960

THIS ADDENDUM IS ALSO PUBLISHED
IN FRENCH, RUSSIAN AND SPANISH

SAFE HANDLING OF RADIOISOTOPES: MEDICAL ADDENDUM, IAEA, VIENNA, 1960

STI/PUB/11

FOREWORD

The International Atomic Energy Agency published in 1958 a Manual entitled "Safe Handling of Radioisotopes" (Safety Series No. 1-STI/PUB/1), based on the work of an international panel convened by the Agency. As recommended by that panel and approved by the Agency's Board of Governors, this Addendum has now been prepared, primarily as a supplement to the Manual. It contains information necessary to medical officers concerned with the implementation of the controls given in the Manual. In addition, it is intended to serve as a brief introduction to the medical problems encountered in radiological protection work and to the methods of resolving them.

As in the case of the Manual itself, the information given in this Addendum is particularly relevant to the problems encountered by the small user of radioisotopes. Although the basic principles set forth in it apply to all work with radiation sources, the Addendum is not intended to serve as a radiological protection manual for use in reactor installations or large-scale nuclear industry, where more specialized techniques and information are required.

The Addendum has been prepared by the Secretariat with the assistance of two consultants appointed by the Agency, Dr. F. Herčík (Institute of Biophysics, Czechoslovak Academy of Sciences, Brno) and Dr. H. Jammet (Saclay Nuclear Research Centre, France) both of whom were among the experts forming the international panel mentioned above. The Agency believes that this Addendum will provide information of great value and publishes it for whatever use Member States and others may wish to make of it. However, it should not be regarded as representing the Agency's official judgment or policy on the matter.

August 1960.

Director General

TABLE OF CONTENTS

1. BASIC CONCEPTS

A. Radiobiology

I. Action of ionizing radiation

(a) Types of radiation. Primary events

This handbook surveys some of the medical aspects of ionizing radiations and is mainly intended as a guide for the small user of ionizing radiation. The types of ionizing radiation which are likely to be encountered in a small user's laboratory may be alpha, beta or gamma rays emitted from radioactive substances as well as X-rays from various types of X-ray machines. Protons and neutrons are not likely to be met with under these conditions but they do not differ basically in their action on the biological system. In the biological system, the absorbed energy from these kinds of radiation is dissipated in primary events, of which the most important are ionization and excitation. Such primary events last for an extremely short time, even less than 10^{-6} second, and give rise to chemical reactions; these in turn produce a biological reaction which may or may not be of significance to the organism as a whole. The absorption of radiant energy by matter is a quantum phenomenon, so that the maximum energy which may be imparted to a molecule is equivalent to the quantum energy of the radiation in question. For this reason quanta of light and of low-energy ultra-violet rays are unable to produce as strong an effect as, for example, X-rays or gamma rays, where the energy of the individual quantum is high and is sufficient to detach electrons from the atom. Thus, it may be stated in general that, as a result of ionizing radiation, matter is penetrated by electrons of various velocities and simultaneously a considerable number of atoms are excited, i. e. become more reactive with respect to other atoms or molecules.

(b) Direct and indirect action of radiation

The absorption of a quantum of radiation may result in a direct modification of the structure of a biologically important molecule, a process which may then lead to further changes that can become visible. The indirect effect takes the form of the decomposition of water or of organic molecules occurring in living matter, with the result that either short-lived radicals (e. g. OH, HO_2) or long-lived organic radicals, which may survive up to weeks or months, are produced. In both direct and indirect effects, a chain of chemical reactions is induced which may result in a visible biological effect.

(c) *Biological effect of ionizing radiation*

The biological effect depends on the size of the absorbed dose, its distribution in space and time, the sensitivity of the recipient organism, the length of the latent period, and the organism's powers of recovery. There is a marked difference in the space distribution of ions brought about by X-rays and by alpha-rays. In the former case the ions occur in widely-spaced clusters while in the latter they form a dense column of ionization. As a result of this uneven distribution and the influence of other factors, an alpha-ray dose of 1/10 rad may produce the same biological effect as an X-ray dose of 1 rad. In other words, the relative biological effectiveness (RBE) is different in each case.

The effect of radiation may be manifested immediately during irradiation or after a certain latent period, which in man may apparently be as long as several decades.

(i) Effects of ionizing radiations on biologically important macromolecules

A whole range of biologically important substances such as enzymes, proteins and nucleic acids, are also decomposed *in vitro* by relatively large doses of radiation. In certain cases direct action is exerted on the intra-molecular bonds; in others, however, the action is indirect through the medium of radicals. In this way some enzymes are inactivated. In the case of nucleic acids it has been observed that certain characteristics, viscosity for example, are modified even after the radiation has ceased. The majority of macromolecules forming important cellular constituents are, however, quite resistant *in vivo*. This is particularly true of proteins and of some enzymes, which at the same time are quite sensitive in dilute solution *in vitro*. On the other hand, the nucleo-protein metabolism in the cell seems to be modified even by small radiation doses. The end effect of radiation, it should be borne in mind, is a highly complex event, as changes in individual components interact and call forth new qualitative changes.

(ii) Morphological changes in the cell

After irradiation a characteristic change occurs both in the cell nucleus and in the cytoplasm. In the dividing nucleus, chromosome breaks may occur, and if these take place in gonadal cells, hereditary changes may ensue. In many cases the nucleus and cytoplasm increase in volume, vacuoles are formed and, after large doses of radiation, collapse of the entire cell structure ensues. The cell organelles, such as the mitochondria, appear to be markedly sensitive to radiation. On the other hand, the cytoplasm may continue to perform its movements in plant cells even after doses of several hundreds of thousands of rads.

(iii) Cell division

A sensitive indicator of post-radiation changes is a delay in cell division. This is particularly the case when the cells are irradiated before division commences. This circumstance is of extreme importance, since, during cell division, reduplication of DNA (desoxyribonucleic acid) occurs. In some cases one or two further divisions occur after irradiation, before the complete cessation of activity and the death of the cell supervenes. It may be said that all rapidly dividing cells are much more sensitive to radiation than are non-dividing cells, with the exception of non-dividing lymphocytes and possibly ovarian cells, which do show enhanced sensitivity.

(iv) Occurrence of mutations

Irradiation of the nuclear structure of sexual cells induces mutations which manifest themselves in subsequent generations and are generally deleterious. In addition to these mutations of the germ cells, mutations of the somatic cells may also occur and subsequently become apparent as somatic lesions. The evidence at present available indicates that once a mutation has occurred it persists, the only possible way in which it might be eliminated being by reverse mutation, which is rare, or by the process of selection. The relationship between the radiation dose and the frequency of mutations is linear, although recent work on mice has tended to show some variation of effect with dose-rate. There is considered to be no threshold dose, which means that each individual elementary process (cluster of ions and excitations) has a low probability of causing mutation.

(v) Effect of radiation on embryonic development

Ionizing radiation has a deleterious effect on the development of the embryo, particularly in its early stages. During organogenesis, the effect of radiation may assert itself, with the result that malformations appear in the new-born child. In this respect the retina, brain, skeleton and a number of other parts of the body are particularly vulnerable.

(vi) Lethal effect

The individual parts of the human body are able to withstand comparatively high radiation doses, a circumstance of which advantage is taken in therapy. Such is not, however, the case with irradiation of the whole body, when even a dose of 500 to 600 r may be lethal. The volume irradiated is most important. The various symptoms characteristic of radiation sickness occurring after less than a lethal dose are described in section B: radiopathology.

(vii) Shortening of the life-span

Experiments with animals have convincingly shown that even relatively low doses of radiation, which do not produce typical radiation sickness, may lead to a reduced life expectancy.

(viii) Induction of tumours

It has been established beyond doubt that malignant tumours may be induced by radiation doses much larger than those permitted under the recommendations of the International Commission on Radiological Protection (ICRP), after a latent period which in man sometimes lasts for decades. With leukaemia, the maximum incidence of cases is reached five to eight years after acute whole-body irradiation. Among the malignant diseases most frequently occurring in man after exposure to radiation, the most important are leukaemia and bone tumours. In contra-distinction to genetic changes, it is not entirely clear whether the occurrence of tumours is directly related to the radiation dose received. Some experiments indicate that some kind of threshold dose exists, below which tumours are not induced.

(ix) Relation between dose and effect

A certain relationship exists between the amount of the dose and its biological effect, implying that small doses produce a smaller biological effect than large ones. This dose-effect ratio is sometimes linear in the case of somatic changes (for example, the lower weight at birth of mice from embryos irradiated *in utero*). As already pointed out, there is a linear correlation, in the case of genetic injury, between the dose and the degree of injury. Here we are evidently dealing with a general biological law, to the effects of which man himself is not immune. In other words, this linear correlation signifies that even smaller doses of radiation, an ion pair or an ion cluster, have a slight chance of producing genetic consequences. This circumstance is of particular importance in the estimation of the genetic implications of small doses of radiation. Not only mutations conditioned by change in the germ cells occur in this way without there being a threshold dose, but clearly somatic mutations as well, and the possibility must not be excluded that leukaemia likewise is thus induced.

Another factor as far as the genetic effect is concerned is that the dose-rate is of comparatively small significance. In other words, a large dose given over a short period has the same genetic effect as an identical dose received in small fractions over a longer period, though, as mentioned previously, the dose-rate has been recently shown in experiments with mice to have some significance. With acute somatic effects, on the other hand, a single dose may produce a greater effect than the same amount spread over a long period. This is due to repair processes. It is not yet clear whether the organism's normal regenerative mechanism comes into play during recovery or whether specific post-irradiation repair processes exist.

II. Factors governing the biological effect of radiation

It has already been said that from the primary process occurring after the absorption of radiation a complicated reaction develops, which may finally emerge as a visible reaction to radiation. As might be expected, this chain of reactions can be influenced in various ways, particularly in more complex organisms. Among the agents which thus govern the final reaction to radiation are physico-chemical conditions, including temperature and degree of hydration, oxygen and the various so-called protective substances.

(a) Physico-chemical conditions (temperature, degree of hydration)

In general it may be said that a lowering of temperature reduces the effect of radiation. This should not be regarded as a fixed rule, because in some cases (bacteria) there exists a certain optimum temperature for the reduction of the radiation effect. In the case of some animals, it has, however, been ascertained that if they are kept at a low temperature after irradiation, the effect appears only when the temperature again rises to the normal level. The ultimate radiation injury however remains the same.

Similarly, it may be said that the level of hydration of the organism influences the effect of radiation, in the sense that the effect of radiation is increased under conditions of increased hydration. This is evidently connected with the production of radicals.

(b) Role of oxygen

If, during irradiation, the partial pressure of oxygen in the cells is lowered, the sensitivity of these cells to radiation and its effects is reduced, irrespective of whether we are dealing with chromosome breaks, biochemical changes or lethal events. It may thus be affirmed that a lowered oxygen concentration constitutes a protection against radiation. However, in some cases the presence of oxygen assists in recovery and renders possible the reunion of the chromosome. The oxygen effect is not manifest in the presence of densely ionizing radiation such as alpha rays or slow electrons.

(c) Protective substances

The fact that it is possible to decrease the radiosensitivity of the organism by outside intervention led to a search for substances which would provide a measure of protection against radiation. In the majority of cases it has been shown that such a protective substance must be present during irradiation in order to be sufficiently effective. Among the best-known protective substances of this kind is cysteamin, which is effective both *in vivo* and *in vitro*. It has been shown that its presence reduces the major effects of radiation, whether they are biochemical or morphological changes or even certain types of mutation, and the survival rate of the cells and tissues accordingly shows a corresponding rise. The hypothesis usually advanced to explain this phenomenon is that the protective substances exercise a neutralizing influence on the free radicals, or that the partial pressure of oxygen within the cells is lowered.

(d) Recovery

It has been observed in numerous experiments that the effect of radiation, particularly on the mammalian organism, may be decreased or completely eliminated by the action of the organism itself. This follows from the fact that irradiation places the organism under a certain stress, to which it reacts by mobilizing its general adjustment mechanisms for dealing with stress phenomena.

When the cell is provided with a suitable energy source (e. g. by adding adenosine triphosphate), chromosome breaks can be helped to re-join. This points to the probability that irradiation damage can be reduced by prompt administration of energy sources.

A greater effect may be obtained in mammals by transplantation of tissue not injured by radiation. In particular, the grafting of bone marrow has given specific evidence of this in mammals. All transplantation operations of this kind pre-suppose, however, that the immune reaction obtained on grafting heterogeneous tissue is inhibited.

(e) Adaptation

There is at present no convincing evidence that organisms can adapt themselves to high levels of radiation. It is, however, not impossible that organisms so adapted will be found in geographic regions where a high level of natural radioactivity exists. Certain densely populated areas of the globe (parts of India and Brazil) are known to have an unusually high content of radioactive substances in the environment. However, even if such adaptation occurs in the population, it is always necessary to bear in mind the influence of selection, in which the more resistant organism survives.

(f) Individual sensitivity

It has been observed that the radioresistance of certain bacterial cells is substantially increased by mutation. Clinical experience in radiotherapy also indicates that there are probably certain individuals more resistant to radiation. However, since this experience is based largely on the effects of partial irradiation, the significance of the observation cannot be extended to the whole body. Thus in the meantime we can only say that there is a wide variation in the degree of sensitivity of various organisms, since a few rad are sufficient to kill lymphocytes, whereas some hundreds of thousands of rad are required to kill an adult insect, and over a million rad to destroy viruses and bacteria completely.

The various organs differ considerably in their radioresistance. Although it is not possible to construct an exact scale of radioresistance for the organs, it may be roughly concluded that the blood-forming organs, gonads and lenses of the eyes are among the most sensitive. Muscle, connective tissue and adult bone have a relatively high resistance to radiation. The skin, intestines and endocrine glands fall in an intermediate category. This classification cannot, however, be exact, because it depends on many factors (physiological state, oxygen content, temperature, etc.) and on the method of observation, i. e. whether morphological or physiological changes are registered.

III. Conclusions

It should be emphasized that today's knowledge of the effects of radiation on living organisms is as yet incomplete, because the present knowledge of biology is not sufficient to establish sound criteria for distinguishing injury from the normal state of the organism. Nevertheless, our knowledge of radiation injury from both human experience and animal experiment is sufficient to make it possible to establish maximum permissible doses of radiation with a considerable degree of confidence.

B. Radiopathology

(a) Radiation sickness

After irradiation of the greater part of the body, a series of pathological symptoms ensue, which originally were described as "Röntgen sickness". It was only after the experience gained as a result of the atom-bombing of Hiroshima and Nagasaki that these were shown to be the symptoms of typical radiation disease. Basically, this disease can occur either as acute sickness (acute radiation syndrome) resulting from whole-body irradiation by a single dose of over 100 rem, or as chronic sickness developing over a number of years after small repeated radiation doses. Radiation sickness is caused principally by irradiation with gamma-rays, X-rays and neutrons. Alpha and beta rays exercise an effect when radioisotopes have been taken into the organism and deposited there.

Acute radiation disease is characterized by a latent period, which supervenes after initial symptoms of malaise, loss of appetite and fatigue, during which the sufferer feels no other untoward symptoms, and the length of which is indirectly proportional to the radiation dose received. At the end of the latent period, the onset of the illness proper occurs; the degree of severity which it attains depends upon the radiation dose. In the course of radiation sickness and, naturally, as a result of strong local irradiation, characteristic changes in the individual organs develop.

Radiation sickness may be followed after a lapse of several years by late effects in the form of malignant changes (leukaemia, tumours of the skin, etc.).

(b) Lymphatic haematopoietic tissues

Lymphatic tissues are among the highly radiosensitive systems. It is here that the lymphocytes which pass into the blood and become part of the white corpuscle group are formed. Even after small radiation doses the number of lymphocytes temporarily falls in some cases. After high doses, the lymphatic tissue ceases to be active and the lymphocyte count in the peripheral blood falls immediately, the degree and duration of the drop depending upon the radiation dose received.

The bone marrow, where the red corpuscles and leukocytes are formed, is highly radiosensitive. Particularly liable to damage are the immature blood cells in the process of formation; the earlier their stage of development, the greater is their sensitivity. After small radiation doses, a moderate multiplication of the young red and white cells occurs, but after large doses a crushing effect upon the marrow is observed, leading to the complete depopulation of the marrow tissue. The marrow begins to resume activity in the first or second week after irradiation and the duration of the process is governed directly by the radiation dose. During the process itself, recovery of white cell production is more rapid than erythrocytopoiesis.

It may be said, very broadly speaking, that reactions to radiation as manifested in the peripheral blood depend on the radiation dose, species specificity, the life span of the different corpuscular elements, their sensitivity and powers of renewal and the state of the organism at the time.

Immediately after irradiation a short period of leukocytosis ensues, occasioned by the release of leukocytes from the bone marrow. Then follows a drop of the total leukocyte count, the severity and duration of which are proportional to the degree and length of radiation exposure. A fall in the lymphocyte count is an early feature. Reduction of the neutrophil count is characteristic, and recovery from neutropenia may be taken as a good prognostic sign. The eosinophil count drops only after a larger dose. The number of reticulocytes is also reduced, and early reticulocytosis is a favourable indication of recovery. The red-corpuscle count drops only very slowly after irradiation. Marked anaemia does not occur until two to four weeks after a large radiation dose. In cases of severe damage this turns to aplastic anaemia.

After irradiation, the blood-platelet count also falls, the radiosensitivity of the platelets being greater than that of erythrocytes. The lack of blood platelets leads to a tendency to bleeding. The recovery of the blood-platelet count is generally very slow. The monocytes behave in the same manner as eosinophils, and an increase in their number is a favourable indication of recovery.

(c) Gastro-intestinal system

Small doses of ionizing radiation affect the motility of the intestine and enzyme secretion, whereas large doses lead to ulceration of the intestinal mucosa. The intestinal bacteria penetrate the damaged intestinal tract, enter the blood system and are carried throughout the body, causing serious septic conditions. Changes in the gastro-intestinal tract are frequently decisive in the outcome of radiation disease. Naturally, direct irradiation from considerable quantities of ingested radioactive substances may severely damage the intestinal wall in a similar manner.