

## Section 2

# **BIOLOGICAL EFFECTS OF IONIZING RADIATION**

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## A. Introduction

The fact that ionizing radiation produces biological damage has been known for many years. The first case of human injury was reported in the literature just a few months following Roentgen's original paper in 1895 announcing the discovery of x-rays. As early as 1902, the first case of x-ray induced cancer was reported in the literature.

Early human evidence of harmful effects as a result of exposure to radiation in large amounts existed in the 1920s and 1930s, based upon the experience of early radiologists, miners exposed to airborne radioactivity underground, persons working in the radium industry, and other special occupational groups. The long-term biological significance of smaller, repeated doses of radiation, however, was not widely appreciated until relatively recently, and most of our knowledge of the biological effects of radiation has been accumulated since World War II.

## B. Sequential Pattern of Biological Effects

In general, the sequence of events following radiation exposure may be classified as follows:

### 1. Latent Period

Following the initial radiation event, and before the first detectable effect occurs, there is a time lag referred to as the latent period. There is a vast time range possible in the latent period. The biological effects of radiation are arbitrarily divided into short-term and long-term effects on this basis. Those effects which appear within a matter of minutes, days, or weeks are called short-term effects and those which appear years, decades, and sometimes generations later are called long-term effects.

### 2. Period of Demonstrable Effects on Cells and Tissues

During or immediately following the latent period, certain discrete effects can be observed.

One of the phenomena that is seen most frequently in growing tissues exposed to radiation is the cessation of mitosis, or cell division. This may be temporary or permanent, depending upon the radiation dosage. Other effects include breaking or clumping of chromosomes, and formation of giant cells or other abnormal

mitoses. It should be pointed out that many of these effects can be duplicated individually with other types of agents, such as chemicals. However, the entire gamut of effects cannot be reproduced by any other single agent.

### 3. Recovery Period

Following exposure to radiation, recovery can take place to a certain extent. This is particularly apparent in the case of the short-term effects, i.e., those appearing within a matter of days or weeks after exposure. However, there may be a residual damage from which no recovery occurs, and it is this irreparable injury which can give rise to later long-term effects.

## C. Determinants of Biological Effects

### 1. The Dose Response Curve

For any biologically harmful agent, it is useful to correlate the dosage administered with the response of damage produced, in order to establish acceptable levels of exposure. “Amount of damage” in the case of radiation might be the frequency of a given abnormality in the cells of an irradiated animal, or the incidence of some chronic disease in an irradiated human population. In plotting these two variables, a dose-response curve is produced. With radiation, an important question has been the nature and shape of this curve. Two possibilities are illustrated in figures 1 and 2.

Figure 1 is a typical “threshold” curve. The point at which the curve intersects the abscissa is the threshold dose, i.e., the dose below which there is no response. If an easily observable radiation effect, such as reddening of the skin, is taken as “response,” then this type of curve is applicable. The first evidence of the effect does not occur until a certain minimum dose is reached, although unobserved effects may exist.

Figure 2 represents a linear, non-threshold relationship, in which the curve intersects the abscissa at the origin. Here it is assumed that any dose, no matter how small, involves some degree of response. There is some evidence that the genetic effects of radiation constitute a non-threshold phenomenon, and one of the underlying (and prudent) assumptions in the establishment of radiation protection guides and in radiation control activities in public health programs has been the existence of a non-threshold effect. Thus some degree of risk is assumed when large populations of people are exposed to even very small amounts of radiation. This assumption often makes the establishment of guidelines for acceptable radiation exposure a complex task, since the concept of “acceptable risk” comes into play, in which the benefit to be accrued from a given radiation exposure must be weighed against its hazard.

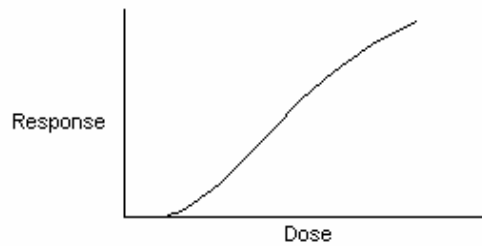


Figure 1

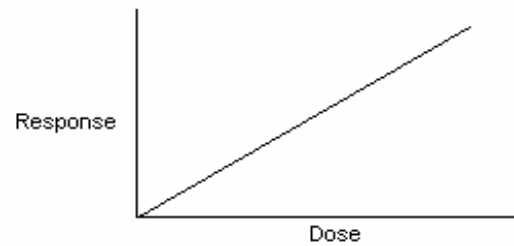


Figure 2

## 2. Rate of Absorption

The rate at which the radiation is administered or absorbed is important in the determination of what effects will occur. Since a considerable degree of recovery occurs from the radiation damage, a given dose will produce less effect if divided or prolonged (thus allowing time for recovery between dose increments) than if it were given as a single exposure.

## 3. Area Exposed

The portion of the body irradiated is an important parameter because the larger the area exposed, other factors being equal, the greater the overall damage to the organism. Even partial shielding of the highly radiosensitive blood-forming organs such as the spleen and bone marrow can mitigate the total effect considerably. An example of this phenomenon is in radiation therapy, in which doses which would be lethal if delivered to the whole body are commonly delivered to very limited areas; e.g., to tumor sites.

Generally when expressing external radiation exposure without qualifying the area of the body involved, whole-body irradiation is assumed.

## 4. Variation in Species and Individual Sensitivity

There is a wide variation in the radiosensitivity of various species. Lethal doses for plants and microorganisms, for example, are usually hundreds of times larger than those for mammals. Even among different species of rodents, it is not unusual for one to demonstrate three or four times the sensitivity of another.

Within the same species, individuals vary in sensitivity. For this reason the lethal dose for each species is expressed in statistical terms, usually as the  $LD_{50/30}$  for that species, or the dose required to kill 50 percent of the individuals in a large population in a thirty-day period. For man, the  $LD_{50/30}$  is estimated to be approximately 450 rads for whole-body irradiation.

## 5. Variation in Cell Sensitivity

Within the same individual, a wide variation in susceptibility to radiation damage exists among different types of cells and tissues. In general, those cells which are rapidly dividing or have a potential for rapid division are more sensitive than those which do not divide. Further, cells which are non-differentiated (i.e., primitive or non-specialized) are more sensitive than those which are highly specialized. Within the same cell families, then, the immature forms, which are generally primitive and rapidly dividing, are more radiosensitive than the older, mature cells which have specialized in function and have ceased to divide.

Based upon these factors, it is possible to rank various kinds of cells in descending order of radiosensitivity. Most sensitive are the white blood cells called lymphocytes, followed by immature red blood cells. Epithelial cells, which line and cover body organs, are of moderately high sensitivity; in terms of injury from large doses of whole-body external radiation, the epithelial cells which line the gastrointestinal tract are often of particular importance. Cells of low sensitivity include muscle and nerve, which are highly differentiated and do not divide.

## D. Short Term Effects

An acute dose of radiation is one which is delivered to the body during a very short time. If the amount of radiation involved is large enough, acute doses may result in effects which can manifest themselves within a period of hours or days. Here the latent period, or time elapsed between the radiation insult and the onset of effects, is relatively short and grows progressively shorter as the dose level is raised. When the radiation is delivered to the whole body, the signs and symptoms which comprise these short-term effects are collectively known as the Acute Radiation Syndrome.

### 1. Stages in the Acute Radiation Syndrome

#### a. Prodrôme

This is the initial phase of the syndrome, and is usually characterized by nausea, vomiting and malaise.

#### b. Latent Stage

During this phase, which may be likened to the incubation period of a viral infection, the subjective symptoms of illness may subside, and the individual may feel well. Changes, however, may be taking place within the blood-forming organs and elsewhere which will subsequently give rise to the next aspect of the syndrome.

c. **Manifest Illness Stage**

This phase reflects the clinical picture specifically associated with the radiation injury. Among the possible signs and symptoms are loss of hair (epilation), fever, infection, hemorrhage, severe diarrhea, prostration, disorientation, and cardiovascular collapse. Observation of the foregoing phenomena in a given individual is largely dependent upon the radiation dose received.

d. **Recovery or Death**

2. **Relation of Dose to Type of Acute Radiation Syndrome**

Recalling the different sensitivities of various kinds of cells, one can predict roughly the biological systems which will be affected as radiation dose increases. At relatively low doses, for example, the most likely cells to be injured are those with greatest sensitivity, i.e., immature white blood cells of lymph and bone marrow, so that the observable effects during the manifest illness stage would relate to these cells; one would thus expect to observe fever, infection and hemorrhage. This is known as the **hematopoietic form** of the acute radiation syndrome.

At higher doses, usually over 600 rads, cells of somewhat lower sensitivity will also be injured. Of particular importance are the epithelial cells which line the gastrointestinal tract, for when these are destroyed a vital biological barrier is broken down. As a result, there may be fluid loss, overwhelming infection and severe diarrhea in this **gastrointestinal form** of the acute radiation syndrome.

In the **cerebral form**, which may result from doses of 10,000 rads or more, the relatively resistant cells of the central nervous system are damaged, and the affected individual undergoes a rapid illness, characterized by disorientation and shock.

Considering the large degree of individual variation which exists with respect to radiation injury, it is difficult to assign a precise dose range to each of the above forms of the syndrome. The following generalizations, however, may serve to provide a rough indication of the kinds of doses involved. At 50 rads or less, ordinary laboratory or clinical methods will show no indications of injury from whole-body irradiation. At 100 rads, most individuals show no symptoms, although a small percentage may show mild blood changes. At 200 rads, most persons show definite signs of injury; this dose level may prove fatal to those individuals most sensitive to the effects of radiation. At 450 rads, the median lethal dose has been reached, and 50 percent of exposed individuals will succumb. Approximately 600 rads usually marks the threshold of the gastrointestinal form of the acute radiation syndrome, with a very poor prognosis for all individuals involved; a fatal outcome may well be certain at 800 to 1,000 rads. (For a detailed

account of the Acute Radiation Syndrome, including symptomatology, laboratory findings, diagnosis and patient management, see: Thoma, George E., and Wald, Neil, “The Diagnosis and Management of Accidental Radiation Injury,” *Journal of Occupational Medicine*, 1: 421-427, August 1959.)

### 3. Summary

The Acute Radiation Syndrome represents the signs and symptoms which result from large doses of radiation, generally over 100 rads, delivered to a major portion of the body; it is important to recall that this type of injury occurs only when the dose is received over a short period of time. The total effect may vary from mild and transient illness to death.

Because of the variation in susceptibility to radiation injury which exists among different individuals, it is extremely difficult to predict with accuracy the degree of effect in a given person, even when the dose is known. Within certain broad ranges, however, certain effects may be correlated with various dose levels on a population basis.

The course of the syndrome may vary from hours to several weeks. This time element is generally related to the radiation dose; other factors being equal, the duration of the various phases of the syndrome is inversely proportional to the amount of radiation received, with a rapid, illness being characteristic of very high doses.

The following graphical representation of the above information attempts to summarize the Acute Radiation Syndrome.

Effects	Exposure (Roentgens)				
	0	100	400	600	1000 // 5000
Organs Affected	Nil		Hemopoiesis	GI Tract	CNS
Signs	Nil		Leukopenia Hemorrhages Infection	Diarrhea, Electrolyte Imbalance	Convulsions, Tremors, Ataxia
Critical Period			4-6 weeks	1-2 weeks	0-2 days
Cause and Time of Death			Hemorrhage, Infection, 2 months	Circulatory Collapse, 2 weeks	Respiratory Failure Cerebral Edema 2 days
Prognosis		Good	50% Deaths	100% Deaths	

## E. Long Term Effects

### 1. Introduction

Long-term effects of radiation are those which may manifest themselves years after the original exposure. The latent period, then, is much longer than that associated with the acute radiation syndrome. Delayed radiation effects may result from previous acute, high-dose exposures or from chronic low-level exposures over a period of years. From the standpoint of public health significance, the possibility of long-term effects on the large number of people receiving low, chronic exposures is cause for greater concern than the short-term radiation effects from acute exposures which involve only a few individuals.

It should be emphasized that there is no unique disease associated with the long-term effects of radiation; these effects express themselves in human populations simply as a statistical increase in the incidence of certain already-existing conditions. Because of the low normal incidence of these conditions, it is usually necessary to observe large populations of irradiated persons in order to measure this kind of increase, and employ biostatistical and epidemiologic methodology. In addition to the large numbers of people needed for human studies of long-term radiation effects, the situation is further complicated by the latent period; in some cases, a radiation-induced increase in a disease may go unrecorded unless the study is continued for many years.

It should also be noted that although it is possible to perform true experiments with animal populations, in which all factors with the exception of radiation exposure are kept identical in study populations, human data is limited to “second-hand” information, accrued from populations which have been irradiated for reasons other than radiobiological information. It is often the special characteristics of irradiated human populations, e.g., the presence of some pre-existing disease, which makes for caution in drawing meaningful conclusions when these groups are compared with non-irradiated ones.

Despite the above difficulties, many epidemiologic investigations of irradiated human beings have provided convincing evidence that ionizing radiation may indeed result in an increased risk of certain diseases long after the initial exposure. This information supplements and corroborates that gained from animal experimentation which demonstrates these same effects.

Among the long-term effects thus far observed have been somatic damage, which may result in an increased incidence of cancer, embryological defects, cataracts, and life span shortening; and genetic mutations, which may have an adverse effect for generations after the original radiation damage.

## 2. Carcinogenic Effects

With proper selection of animal species and strains, and of dose, ionizing radiation may be shown to exert an almost universal carcinogenic action, resulting in tumors in a great variety of organs and tissues. There is human evidence as well that radiation may contribute to the induction of various kinds of neoplastic diseases.

### a. Possible Carcinogenic Mechanisms

It should be made clear that even with high doses of radiation, most irradiated individuals will not suffer long-term consequences despite the fact that the incidence of certain diseases, such as leukemia and other forms of cancer, may be increased manyfold. The explanation may lie in the fact that most diseases are probably “caused” by the simultaneous interaction of several factors, and that the presence of some of these factors without the others may not be sufficient to induce the disease. Radiation, like other chemical and physical agents which are considered carcinogenic, may be only one of a number of interacting factors which, in a given individual, must be present in order to result in the disease.

Among the tentative explanations thus far proposed for the carcinogenic action of radiation are the following:

#### 1) Activation of a Latent Carcinogenic Virus

The essential factor in the production of cancers may be a virus which attacks normal cells by injecting itself into the cell nucleus. The genetic material of the virus, now within the host cell, stimulates the cell to reproduce wildly, thus initiating the neoplastic growth. The virus, it would seem, is ubiquitous, and even may be passed from mother to fetus during prenatal life. It would follow, then, that normal cells have a natural mechanism whereby the action of these viruses is resisted; it is possible that radiation and other carcinogenic agents may activate the latent virus or interfere with the cell's resistance. In this case, the presence of the virus in the cell would be the primary, initiating event, and the radiation would act as a promoting (catalytic) agent.

#### 2) Damage of Chromosomes

Certain diseases, among them leukemia, have been associated with specific chromosome aberrations. It may be that radiation damage can produce these abnormalities in the chromosomes and that these changes in turn initiate the disease.

### 3) Mutations in Somatic Cells

Radiation can produce mutations in many kinds of cells in the body including those in the reproductive organs (germ cells) as well as those in other parts of the body (somatic cells). It may be that a sufficient accumulation of mutations in a colony of cells can result ultimately in the kind of uncontrolled growth which results in cancer. The somatic mutation concept is an attractive one since it provides a means by which to relate both the carcinogenic effects of radiation and aging. Somatic mutations probably occur constantly at a low rate in all organisms and the resultant damage accumulates gradually in the affected tissues. When the level of malfunction or damage reaches a critical point, cell death or carcinogenesis could occur. Radiation, like other harmful agents, may accelerate the rate at which these mutations occur, thus hastening the death of the organism or the production of cancers.

When radiation doses are large enough to destroy a portion of the cells in an organ, the surviving cells, many of which may have undergone mutations as a result of the radiation exposure, are stimulated to rapid division in order to replace the missing ones. This resulting rapid division may be a concomitant factor in cancer production. In the somatic chromosome aberration or mutation processes, the radiation-induced change may be the primary or initiating event, with other factors playing a contributory or promoting role.

### 4) Formation of Free Radicals

As a result of the irradiation of water molecules, which are abundant in all living cells, certain short-lived but potent damaging agents called “free radicals” are formed and may play an important role in both cancer and aging. There is some evidence that these radicals are generated continually at a low rate as a byproduct of certain normal biochemical reactions in living cells, and that radiation simply accelerates their formation.

None of the above speculations need exclude the others. For example, free radicals are formed wherever living cells are irradiated, and so this takes place during all of the above processes. That cancer, mutations, and aging are interrelated seems reasonably clear, but the precise mechanisms involved have yet to be elucidated.

## **b. Human Evidence for Radiation Carcinogenesis**

Both empirical observations and epidemiologic studies of irradiated individuals have more or less consistently demonstrated the carcinogenic properties of radiation. Some of these findings are summarized below.

1) Radium Dial Painters

Early in this century, when long-term radiation effects were little recognized, luminous numerals on watches and clocks were painted by hand with fine sable brushes, dipped first in the radium-containing paint and then often tipped on the lips or tongue. Young girls commonly were employed in this occupation. Years later, studies of these individuals who had ingested radium paint have disclosed an increased incidence of bone sarcomas and other malignancies, resulting from the burdens of radium which had accumulated in their bones.

2) Radiologists and Dentists

Some early medical and dental users of x-rays, largely unaware of the hazards involved, accumulated considerable doses of radiation. As early as the year 1910, there were reports of cancer deaths among physicians, presumably attributable to x-ray exposure. Skin cancer was a notable finding among these early practitioners; dentists, for example, developed lesions on the fingers with which they repeatedly held dental films in their patients' mouths.

Of course, the excesses associated with the very early use of x-rays have diminished. Nonetheless, a more recent study comparing radiologists of various ages with physicians who do not use x-rays has shown that some groups of radiologists have a significantly higher incidence of leukemia than their non-radiologist counterparts. This difference seems to be largely confined to older radiologists who presumably received much of their exposure in the 1930's through 1950's when protective measures were not as widely employed as they are today.

3) Uranium Miners

Early in this century, certain large mines in Europe were worked for pitchblende, a uranium ore. Lung cancer was highly prevalent among the miners as a result of the inhalation of large quantities of airborne radioactive materials. It was estimated that the risk of lung cancer in the pitchblende miners was at least 50 percent higher than that of the general population.

Modern mining conditions have greatly improved. Nonetheless, recent studies have indicated a slight but statistically significant excess risk of lung cancer even among contemporary American uranium miners.

4) Atomic Bomb Survivors

One of the strongest supports for the concept that radiation is a leukemogenic agent in man comes from the epidemiologic studies of the

survivors of the atomic bombing of Hiroshima. Survivors exposed to radiation above an estimated dose of approximately 100 rem showed a significant increase in the incidence of leukemia. In addition, leukemia incidence correlated well with the estimated dose, thus strengthening the hypothesis that the excess leukemia cases were indeed attributable to the radiation exposure. Thyroid and breast cancers have also shown an increase among the heavily irradiated survivors. The latent period for these cancers appears to have been longer than that for the radiation-induced leukemias, ranging from approximately 10 to more than 20 years.

5) Ankylosing Spondylitis Patients

Ankylosing spondylitis, a progressively disabling arthritic disease of the spine, has been treated with large x-ray doses delivered to the vertebrae to slow the progress of the disease and to relieve its symptoms. Persons thus treated accumulated large doses of radiation to the bone marrow. A study of a large population of such persons revealed a much higher incidence of leukemia than might be expected in the general population. It is generally agreed that radiation received by these patients was a major factor in producing the excess leukemias. However, since a control group of spondylitis patients who had not been treated with x-rays was not available for comparison in the study, it is possible that a part of the observed increase in leukemia might have been caused by (a) a possible predisposition to leukemia on the part of ankylosing spondylitis patients, and/or, (b) a possible carcinogenic effect from the drug therapy which the patients may have received along with the x-ray treatments.

6) Children Irradiated for Thymus Enlargement

Many young children with respiratory distress were diagnosed in former years as having enlarged thymus glands and were treated with therapeutic doses of x-rays to the thymic region. A number of follow-up studies were performed on these children, and although results varied, it is generally agreed that these persons have experienced a significantly increased incidence of thyroid cancer and other malignancies of the head and neck. Such findings are not limited to thymic irradiation; further studies have demonstrated excess thyroid cancers and other head and neck malignancies as a result of childhood irradiation to this area of the body for the treatment of a wide variety of benign conditions such as enlarged tonsils and adenoids, acne, etc.

7) Tinea Capitis Patients

X-ray epilation was a widely used treatment for children with tinea capitis (ringworm of the scalp). A study of a group of such children in

New York City, and a similar investigation in Israel, indicate an increased incidence of thyroid cancer and leukemia in the irradiated children, as well as the possibility of functional changes in the central nervous system.

8) Patients Receiving Breast Irradiation

A link between high doses of radiation to the chest and breast cancer was discovered in a survey of women who had been treated for tuberculosis by artificial pneumothorax, a procedure which consisted of intentionally collapsing the affected lung for a period of time and then reinflating it. This was accomplished with the assistance of the fluoroscope, and in many cases the pneumothorax treatment was repeated, sometimes more than 100 times. The patient was often positioned in the vertical fluoroscope machine facing the x-ray tube, so that the largest radiation dose was delivered to the anterior surface of the chest. The incidence of breast cancer among these heavily irradiated patients was found to be 4 to 8 times the expected rate for this disease. Further, the investigators were able to show a correlation between the side of the chest receiving the treatment and the affected breast. A similar increase in breast cancer incidence was found in a group of women who had received x-ray treatment of the breast for postpartum mastitis.

9) Children Whose Mothers Were Irradiated During Pregnancy

A pioneering study in this area purported to show an increased risk of leukemia among young children if they had been irradiated in utero as a result of pelvic x-ray examination of the mother. Mothers of leukemic children were questioned as to their radiation histories during pregnancy with the child in question, and these responses were compared with those of a control group, consisting of mothers of healthy playmates of the leukemic children. Originally this work received much criticism, based partly on the questionnaire technique used to elicit the information concerning the radiation history. It was believed that the differences in recall between the two groups of mothers might have biased the results. A larger subsequent study designed to correct for the objections to the first one corroborated its essential findings.

It should be noted the investigations presented thus far which demonstrate the carcinogenic properties of radiation involve large doses, such as those received in therapeutic x-ray procedures, with the exception of these childhood leukemia investigations. Here, doses of radiation are low, in the diagnostic radiographic range. Such findings bear out the high sensitivity of embryonic tissues to radiation damage.

### c. Significance of Human Studies on Radiation Carcinogenesis

#### 1) Considerations in Epidemiologic Studies

In evaluating human studies of the kind described above, two important concepts should be borne in mind. Because the studies were not designed as radiobiological experiments in which all factors are held constant with the exception of radiation exposure, caution is required before the association between radiation and some later disease can be labeled as a cause-effect relationship. This is particularly true when the study group consists of patients irradiated for some disease or abnormality, since the question arises as to whether the abnormality itself might not account for the later disease rather than the irradiation. Sometimes further studies or the selection of a proper control group with which to compare the irradiated subjects can help to resolve these doubts. For example, in the spondylitis investigation, a valid question arose as to whether the disease itself might predispose the patient to develop leukemia later. A follow-up study which ascertained the leukemia incidence among non-irradiated rheumatic patients, helped to answer this question. Doubts concerning the studies of children with thymic irradiation could have been forestalled, had the control group consisted of children with diagnosed thymic enlargement who had not been treated with x-rays. It was not possible, however, to select such a control group; instead healthy siblings or cancer incidence from general population statistics were employed. Thus, although the weight of evidence in these studies points toward true radiation carcinogenesis, there is room for speculation as to whether the infants with enlarged thymus glands might not have been at least somewhat predisposed to the development of malignant diseases.

Even the studies of the relationship of prenatal x-ray examinations to childhood leukemias have been subject to the same kind of question, e.g., whether the special characteristics of the mothers and children in question which necessitated the pelvic x-rays in the first place might not be a predisposing factor in the development of leukemia, irrespective of, or in addition to, the radiation received. Despite these reservations, all of the above studies, when taken together, comprise an impressive accumulation of evidence indicating that ionizing radiation is a true carcinogen in man.

#### 2) Risk Versus Benefit

Assuming that studies such as these are valid, the question arises as to their practical implications. Even in investigations such as the spondylitis studies in which roughly a ten-fold increase in leukemia was observed, the additional risk to an irradiated individual remains small because of the relatively low normal incidence of leukemia. The small

but real increase in risk to the individual calls for an intelligent balancing in each case of the benefits to be accrued from the radiation exposure and techniques which are of great benefit to patients cannot be abandoned because of the risk of delayed harmful effects. On the other hand, if the same diagnostic information or therapeutic results can be obtained using techniques which reduce radiation exposure to the patient, or if equally effective non-radiologic procedures which do not involve such risk are available, such methods should be used.

### **3. Embryological Effects**

Considering the fact that immature, undifferentiated and rapidly dividing cells are highly sensitive to radiation, it is not surprising that embryonic and fetal tissues are readily damaged by relatively low doses of radiation. It has been shown in experiments with mice that deleterious effects may be produced with doses of only 10 rads delivered to the embryo during the period of organogenesis. There is no reason to doubt that the human embryo is equally susceptible. It should be emphasized that radiation is not unique in producing embryological effects and that a growing body of evidence exists which indicates that a host of external insults, including certain drugs, chemicals, and viral infections also can damage the highly sensitive embryo and fetus.

#### **a. Embryological Effect vs. Stage of Pregnancy**

The majority of the anomalies produced by prenatal irradiation involve the central nervous system, although the specific type of damage is related to the dose and to the stage of pregnancy during which irradiation takes place. In terms of embryonic death, the very earliest stages of gestation, perhaps the first few weeks of pregnancy in the human being, are most radiosensitive.

For the production of congenital anomalies in the newborn, irradiation during the period of organogenesis is of greatest importance. This period occurs during approximately the second through the sixth week of human gestation, when pregnancy could still be unsuspected. During the period, embryonic death is less likely than in the extremely early stage, but the production of morphological defects in the newborn is the major consideration.

During later stages of pregnancy, fetal tissue is more resistant to gross and easily observable damage. However, functional changes, particularly those involving the central nervous system, may result from such late exposures and would be difficult to measure or evaluate at birth. They usually involve subtle alterations in such phenomena as learning patterns and development and may have a considerable latent period before they manifest themselves. There is some evidence that the decreasing sensitivity of the fetus to gross radiation damage as pregnancy progresses may not apply for the leukemogenic effects of prenatal irradiation. Another important factor to be

considered in evaluating the radiation hazard during late pregnancy is that irradiation may produce true genetic mutations in the immature germ cells of the fetus for which no threshold dose has been established.

**b. Human Evidence for Embryological Effects**

Human evidence for embryological damage has been found among persons exposed in utero at the time of the atomic bombing of Hiroshima. Data obtained from their follow-up through childhood and adolescence into adulthood, in which groups exposed during gestation were compared with each other and with non-exposed controls on the basis of distance from the detonation and stage of pregnancy, shows a growth stunting effect among the exposed, particularly with regard to head size, and an increased incidence of mental retardation. The risk of these developmental defects correlates well with proximity to the bomb and thus with estimated dose; also, the results further corroborate the increased sensitivity to embryological damage during the first trimester of pregnancy.

**c. The Problem of Unsuspected Pregnancy**

The increased susceptibility to radiation damage during very early gestation, when pregnancy may still not be apparent, underscores the importance of taking possible pregnancy status into account when a physician is considering pelvic, abdominal or lower back x-rays for a woman of childbearing age. It is important to ascertain whether she is or may be pregnant, and to take this information into account in deciding on the necessity of the x-ray examination.

**4. Cataractogenic Effects**

The fibers which comprise the lens of the eye are specialized to transmit light. Damage to these, and particularly to the developing immature cells which give rise to them, can result in opacities in the lens called “cataracts,” which, if they are large enough, can interfere with vision. Radiation in sufficiently high doses can induce the formation of cataracts; the required dose for humans, which is difficult to ascertain, probably is in the order of several hundred rads for x- or gamma rays, and 1/5 to 1/10 of this for neutron irradiation.

Human evidence for radiation cataractogenesis is derived mainly from a relatively small number of workers inadvertently exposed to large doses of radiation to the eye, including several nuclear physicists working with cyclotrons; patients exposed to therapeutic radiation (sometimes from radium plaques applied to the eye); and Japanese atomic bomb survivors who were heavily irradiated.

## 5. Life Span Shortening

In a number of animal experiments, repeated large doses of radiation have been demonstrated to have a life span shortening effect. The aging process per se is complex and largely obscure, and the exact mechanisms involved in this effect are as yet uncertain. Irradiated animals in these investigations appear to die of the same diseases as the non-irradiated control animals, but they do so at an earlier age. How much of the total effect is due to premature aging and how much to an increased incidence of radiation-induced diseases is still unresolved.

### a. Mechanisms

A number of theories have been proposed to account for the phenomenon of aging in general, and for the aging effects of radiation in particular. One theory is that a variety of extrinsic insults produce tissue damage in organisms, some of which is repairable and some of which is irreparable. The irreparable, or residual components of various insults to the organism (infections, trauma, etc) are additive and cumulative, and when a certain critical amount of injury has accumulated, the organism dies. Because irradiation is one of the agents which can produce such injury, irradiated animals arrive at a lethal accumulation sooner than do the non-irradiated controls. Another theory proposes that radiation exerts its life span shortening effect by producing somatic mutations in the cells, which lower the organism's ability to function properly. It further states that organs having cells which seldom, if ever, divide are affected most by these mutations, and play a major part in the aging process.

### b. Human Evidence

A study in which death rates from various causes were established for radiologists and for two control groups, consisting of physicians who used radiation occasionally and those who did not use it at all, seems to show a true life span shortening effect among the radiologists. An association, of course, between two phenomena (in this case, being a radiologist and having a shorter life span than a non-radiologist) does not necessarily indicate that one is a cause of the other, and, recalling the caution with which epidemiologic studies must be interpreted, one might propose explanations for the association other than that the radiation causes the shortened life span. It is conceivable, for example, that those individuals choosing radiology as a specialty could be somewhat less healthy as a group than those selecting other fields, and thus a slightly shorter life span among the former would not necessarily relate to their radiation exposure. The investigators have considered such alternative explanations of the data, however, and because of certain strengthening factors in their findings, they nonetheless hold that a true life span-shortening effect was operative. An important finding in this study, which helps to support the general adequacy of current occupation radiation protection guidelines, is that the excess risk

of death among the radiologists is largely confined to those who practiced during the earlier years of x-ray use when safety practices were more lax and occupational exposures among radiologists were presumably much higher than today.

## 6. Genetic Effects

### a. Background

The fertilized egg, which is a single cell resulting from the union of sperm and egg, and which after millions of cell divisions results in a new organism, contains all of the genetic information necessary to produce all of the organs and tissues of the new individual. This information is carried in the nucleus of the fertilized egg on rod-shaped structures called chromosomes, arranged in 23 pairs in man. In each pair, one member is contributed by the mother and the other by the father. With each cell division which the rapidly developing embryonic tissue undergoes, all of this information is faithfully duplicated, so that the nucleus in each cell of the new organism contains essentially all of the information. This, of course, includes those germ cells in the new organism which are destined to become sperm and egg, and thus the information is transmitted from one generation to the next. This hereditary information is often likened to a template, or to a code, which is reproduced millions of times over with remarkable accuracy. It is possible to damage the hereditary material in the cell nucleus by means of external influences, and when this is done the garbled or distorted genetic information will be reproduced just as faithfully when the cell divides as was the original message. When this kind of alteration occurs in those cells of the ovaries or testes which will become mature sperm and egg, it is referred to as genetic mutation; if the damaged sperm or egg cell is then utilized in conception, the defect is reproduced in all of the cells of the new organism which results from this conception, including those which will become sperm or egg, and thus whatever defect resulted from the original mutation can be passed on for many generations.

Most geneticists agree that the great preponderance of genetic mutations are harmful. By virtue of their damaging effects, they can be gradually eliminated from population by natural means, since individuals afflicted with this damage are less likely to reproduce themselves successfully than normal individuals. The more severe the deficit produced by a given mutation, the more rapidly it will be eliminated, and vice-versa; mildly damaging mutations may require a great many generations before they gradually disappear.

As a balance to this natural elimination of harmful mutations, fresh ones are constantly occurring. A large number of agents have mutagenic properties, and it is probable that our current knowledge includes just a fraction of these. In addition, it may be that mutations can arise with the germ cells of

an organism without external insult; free radicals, which may be produced as a natural byproduct of normal metabolic reactions in the body, may have a mutational effect. Among the various external influences which have been found to be mutagenic are a wide variety of chemicals, certain drugs, and physical factors such as elevated temperatures and ionizing radiation. Natural background radiation probably accounts for a small proportion of naturally occurring mutations. For man, it has been estimated that background radiation probably produces less than ten percent of these. Manmade radiation, of course, if delivered to the gonads, can also produce mutations, over and above those which occur spontaneously. Radiation, it should be noted, is not unique in this respect, and is probably one of a number of manmade environmental influences that is capable of increasing the mutation rate.

## **b. Observing Mutations**

### **1) The Difficulties of the Task**

Measuring changes in the normal mutation rate in humans is extremely difficult for several reasons. First, the majority of mutations are recessive, that is, their full effects do not manifest themselves in an individual unless he or she carries the same mutational defect in the same location of a given pair of chromosomes, i.e., unless both the mother and father were afflicted with the same kind of genetic damage. It can be seen from this that it might take many generations after a genetically damaging event occurred in a population before enough individuals carrying the recessive mutation mated with one another to produce offspring who would demonstrate overt damage. Secondly, contrary to popular impression, the damage produced by most mutations is subtle in its effects and difficult to measure. Mutations, for example, may result in a slightly altered metabolism, in which there is a less efficient utilization of certain nutritional elements, or a slightly greater predisposition to a given disease, or a slightly lower intelligence than would otherwise have been attained. Adding to this is the difficulty encountered in extricating true genetic phenomena from other influences which may produce the same results. It would be most difficult, for example, to determine whether an individual's predisposition to heart disease were due to a subtle genetic defect in his cardiovascular system, or to environmental stresses such as diet or occupation, or to personality and developmental factors in childhood, etc.

### **2) Indicators of Change in the Mutation Rate**

Despite these difficulties, it is possible to observe fluctuations in the mutation rate if large enough populations are available for close study. Certain diseases, for example, have been linked to specific genetic defects, and an increase or decrease in the incidence of these diseases

would indicate a concomitant change in the mutations rate. Certain mutations are lethal; they are highly damaging and result in intrauterine death. Other factors being equal, significant fluctuations in the incidence of these deaths in a population might serve as a rough barometer for changing mutation rates. Observing a population for evidence of genetic mutations can be likened to watching an iceberg; most of the iceberg is invisible, with only a small portion above the water. Changes in the size of the observable part serve to give some indication of the more significant changes taking place beneath the surface. (For a discussion of the difficulties and techniques in finding and evaluating genetic radiation damage, see Chapter 7, "The Quantitative Assessment of Hereditary Damage Induced by Radiation," by James and Newcombe, in *Progress in Medical Genetics*, Vol. 3, Grune and Stratton, Inc., New York, 1964.

### 3) What Can Be Observed in the First Generation

Even in the first generation after a population has been exposed to a possibly mutagenic event, it is possible to observe the effects of certain kinds of mutations. Dominant mutations, i.e., those which manifest their full effects even when only one parent carries the mutation, may be evident in the offspring. Those which are also lethal will appear as an increase in intrauterine deaths. There is a particular kind of recessive mutation which can also be observed in the first generation, the sex-linked mutation. Of the 23 pairs of chromosomes in the fertilized egg, one pair determines the sex of the offspring. In this pair, females carry two full-sized chromosomes, called X chromosomes, while males carry one X chromosome and one Y chromosome, which is much smaller and which probably does not carry a full complement of genetic information. If a recessive mutation arises on one of the X chromosomes of the mother, female offspring who inherit it, but now have the benefit of the matching normal X chromosome of the father, will not demonstrate this recessive characteristic. Male offspring, however, to whom the mother has contributed this defective X chromosome, have only the small Y chromosome contributed by the father to offset the deficit, and as a result the damage will appear in these males, despite its having been produced by a recessive mutation. Recessive sex-linked mutations of this kind which are also lethal will thus show up as an increase in the number of intrauterine deaths among boys, and not among girls. This provides a useful yardstick for assessing genetic damage in an irradiated population, for if a sub-population is selected in which mothers have been irradiated and fathers have not, then a lowering in the percentage of boys born versus girls, i.e., a reduction in the sex-ratio, might be an indicator of genetic damage.

### c. Animal Evidence of Genetic Effects

The mutagenic properties of ionizing radiation were first discovered in 1927, using the fruit fly as the experimental animal. Since that time, experiments have been extended to include other species, and a great deal of recent investigation has been carried out on the mouse. Animal experimentation remains our chief source of information concerning the genetic effects of radiation, and as a result of the intensive experimentation which has been carried out during recent years, certain generalizations may be made. Among those of health significance are (1) that there is no indication of a threshold dose for the genetic effects of radiation, i.e., a dose below which genetic damage does not occur, and (2) that the degree of mutational damage which results from radiation exposure seems to be dose-rate dependent, so that a given dose is less effective in producing damage if it is protracted or fractionated over a long period of time.

### d. Human Evidence of Genetic Effects

#### 1) Atomic Bomb Survivors (Prenatal Exposure)

A major human study on genetic effects has concerned the Japanese atomic bomb survivors. As the index of a possible increase in the mutation rate, the sex-ratio in the offspring of certain irradiated groups (families, for example, in which the mother had been irradiated but the father had not) was observed, using the approach described earlier. Although early reports showed a shift in the ratio of boys versus girls in these families, later evaluation of more complete data did not bear out the original suggestion of an effect on the sex-ratio.

#### 2) Cancer in Children Exposed *In Utero* to Diagnostic X-rays

The pre-conception radiation histories of the parents of leukemic children as compared with those of normal children was a part of the subject of another investigation. From the results, it appears that there may be a statistically significant increase in leukemia risk among children whose mothers had received diagnostic x-rays during this period. The effect here is apparently a genetic rather than an embryologic one, since the irradiation occurred prior to the conception of the child. This finding remains to be confirmed with further study.

A somewhat similar study ascertained the radiation exposure histories of the parents of children with Down's Syndrome; most of this exposure too, was prior to the conception of the child. A significantly greater number of the mothers of children with Down's Syndrome reported receiving diagnostic fluoroscopy and x-ray therapy prior to the birth of the Down's child than did mothers of normal children comprising a control group.

The finding of these two studies would seem to provide evidence that ionizing radiation is a mutational agent in man. On the other hand, they can be viewed with the same kind of reservations as were explained previously, i.e., there could be significant differences to begin with between populations of people requiring x-rays and those not requiring x-rays. These differences alone might account for a slightly higher incidence of leukemia or Down's Syndrome in the offspring of the former group, irrespective of the radiation received; however, when viewed in conjunction with available evidence concerning the mutagenic nature of ionizing radiation, the most reasonable and prudent interpretation of studies such as these is that the effects observed are due at least in part to the x-rays received by the children.

**e. Health Significance of Genetic Mutations**

Recalling the previous discussion concerning the natural elimination of harmful mutations and the simultaneous introduction of fresh ones into a population, the total number of mutations present may be likened to the water in a tank, in which in-flow at the top represents new mutations and out-flow at the bottom represents the elimination of old mutations. The water level does not necessarily remain constant; if the rate at which new mutations are produced exceeds that at which old ones are discarded, the pool of mutations grows larger. The reverse is true if the output exceeds the input, with a resultant lowering of the pool. With contemporary human populations, it is highly desirable to keep the level of the mutational pool as low as possible, since the pool largely represents diseases and defects which tend to lower overall biological fitness. However, two factors unique to modern life may tend to increase the level. First, human populations are being exposed to a greater and greater number of potential mutagens as a result of a progressive increase in the variety and quantity of manmade chemical and physical agents which are a product of our technological advances. Secondly, modern medical knowledge and techniques result in the salvage of more and more individuals with genetic defects so that they may reproduce themselves, thus distributing these defects to an ever-larger number of people. In the face of these factors which tend to increase the mutational load in the world's population, it is all the more important, if the level of the pool is to be kept at a minimum, to make every effort to maintain the influx of new mutations as small as possible. Considering the potent mutagenic properties of ionizing radiation, the goal, then, is clear: to avoid any unnecessary irradiation of the gonads.

## Suggested General References

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## Glossary

**abscissa:** Coordinate representing the distance of a point from the y-axis in a plane Cartesian coordinate system, measured along a line parallel to the x-axis.

**acute radiation syndrome:** A term used to refer to the signs and symptoms which comprise short-term effects after radiation is delivered to the whole body.

**ankylosing spondylitis:** Progressively disabling arthritic disease of the spine.

**biological:** Of, pertaining to, caused by, or affecting life or living organisms.

**carcinogenic:** Cancer causing substance.

**cerebral:** Of or pertaining to the brain or cerebrum.

**chromosome:** A DNA-containing linear body of the cell nuclei of plants and animals, responsible for the determination and transmission of hereditary characteristics.

**dose response curve:** The curve plotted by correlating the dosage administered with the response of damage produced, in order to establish acceptable levels of radiation exposure.

**Down's Syndrome:** A congenital disorder characterized by moderate to severe mental retardation, a short flattened skull, and slanting eyes.

**free radicals:** An atom or group of atoms having at least one unpaired electron.

**fluoroscope:** A fluorescent screen on which the internal structure of an optically opaque object, as of the human body, may be continuously viewed by transmission of x-rays through the object.

**gastrointestinal:** Of or pertaining to the stomach and the intestines.

**hematopoietic:** The formation of blood in the body.

***in utero:*** Within the uterus.

**irradiate:** To expose to radiation.

**latent period:** Time lag between the initial radiation event and occurrence of the first detectable effect.

**leukemia:** Any of a group of usually fatal diseases of the reticuloendothelial system involving uncontrolled proliferation of leukocytes.

**long-term effects:** Effects which appear years, decades, and sometimes generations after an event.

**mastitis:** Inflammation of the breast.

**mutation:** An alteration or change.

**neoplasm:** An abnormal new growth of tissue in animals or plants; tumor.

**non-threshold phenomenon:** In the dose response curve, where the curve intersects the abscissa at the origin, it is assumed that any dose, no matter how small, involves some degree of response.

**organogenesis:** The origin and development of biological organs.

**pitchblende:** Principal ore of uranium, a brownish-black mineral of uraninite and uranium trioxide with small amount of water and uranium decay products.

**pneumothorax:** Accumulation of air or gas in the pleural cavity, occurring as a result of disease or injury, or sometimes induced to collapse the lung in the treatment of tuberculosis and other lung diseases.

**prodrome:** A symptom of the onset of a disease.

**rad:** Unit of energy absorbed from ionizing radiation, equal to 100 ergs per gram of irradiated material.

**radiosensitive:** Sensitive to radiation.

**short-term effects:** Effects which appear within a matter of minutes, days, or weeks.

**somatic cell:** A bodily cell other than a germ cell.

**tinea capitis:** Ringworm of the scalp.