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INTRODUCTION

Shortly after the discovery of natural radioactivity and of x-rays (now more properly known as roentgen rays) during the final decade of the last century, it became apparent that these invisible radiations could produce serious effects on the human body in a relatively short period of time. Three or four decades ago additional effects became apparent in individuals who had received relatively large radiation exposures. The cumulative nature of radiation effects and the fact that detectable changes may be delayed for many years have become increasingly apparent with the passage of time. The rapid expansion in potential exposure accompanying the discovery of the process of nuclear fission and the development of atomic weapons was accompanied by a greatly accelerated research program to investigate the actual and potential damage which might result from protracted or repeated low level radiation exposures. Although much of this work has tended to heighten concern over possible radiation injuries, the magnitude of the problem, the similarity of certain effects to diseases and abnormal conditions ordinarily present in the population, and the inherent difficulty of compiling satisfactory human data have combined to leave unanswered many questions concerning the biological effects of low level continued or repeated radiation exposures.

ACUTE RADIATION EFFECTS

It is absolutely essential to clearly differentiate between acute and delayed radiation effects. Although acute radiation effects may not become apparent for a period of hours, days, or even weeks following the exposure, delayed effects may not produce detectable changes for a period of years or even generations.

The nature of acute radiation effects will depend on many variables, including the radiation dose, portion of the body exposed, duration of exposure, and physical characteristics of the radiation. If the dose is sufficiently high, a sufficiently large portion of the body exposed, and the physical nature of the radiations such that there is adequate penetration of the body tissues, death may be produced with rather characteristic signs and symptoms. The so-called "acute radiation

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syndrome" has been adequately described in the medical literature on the basis of observations of individuals in or near the Japanese cities of Hiroshima and Nagasaki as well as a small number of individuals inadvertently or accidentally exposed.[1] This syndrome is characterized primarily by nausea and vomiting during the first few hours after exposure, sometimes followed by a period of some hours or days of apparent good health, then a down-hill course with death resulting in from a few days to a few weeks. During this latter period the circulating blood, which will show profound changes within a day or less of the exposure, becames even more seriously affected. In addition, there are usually signs of abnormal bleeding (particularly from the gums and into the skin), nausea, vomiting and diarrhea (often bloody), general weakness, and accompanying serious infections. Because of the complete description of the rather classical findings in the medical literature and their rather technical nature, they will not be discussed in more detail here. It is usually possible to attribute this condition to radiation exposure on the basis of adequate medical diagnostic procedures alone, although a history of radiation exposure is most helpful in reaching a final diagnosis.

Although many drugs and treatment procedures have been advocated and have been shown to be of at least some benefit in animals, their use in humans should not be expected to produce a dramatic change in persons suffering from the acute radiation syndrome. If the radiation dose delivered and other factors resulted in sufficiently severe damage to the body, there is no known method of preventing death, and the patient faces a period of conscious suffering for several days or even weeks during which the physician is unable to interrupt the fatal processes.

Not all exposures to even large doses of radiation will result in death, however. If only a portion of the body is exposed, the detectable effects may be limited to that portion of the body which received the radiation. As an example, patients undergoing intensive radiation treatment, as for malignant diseases, often receive doses to a small portion of the body many times that which would produce death if the whole body were exposed. In such cases, the local effects may be quite striking. For example, essentially all patients undergoing intensive radiotherapy suffer significant or serious skin damage except those treated with x-ray equipment operating in the million volt range. Here again, the onset of detectable changes is usually delayed for days or even weeks and the maximum effect is not reached until some time after treatment had been completed. In a typical case, the skin turns red, becomes tender and painful, and often peels and becomes moist

1. Hempelmann, Lisco & Hoffman, *The Acute Radiation Syndrome: A Study of Nine Cases and a Review of the Problem,* 36 Ann. Int. Med. 279 (1952).

and weeping. Less commonly, the damage of the skin would be so severe that open ulcers form and persist, sometimes indefinitely, without healing. With lesser doses, milder effects are seen, for example, only a reddening of the skin of varying degrees. Although such radiation damage as that just described is not often seen with the use of so-called "super-voltage" equipment (that operating in the range of one million volts or more) it is an expected and justifiable consequence in patients treated with other types of equipment, as is still the case with the majority of patients.

The duration of time over which a given total dose of radiation is delivered has a significant effect on the acute radiation response. For example, a dose of 600 roentgens of penetrating radiation delivered to the entire body would be expected to produce death within a few days or weeks in the majority, if not all, of the individuals exposed. The same total exposure delivered as 100 doses of 6 roentgens each at weekly intervals might well cause few deaths and relatively insignificant acute symptoms. However, the general principle that protraction of radiation exposure results in less acute damage than the same total dose delivered in a shorter period of a time does not necessarily apply when one is concerned with delayed radiation effects, as will be discussed below.

The physical nature of the radiation to which a person is exposed is also of extreme importance with regard to the acute signs and symptoms which may develop. The above discussion was concerned with radiations of sufficient penetrating power to affect even organs located deep within the body. Examples of such penetrating radiation are x-rays of the deep therapy type, and to a lesser degree other therapeutic x-rays and diagnostic x-rays. In addition, most of the gamma radiation resulting from nuclear fission or the decay of radioactive isotopes is of a highly penetrating nature. On the other hand, alpha radiation (which occurs almost solely from the radioactive decay of certain naturally radioactive materials) and beta radiation (which results from the radioactive decay of many natural and artificial radioisotopes) are much less penetrating and their effects in man may be limited to relatively external portions of the body. Alpha radiation has a penetrating power so low that the radiation itself will not, in most cases, penetrate the outer layers of the skin. The usual types of beta radiation will not penetrate deeper than fractions of an inch below the body surface. Particularly with beta radiation however, there may be secondary effects produced in various body organs, especially if the damage to the skin has been sufficiently serious to result in peeling, ulceration, or the need for skin grafting. In general, the local effects produced by external beta radiation will be similar to the skin changes which follow sufficiently high doses of x-ray.

It should be noted that there is a range of doses in which the effects will be relatively slight and rather difficult to differentiate from skin damage from other causes in the absence of an accurate history of radiation exposure. In such cases, the most valuable single distinguishing feature may be the time sequence, as the skin effects of radiation are delayed in their onset and follow a rather protracted course. In this connection, radiation "burns" have been described as "burns in slow motion."

All of the above discussion has concerned itself primarily with the acute effects of external exposure to radiation. In addition, acute body changes can be produced if sufficiently large amounts of radioactive material enter the body through the lungs, gastro-intestinal tract, or the skin. Here, our human experience is essentially non-existant. However, it seems reasonable, on the basis of animal experimentation and current knowledge of biological effects of radiation in general, to assume that such acute injury would depend primarily upon the portion or organs of the body in which most of the material becomes deposited, the total amount of radioactive materials involved, and the physical nature of the radiation involved. Thus, a large amount of radioactive material which does not tend to concentrate in any particular portion of the body and which emits penetrating gamma radiation might well produce all of the symptoms mentioned above as the acute radiation syndrome. On the other hand however, certain other materials, such as the bone-seeking elements radium and strontium, which emit primarily non-penetrating radiation, would be characterized by effects directly upon the bone and bone marrow and indirectly on the circulating blood.

The measurement of the amount of radioactive material which has entered or become deposited in any individual's body can be extremely difficult. There now exist in this country a few "whole-body" counters which will measure internally deposited radioactive materials if the amounts are sufficiently large and if the radiations they emit are sufficiently penetrating. Such techniques are not readily applicable however, where the radioactive material has been deposited deep in the body and emits a relatively non-penetrating radiation, such as alpha or beta. Additional measurements of internally deposited radioactive materials may be made by several techniques, one of the oldest from the historical standpoint being the measurement of the radioactive gas, radon, which is exhaled in the breath of individuals who have radium deposited in their bones. In addition, direct measurement of radioactive materials in the urine are also possible, and portions of body tissues removed by operation or at post-mortem examination can be measured by relatively standardized techniques to provide an index of the amount of radioactive material in the body of an individual. Although these latter techniques are difficult to apply with accuracy at very low levels, they would be most useful in cases where internal contamination is sufficiently great to be causing acute radiation effects.

In actual practice, it is likely that acute radiation injury might occur, not from pure external or internal exposure to a single type of radiation, but rather from exposure to mixed types of radiation, possibly from both external and internal sources. As an example, the acute radiation effects of persons exposed to large doses of radiation in connection with certain weapons tests have been described in the medical literature.[2] Here, the symptoms and signs were attributable to and characteristic of both gamma and beta external radiation, and the internally deposited radioactive materials appeared to play a rather minor role.

It appears likely that, barring nuclear warfare or a major accident resulting in wide-spread high level radioactive contamination, the legal problems of acute phases of radiation injuries are relatively simple, since the diagnosis is reasonably easy to establish, and the nature of any precipitating incident is likely to be such that its occurrence is rather easy to detect. Thus, the cause-effect relationship can be established with relative ease.

The terms "acute radiation exposure" and "acute radiation effects" are not synonymous. In addition to the acute radiation effects discussed above, an acute exposure to ionizing radiation can also be the cause of, or contributory to, delayed radiation effects. Thus, there can be no assurance that apparent recovery from acute radiation injury will not be followed by other effects at a later date.

Delayed Radiation Effects

Delayed radiation effects, on the other hand, have several characteristics which seriously complicate the legal problems. In the first place, these delayed effects may not occur until a period of several years after the exposure. In fact, certain effects will not become manifest for one or more generations. Also, they may result from a series of individual exposures received from different sources over an extended period of time. In addition, the majority of delayed radiation effects are similar to disease conditions or abnormalities that appear from time to time in the population without exposure to man-made radiation. Because the only detectable result of exposure to radiation may be a statistically significant increase in the incidence of certain conditions which already exist in the population, it will be impossible to state, in individual cases, whether the abnormality results

2. Cronkite, *Response of Human Beings Accidentally Exposed to Significant Fallout Radiation,* 159 J.A.M.A. 430 (1955).

from radiation exposure or would have occurred without such exposure. Thus the cause-effect relationship may be almost impossible to establish. Indeed, our current knowledge in many cases will not even permit an accurate estimation of the probability of such relationship. With delayed injuries we face serious legal problems with certain of the present statutes of limitations, as well.

Significant differences of opinion exist among reputable scientists as to the quantitative significance of any given low level radiation exposure in terms of human damage. Indeed, there is not even unanimity of opinion as to whether or not there is a minimum radiation dose (threshold) below which absolutely no effect will be produced, or whether even the most minute doses are accompanied by a perhaps undetectable, small effect. This is a key point, yet one on which widely divergent opinions still exist.

For purposes of this discussion, delayed radiation effects will be divided into (1) genetic effects, (2) cancer, leukemia, and similar disorders, (3) effects on growth and development, and (4) life span shortening.

It has been known for some time that exposures of the reproductive organs to ionizing radiation can result in abnormal offspring, and that these abnormalities can be passed on from generation to generation. At the present time we must rely on animal experimentation for any detailed information in this field, as adequate satisfactory human data covering a span of several generations are not available. It appears unlikely to this author that such genetic information in humans will be forthcoming in the near future. Although single cases of normal reproduction following fairly heavy radiation exposure have been reported, they should be considered of little significance beyond indicating that gross congenital abnormalities are not an inevitable consequence of human exposure to radiation below the lethal level. In the Japanese populations of Hiroshima and Nagasaki, the magnitude of exposures, duration of time since exposure, numbers of individuals involved, and other factors currently permit no final conclusions. Neither are there satisfactory data covering other human populations which may have been exposed to radiation and which involve sufficiently large numbers of people to be relied upon to detect small, yet significant, statistical variations. Extensive laboratory experimentation has been conducted in the fruit fly and in other species including the mouse. For mouse experimentation, strains are available in which every animal can, for all practical purposes, be considered an identical twin of every other animal, thus greatly reducing the number of animals required in genetic experiments, but the use of enormous numbers of animals is still necessary for proper study at low doses. It has often been considered that the total effect on future generations of any given amount of radiation would be the same regardless of how it is distributed among individuals of the reproductively significant population, and regardless of the rate of delivery, whether it be in a single dose or a series of smaller doses, so long as it is delivered between conception and child-bearing. If this be true, the significance of radiation from the standpoint of the population geneticist depends not upon the dose delivered to any individual, but upon the product of the average dose per individual times the numbers of individuals exposed. Thus, the total impact on the population of exposing the reproductive organs of one individual to a dose of 100 roentgens would be the same as an exposure of 1/100 of a roentgen to ten thousand individuals, given equal probability of reproduction. The implications of this concept in terms of total genetic effect and the difficulties of establishing a cause-effect relationship in the case of a congenital defect are obvious. Although this concept has recently been subject to additional scrutiny because of recent experimental data in mice, there is still no good evidence to indicate that any particular radiation dose must be exceeded before some increase in the probability of congenital malformations results.

Without any added man-made radiation whatever, some congenital malformations will occur in the population, and there is no reason to believe that radiation induced genetic effects differ in nature from those normally present in the population. In a plant or animal population, the overwhelming number of genetic changes will be harmful rather than beneficial, and it is to be expected that in humans (a presumably more highly developed species) the proportion of harmful to beneficial effects would be even greater than in lower forms of life. Thus, although a small number of beneficial effects might result they would certainly be more than outweighed by the harmful changes. In the human race during the past few decades, we have become increasingly able to counteract the process of natural selection, so that those additional genetic changes which are produced by radiation may be expected to have increasing significance. To maintain perspective, however, it is important to realize that large numbers of grossly abnormal or monstrous offspring will not be produced by exposure of the population to dose levels of the order of magnitude of the current "maximum permissible exposure" limits.

The concern of many geneticists is with the more subtle genetic changes which will not be immediately observable and which are manifest primarily by a weakening in the virility of the offspring. Supporting this contention is some recent experimental work[3] which

3. Russell, *Shortening of Life in the Offspring of Male Mice Exposed to Neutron Radiation from an Atomic Bomb*, 43 PROC. NAT. ACAD. SCIENCES 324 (1957).

indicates that even in the first generation, where the effect would be expected to be less than in later generations, the progeny of male animals exposed to radiation die sooner than do the progeny of animals not exposed to radiation. In this case, the progeny did not appear grossly abnormal nor did they die from any given disease or group of diseases. Rather, their demise resulted from the same spectrum of diseases as was the case in the control group.

It cannot be stressed too strongly that genetic effects from radiation are a probability phenomenon. Thus, even when it can be demonstrated beyond reasonable doubt that a genetic defect exists and that the parent was exposed to radiation prior to the conception, we will have only statistical evidence as to whether these two facts are related.

Defects in growth and development which can result from exposure of the unborn offspring to radiation are often confused with genetic changes but are different in their biological significance. In the event that a mother has an exposure of the abdomen while the progeny is in utero, there may be failure of the infant to mature properly, either in utero or later in life. Such changes, however, are not passed on to subsequent generations. If the defect produced is sufficiently serious, it is possible for the unborn child to die, leading to a miscarriage. Unfortunately, it is probable that the foetus is most sensitive in the rather early stages of pregnancy, perhaps even before the fact of pregnancy would normally be known by the mother. Even after birth, the growing child is presumably more susceptible to a given dose of ionizing radiation than is a mature adult. This has been amply demonstrated in animals and the extremely limited human data available gives no reason to believe that the same is not true in our species. If only a portion of the body is exposed to relatively high doses, significant and gross abnormalities and deformities may result. Exposure of the whole body apparently tends to delay the over-all maturation of the individual without specific or localized effects.

An increased incidence of neoplasms (cancer, leukemia, etc.) is readily and easily demonstrable in the experimental animal as a result of radiation exposure and there is an appreciable amount of data on humans in this regard. An increased incidence of primary bone tumors as a result of deposition of naturally radioactive material in the bones of radium dial painters is a historic and well-documented case in point. Similarly, the increased incidence of neoplasms of the skin in early radiation workers is a matter of established historical fact. Evidence for an increased incidence of leukemia among radiologists as compared to the general population or to other physicians has been presented in several medical reports.[4] Also, an increased

4. March, *Leukemia in Radiologists in a 20-Year Period*, 220 J.A.M.A. 282

incidence in tumors of the thyroid gland has been noted in children who were treated with radiation in infancy.[5] Other human reports cover patients treated with x-ray for arthritis of the spine[6] as well as the survivors of the atomic bombings in Hiroshima and Nagasaki.[7] In all of these cases, however, it can be shown or reasonably assumed that the radiation dose involved was of comparative high level. At the same time, there have been recent reports indicating that even the small doses in irradiation involved in a diagnostic x-ray examination of the mother result in a significant increase in the incidence of leukemia and other malignant tumors in the offspring during the first ten years of their lives.[8]

The question as to whether or not there is a given dose of radiation below which an increased incidence of neoplasms will not be found (a threshold) is a crucial point and one on which there is a major difference of opinion.[9] It does seem reasonable to assume, however, that if a threshold does exist, it may be as low or lower than the relatively small doses involved in certain diagnostic x-ray procedures.

Even where the increased incidence of neoplasms has been striking, as for example the European uranium miners where approximately 50% of the individuals involved died from tumors of the lung, there has been a time lag of ten to twenty years between the beginning of exposure and the onset of symptoms leading to detection of the disease. This fact, coupled with knowledge that radiation induced cancers in man cannot be differentiated by any known diagnostic procedures from cancers occurring spontaneously or from other causes, makes a sound legal approach extremely difficult.

The phenomenon of nonspecific life span shortening is perhaps the most difficult delayed biological effect of radiation exposure to assess from the legal standpoint. It has now been amply demonstrated in experimental animals that doses of radiation well below those neces-

(1950); Henshaw, *Incidence of Leukemia in Physicians*, 4 J. NAT. CANCER INST. 339 (1944).

5. Simpson, Hempelmann and Fuller, *Neoplasia in Children with X-Rays in Infancy for Thymic Enlargement*, 68 RADIOLOGY 840 (1955); Clark, *Association of Irradiation with Cancer of the Thyroid in Children and Adolescents*, 159 J.A.M.A. 1007 (1955); Duffy and Fitzgerald, *Cancer of the Thyroid in Children: A Report of 28 Cases*, 10 J. CLIN. ENDOCRINOL. 1296 (1950).

6. Court-Brown and Doll, *Leukemia and Aplastic Anemia in Patients Irradiated for Ankylosing Spondylitis*, BRITISH MEDICAL RESEARCH COUNCIL SPECIAL REPORT SERIES No. 295 (1956).

7. Wald, *Leukemia in Hiroshima City Atomic Bomb Survivors*, 127 SCIENCE 699 (1958); Moloney and Kastenbaum, *Leukemogenic Effects of Ionizing Radiation on Atomic Bomb Survivors in Hiroshima City*, 121 SCIENCE 308 (1955).

8. Stewart, *Malignant Disease in Childhood and Diagnostic Irradiation in Utero: A Preliminary Report*, 271 LANCET 447 (1956).

9. Brues, *Critique of the Linear Theory of Carcinogenesis*, 128 SCIENCE 693 (1958); Lewis, *Leukemia and Ionizing Radiation*, 125 SCIENCE 965 (1957).

sary to produce acute symptoms can significantly effect longevity on a statistical basis.[10] It is logical to assume that this phenomenon also occurs in man, although current medical literature is controversial in this regard.[11] The individuals affected do not die of any particular disease or group of diseases. Rather, the causes of death show a statistical distribution essentially the same as in the unirradiated population, but the death occurs at an earlier age. Again, we are dealing with a phenomenon which is statistically significant, but undetectable in the individual. The total life span shortening in a population group is not concentrated in a small proportion of the individuals, but rather represents a relatively small effect on essentially all individuals. In the experimental animal not only does death occur sooner, but the basic components of the physiological process of aging appear earlier. Thus, the individuals not only die younger, they become older biologically at a younger chronological age. As with other delayed biological effects, the questions of the presence or absence of the threshold has not been satisfactorily resolved.

The above discussion on delayed radiation effects is equally applicable for external sources of radiation or for radioactive materials deposited within the body. In the latter case, appropriate consideration must be given to the sites of deposition or concentration of the radioactive material, the physical nature of the radiation emitted, and the quantity involved. For proper evaluation, all sources of radiation exposure, both external and internal, must be considered together.

Radiation Exposure Limits and Standards

It is an obvious conclusion from a consideration of the effects of radiation on humans that the currently available data do not permit the establishment of "safe" standards of exposure, and that all exposures not serving a useful purpose are to be avoided. The decision as to the levels of exposure that may be expected to carry a risk that is acceptable when compared to other hazards of life becomes one of reasoned judgment, rather than scientific certainty. For over two decades, suggested maximum permissible limits have been recommended by the National Committee on Radiation Protection and Measurements and its direct ancestors. The recommendations of this group are published as a series of handbooks released by the National Bureau of Standards[12] dealing with many phases of this problem.

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10. Blair, *Data Pertaining to Shortening of Life Span by Ionizing Radiation*, University of Rochester Atomic Energy Project Report No. UR-442 (1956).

11. Seltser and Sartwell, *Ionizing Radiation and Longevity of Physicians*, 166 J.A.M.A. 585 (1958); Warren, *Longevity and Causes of Death from Irradiation in Physicians*, 162 J.A.M.A. 464 (1956).

12. National Bureau of Standards Handbooks, Number 42, 48, 49, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65.

These handbooks are required reading for those directly interested in this field. The discussion of the philosophy of radiation protection contained in *Handbook 59*[13] is particularly recommended.

Although these recommendations have no direct legal status, they have been incorporated into legislation or regulations by several states, serve as a basis for regulations of the Atomic Energy Commission, and represent the combined opinions of many of the foremost scientific experts in this country. In addition, they are in substantial agreement with the recommendations of the National Committee on Radiation Protection's international counterpart, the International Commission on Radiological Protection.

SUMMARY AND CONCLUSION

From the above discussion of our current state of knowledge regarding biological effects of radiation on man the following key points of legal significance emerge:

(1) Sufficiently high doses of radiation can produce various acute effects, including death, which can usually be attributed directly to the radiation exposure, particularly if there is knowledge that such exposure occurred. The doses required to produce acute symptoms are such that with even reasonably satisfactory standard radiation protection techniques the existance of the exposure and some indication as to its magnitude should be known.

(2) There are a series of delayed radiation effects which are most likely to become manifest only after a period of several years or even after generations, and which do not differ in a qualitative manner from diseases and abnormalities normally present in the population. Delayed effects can result from a single exposure (with or without acute radiation effects) or from a series of exposures from the same or different sources. These effects lead to serious problems in the establishment of cause-effect relationships, and may require re-evaluation of certain statutes of limitations.

(3) Delayed radiation effects, in general, are a probability phenomenon. Although they can be demonstrated on a statistically significant basis with a sufficiently large population group, the presence or absence of these effects in any given individual may be impossible to establish.

(4) The currently available scientific information, particularly the information on humans, is not adequate to establish whether a threshold exists for some or all of the delayed radiation effects.

(5) Acute or delayed radiation damage can be produced by external

13. National Committee on Radiation Protection, *Permissible Dose from External Sources of Ionizing Radiation*, NATIONAL BUREAU OF STANDARDS HANDBOOK 59 (1954 as revised January 1957).

sources or by radioactive materials deposited within the body. The degree and nature of the effect will depend upon the total dose, the portion of the body exposed, the penetrating power of the particular radiation involved, and other factors. Techniques are available for the detection of internally deposited radioactive materials in the body within major limitations as to the amount and the type of material.