CHAPTER 5

BIOLOGICAL EFFECTS OF IONIZING RADIATION

BIOLOGICAL EFFECTS OF IONIZING RADIATION

I. 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 1920's and 30's, 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.

II. MECHANISMS OF RADIATION DAMAGE

Radiation damage starts at the cellular level. Radiation which is absorbed in a cell has the potential to impact a variety of critical targets in the cell, the most important of which is the DNA. Evidence indicates that damage to the DNA is what causes cell death, mutation, and carcinogenesis. The mechanism by which the damage occurs can happen via one of two scenarios.

A. Direct Action

In the first scenario, radiation may impact the DNA directly, causing ionization of the atoms in the DNA molecule. This can be visualized as a “direct hit” by the radiation on the DNA, and thus is a fairly uncommon occurrence due to the small size of the target; the diameter of the DNA helix is only about 2 nm. It is estimated that the radiation must produce ionization within a few nanometers of the DNA molecule in order for this action to occur.

B. Indirect Action

In the second scenario, the radiation interacts with non-critical target atoms or molecules, usually water. This results in the production of free radicals, which are atoms or molecules that have an unpaired electron and thus are highly reactive. These free radicals can then attack critical targets such as the DNA (Figure 1). Because they are able to diffuse some distance in the cell, the initial ionization event does not have to occur so close to the DNA in order to cause damage. Thus, damage from indirect action is much more common than damage from direct action, especially for radiation that has a low specific ionization.

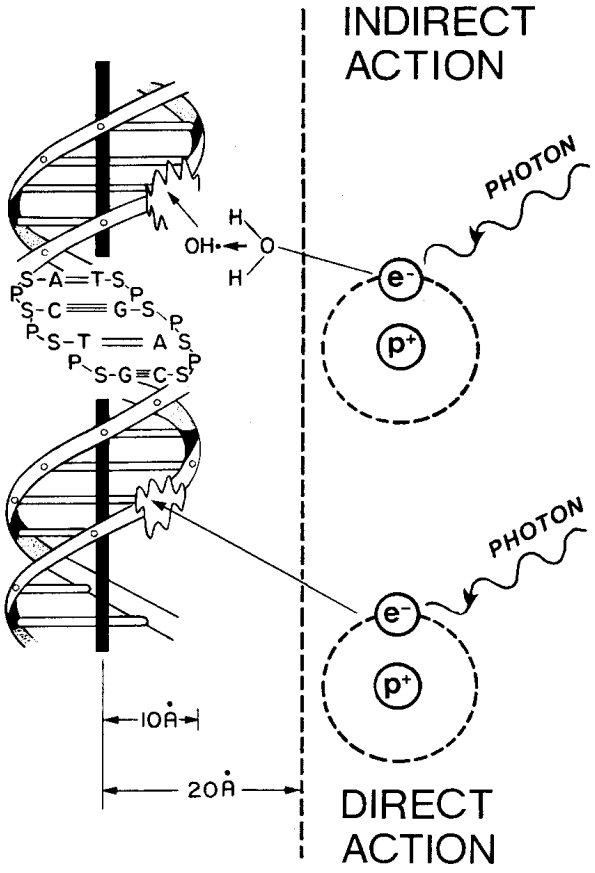

Figure 1: Mechanisms of Radiation Damage

When the DNA is attacked, either via direct or indirect action, damage is caused to the strands of molecules that make up the double-helix structure. Most of this damage consists of breaks in only one of the two strands and is easily repaired by the cell, using the opposing strand as a template. If, however, a double-strand break occurs, the cell has much more difficulty repairing the damage and may make mistakes. This can result in mutations, or changes to the DNA code, which can result in consequences such as cancer or cell death. Double-strand breaks occur at a rate of about one double-stand break to 25 single-strand breaks. Thus, most radiation damage to DNA is reparable.

III. DETERMINANTS OF BIOLOGICAL EFFECTS

A. Rate of Absorption

The rate at which the radiation is administered or absorbed is most 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 (thus allowing time for recovery between dose increments) than if it were given in a single exposure.

B. Area Exposed

The portion of the body irradiated is an important exposure parameter because the larger the area exposed, other factors being equal, the greater the overall damage to the organism. This is because more cells have been impacted and there is a greater probability of affecting large portions of tissues or organs. 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.

C. 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 for animals 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 humans, the $LD_{50/60}$ (the dose required to kill 50 percent of the population in 60 days) is used because of the longer latent period in humans (see section V). The $LD_{50/60}$ for humans is estimated to be approximately 300-400 rad for whole body irradiation, assuming no treatment is given. It can be as high as 800 rad with adequate medical care. It is interesting to note that the guinea pig has a LD_{50} similar to humans.

D. 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. This radiosensitivity is defined as the "Law of Bergoniè and Tribondeau". One exception to this law is mature lymphocytes, which are highly radiosensitive.

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.

IV. THE DOSE-RESPONSE CURVE

For any biologically harmful agent, it is useful to correlate the dosage administered with the response or 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 2a and 2b.

Figure 2a represents 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 a "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 2b 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 carcinogenic effects of radiation constitute a non-threshold phenomenon, so one of the underlying (and prudent) assumptions in the establishment of radiation protection guidelines 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.

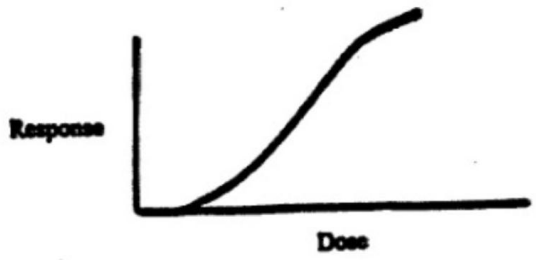

Figure 2(a)

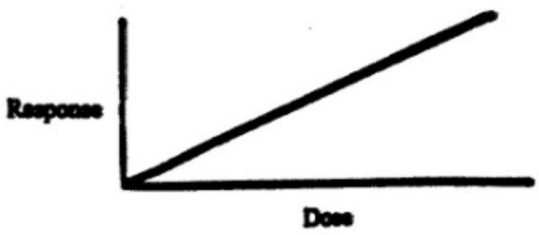

Figure 2(b)

V. PATTERN OF BIOLOGICAL EFFECTS

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

A. Prodromal Stage

Symptoms which appear quickly after radiation exposure are referred to as prodromal radiation syndrome. The severity of the symptoms experienced in this stage can give a rough indication of the magnitude of exposure and the clinical prognosis. Low-level exposures such as those typically encountered in an occupational setting will not produce observable prodromal symptoms, although there is still some reaction on a cellular level. Symptoms during this stage are temporary (except at extremely high exposures) and soon progress to the latent period.

B. Latent Period

Following the initial radiation exposure, and before the full-blown biological 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.

C. Period of Demonstrable Effects on Cells and Tissues

During or immediately following the latent period, certain discrete effects can be observed. The exact nature and range of effects depends on the dose received and area of the body exposed, and will be described in more detail in following sections. 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, formation of giant cells and/or other abnormal mitosis. It should be pointed out that many of these effects can be duplicated individually with other types of agents. However, the entire gamut of effects cannot be reproduced by any single chemical agent.

D. 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.

VI. SHORT-TERM EFFECTS

An acute dose of radiation is one which is delivered to the body over a short time period. 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.

A. Acute Radiation Syndrome

When the radiation is delivered to the whole body in large doses, generally over 100 rad, the signs and symptoms which comprise the short-term effects that occur are collectively known as Acute Radiation Syndrome. This type of injury occurs only when the dose is received over a short period of time, and the total effect may vary from mild and transient illness to death.

Acute Radiation Syndrome progresses in the following stages:

1. Prodrome
   The symptoms present in this initial phase of the syndrome depend on the dose received, and may not be noticeably present at low doses. Lymphocyte counts start to drop measurably following whole-body exposures as low as 50 rad. For whole-body doses in the LD_{50} range, common symptoms include tiredness, nausea, and vomiting. Immediate diarrhea, fever, or hypotension usually indicate a lethal exposure.

2. Latent Stage
   During this phase, which may be likened to the incubation period of viral infection, the subjective symptoms of illness may subside, and the individual may feel well. However, changes may be taking place within the blood-forming organs and elsewhere which will subsequently give rise to the next aspect of the syndrome. The length of this stage can last up to 4 weeks for smaller doses, with the length of time generally decreasing as dose increases. It may not be present at all for very large doses.

3. Manifest Illness Stage
   This phase reflects the clinical picture specifically associated with the radiation injury. The possible manifestations of this stage, which are largely dependent on the dose received, are described below.

4. Recovery or Death
   With adequate medical care, recovery is likely at whole-body doses below 800 rad and possible at doses up to 1,000 rad. Death appears to be inevitable above 1,000 rad.

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. This syndrome is often survivable, but if death occurs, it does so within 60 days following exposure.

At higher doses, usually over 1,000 rad, 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 the gastrointestinal form of the acute radiation syndrome. Death occurs 5-10 days after exposure.

In the cerebrovascular form, which may result from doses of 10,000 rad 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. The latent period is very short or absent, and death typically occurs within 48 hours.

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 rad or less, ordinary laboratory or clinical methods will show no indications of injury from whole-body irradiation. At 100 rad, most individuals show no symptoms, although a small percentage may show mild blood changes. At 200 rad, most persons show definite signs of injury; this dose level may prove fatal to those individuals most sensitive to the effects of radiation. At 400 rad, the median lethal dose has been reached, and 50 percent of exposed individuals will succumb without medical treatment. Death is likely at doses over 800 rad, although survival at that level may be possible with a bone marrow transplant. Approximately 1,000 rad usually marks the threshold of the gastrointestinal form of the acute radiation syndrome, at which point a fatal outcome is fairly certain.

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 (See Table 1).

Table 1: Acute Radiation Syndrome

Dose	100-200 rad	200-400 rad	400-600 rad	600-1000 rad	> 1000 rad
Latent Period	> 30 days	18-28 days	8-18 days	< 7 days	3-5 days
Symptoms	Fatigue, weakness	Fever, infections, bleeding, weakness, hair loss	High fever, infections, bleeding, hair loss	High fever, diarrhea, vomiting, dizziness, low blood pressure	Nausea, vomiting, prolonged diarrhea, lethargy
Lethality	0%	0-50%	20-70%	50-100%	100%

B. Localized Exposure

Injury can also be caused when only localized areas of the body are exposed to radiation. A common example of this is exposure to the skin due to contamination or imprudent use of x-rays. Mild erythema (reddening) of the skin can occur at skin doses of around 200 rad, while doses of 600 rad cause more severe erythema 10-14 days after exposure. A skin dose of 300 rad may cause temporary hair loss, with 700 rad causing permanent hair loss. At doses over 1,000 rad, effects such as desquamation (shedding of the skin) and tissue necrosis may also occur. In most cases skin effects are short-term, although in severe cases, symptoms may persist for years.

It is important to realize that a localized exposure of a given dose is usually not as dangerous as a whole-body exposure of the same dose. This idea is the basis for the use of tissue weighting factors to calculate Effective Dose or Effective Dose Equivalent, as described in Chapter 2. It is also the reason why very high doses of radiation (sometimes up to 10,000 rad) can be used in a highly localized manner to treat cancers, without causing death to the patient.

VII. LONG-TERM EFFECTS

A. 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 exposure 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 exposure 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 lifespan shortening; and genetic mutations, which may have an adverse effect for generations after the original radiation damage.

B. 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 disease.

1. 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 a 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:

a) 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.

b) 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 reached 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.

c) 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 whenever 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.

2. 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.

a) Radium Dial Painters. Early in the 1900's, 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 showed an increased incidence of bone sarcomas and other malignancies resulting from the radium which had accumulated in their bones.

b) 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 patient's mouths.

Of course, the excesses associated with the very early use of x-rays have diminished. A recent study comparing mortality data from radiologists of various ages with physicians who do not use x-rays has shown that radiologists who were in practice prior to the 1920's, when protective measures were not widely employed, showed a statistically significant excess of cancers. This excess was not evident in younger radiologists.

c) 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. Lung cancer incidence has also been found to be elevated in many non-uranium miners due to a build-up of radon gas in the mines.

d) Atomic Bomb Survivors. One of the strongest supports for the concept that radiation is a carcinogenic agent in man comes from the epidemiologic studies of the survivors of the atomic bombing of Hiroshima and Nagasaki. 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.

e) Ankylosing Spondylitis Patients. Ankylosing spondylitis, a progressively disabling arthritic disease of the spine, had 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 slightly 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 leukemia. 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.

f) 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.

g) Tinea Capitis Patients. X-ray epilation was a widely used treatment for children with tinea capitis (ringworm of the scalp) up until the 1950's.

A study of a group of such children in Israel indicated an increased incidence of thyroid cancer, brain tumors, skin cancer, and leukemia in the irradiated children. A study of another group of children in New York showed only two cases of thyroid cancer and an elevated incidence of skin cancer.

h) 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.

i) Children Whose Mothers Were Irradiated During Pregnancy. A 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 techniques used to elicit the information concerning radiation history. It was believed that difference 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 that 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.

3. Significance of Human Studies on Radiation Carcinogenesis

a) 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 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 leukemia 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.

c) 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 the concomitant hazard. Valuable therapeutic and diagnostic x-ray 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-radiological procedures which do not involve such risk are available, such methods should be used.

C. 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, is probably on the order of several hundred rad for x- or gamma rays, and 1/5 to 1/10 of that amount for neutron irradiation. Cataract formation is a deterministic effect, meaning that it does not occur below a minimum threshold dose, and the severity of the cataract is related to the dose. The time required for the cataracts to form can range from 6 months to 35 years, and appears to be inversely related to the dose received.

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.

D. Lifespan Shortening

In a number of animal experiments, repeated large doses of radiation have been demonstrated to have a lifespan shortening effect. The aging process is complex, and the exact mechanisms involved in this effect are not well understood. 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.

1. 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 reparable 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 lifespan 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.

2. Human Evidence

Human evidence for lifespan shortening is inconclusive. One 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 lifespan shortening effect among the radiologists. The investigators considered alternative explanations for the data, but because of certain strengthening factors in their findings, they nonetheless held that a true lifespan shortening effect was operative. An important finding in this study, however, 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.

Other studies have indicated no lifespan shortening effect, or even the opposite effect of lifespan lengthening! It appears that while there may be some lifespan shortening associated with large doses of radiation, the effect on most occupationally exposed individuals is probably negligible.

E. Genetic Effects

1. Background

The fertilized egg, which is a single cell resulting from the union of a sperm and an 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 cell on rod-shaped structures called chromosomes, arranged in 23 pairs in humans. 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 produce mature sperm and egg cells, 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 the ovaries or testes which will produce sperm or egg cells, 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 within 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.

2. Observing Mutations

a) 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 on a given pair of chromosomes, i.e., unless both the mother and the 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 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 was 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.

b) 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 mutation 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 of 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.

c) What Can Be Observed in the First Generation - Even in the first generation after a population has been exposed to a possible 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 who have the benefit of the matching normal X chromosome from 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, i.e., if a sub-population is selected in the percentage of boys born versus girls, a reduction in the sex ratio might be an indicator of genetic damage.

3. 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 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 (a) 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.

4. Human Evidence of Genetic Effects

a) 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.

b) The pre-conception radiation histories of the parents of leukemic children as compared with those of normal children were 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 embryological one, since the irradiation occurred prior to the conception of the child. This finding remains unconfirmed.

A somewhat similar study ascertained the radiation exposure histories of the parents of children with Down Syndrome (trisomy 21); most of this exposure too, was prior to the conception of the child. A

significantly greater number of the mothers of children with Down Syndrome reported receiving diagnostic fluoroscopy and x-ray therapy prior to the birth of the child than did mothers of normal children comprising a control group.

The findings 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 also might account for a slightly higher incidence of leukemia or Down 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 parents.

5. 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 water in a tank, in which in-flow at the top represents new mutations and out-flow at the bottom represents the eliminations 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.

VIII. EMBRYOLOGICAL EFFECTS

The majority of the anomalies which are 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. The severity of embryological effects correlates well with the dose received. Larger doses to the embryo/fetus usually result in effects that are more severe. In terms of embryonic death, the very earliest stages of gestation, perhaps the first few weeks of pregnancy in the human being, are the most radiosensitive.

It has been shown in experiments with mice that deleterious effects may be produced with doses of only 10 rad 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 which are 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. The severity of embryological effects correlates well with the dose received. Larger doses to the embryo/fetus usually result in effects that are more severe. In terms of embryonic death, the very earliest stages of gestation, perhaps the first few weeks of pregnancy in the human being, are the 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 would still be unsuspected. During this period, embryonic death is less likely than in the extremely early stages, 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 exposure 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.

(See Figure 3, page 24).

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 the 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 detonation 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.

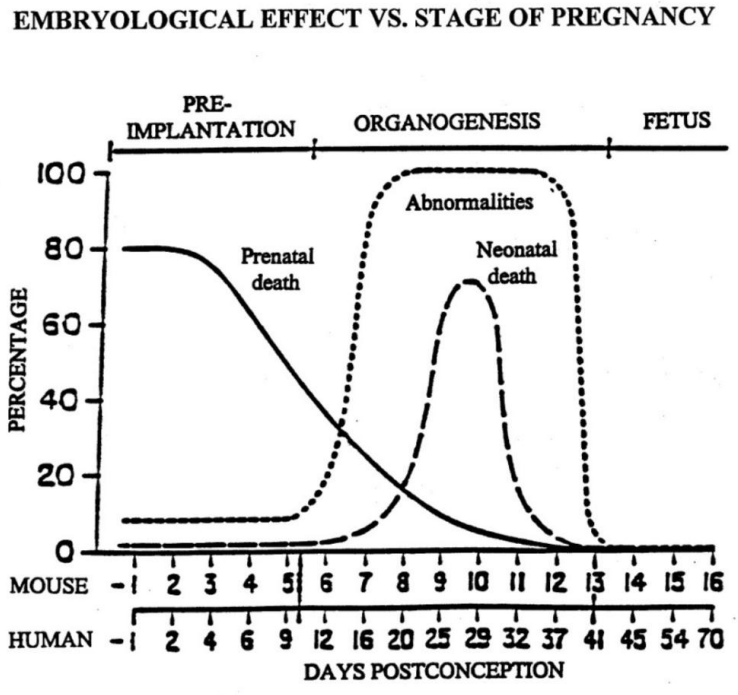

Figure 3: Incidence of abnormalities and of prenatal and neonatal deaths in mice, given a dose of 200 R at various times after fertilization.

IX. INSTRUCTION CONCERNING PRENATAL RADIATION EXPOSURE

A. Introduction

Section 64E-5.902 Chapter 64E-5, FAC, requires that all individuals working in or frequenting any portion of a restricted area be instructed in the health protection problems associated with exposure to radioactive materials or radiation, in precautions or procedures to minimize exposure and in the regulations that they are expected to observe. This section describes the instructions that should be provided concerning biological risk to the embryo/fetus exposed to radiation, a dose limit for the embryo/fetus, and suggestions for reducing radiation exposure.

B. Discussion

It is important to note that the mother assumes all risk until she specifically declares her pregnancy, in a written and signed statement, to her Principal Investigator and the Radiation Control Officer. Upon receipt of the statement by the Radiation Control Office, the University and Principal Investigator become responsible for assuring that the fetus's exposure will not exceed regulatory limits, and the mother is considered a declared pregnant worker. Section 64E-5.311, FAC, places different radiation dose limits on declared pregnant workers than on adult occupational workers. Because of the sensitivity of the unborn child, the exposure to the unborn child of a "declared pregnant worker" shall be limited to 500 millirem (5 mSv) for the entire pregnancy (Refs 20, 25, 26). The guidance also recommends that substantial variations in the rate of exposure be avoided and efforts should be made to avoid exceeding 50 mrem per month to the embryo/fetus. If the dose to the fetus is determined to have already exceeded 500 mrem when a worker notifies her Principal Investigator and the Radiation Control Officer of her pregnancy, the worker shall not be assigned to tasks where additional occupational radiation exposure is likely during the remainder of the gestation period.

It is the responsibility of the pregnant worker to decide when or whether to formally declare her condition; as such declaration of pregnancy is strictly voluntary. In some circumstances, the declared pregnant worker may have to make some adjustments to her working conditions or procedures in order to reduce the exposure to the fetus. However, if a woman chooses not to declare her pregnancy, she will continue to be governed by the guidelines set forth for occupational exposure limits.

C. Regulatory Position

NRC and State regulations and guidance are based on the conservative assumption that any amount of radiation, no matter how small, can have a harmful effect on an adult, child, or unborn child. This assumption is said to be conservative because there are no data showing ill effects from small doses; the National Academy of Sciences recently expressed "uncertainty as to whether a dose of, say, 1 rad would have any effect at all." As it is known that the unborn child is more sensitive to radiation than adults, particularly during certain stages of development, the NRC and State have

established a special dose limit for protection of the unborn child. However, a limit could result in job discrimination for women of childbearing age. The NRC and State has taken the position that special protection of the unborn child should be voluntary and should be based on decisions made by workers and employers who are well informed about the risks involved.

For the NRC and State position to be effective, it is important that both the employee and the employer understand the risk to the unborn child from radiation received as a result of the occupational exposure of the mother. Instructions on radiation risks should be provided to workers, including supervisors, in accordance with Section 64E-5.902 before they are allowed to work in a restricted area. In providing instructions on radiation risks, employers should include specific instructions about the risks of radiation exposure to the embryo/fetus. The instructions should be presented both orally and in printed form, and the instructions should include, as a minimum, the information provided in this Section. Individuals should be given the opportunity to ask questions and in turn should be questioned to determine whether they understand the instructions.

D. Effect On The Embryo/Fetus Of Exposure To Radiation And Other Environmental Hazards

For the NRC and State position to be effective, it is important that both the employee and the Principal Investigator understand the risk to the unborn child from radiation received as a result of the occupational exposure of the mother. This section tries to explain the risk and to compare it with other, more familiar, risks to the unborn child during pregnancy. This will hopefully help pregnant employees evaluate the risk to the unborn child against the benefits of employment. In order to decide whether to continue working while exposed to ionizing radiation during her pregnancy, a woman should understand the potential effects on an embryo/fetus, including those that may be produced by various environmental risks such as smoking and drinking. This will allow her to compare these risks with those produced by exposure to ionizing radiation.

Table 2 provides information on the potential effects resulting from exposure of an embryo/fetus to radiation and nonradiation risks. The second column gives the rate at which the effect is produced by natural causes in terms of the number per thousand cases. The fourth column gives the number of additional effects per thousand cases believed to be produced by exposure to the specified amount of the risk factor.

The following section discusses the studies from which the information in Table 2 was derived. The results of exposure of the embryo/fetus to the risk factors and the dependence on the amount of the exposure are explained.

1. Radiation Risks

   a) Childhood Cancer -Numerous studies of radiation-induced childhood cancer have been performed, but a number of them are controversial.

The National Academy of Science (NAS) BEIR reports reevaluated the data from these studies and even reanalyzed the results. Some of the strongest support for a causal relationship is provided by twin data from the Oxford survey (Ref. 4). For maternal radiation doses of 1,000 millirem, the excess number of deaths (above those occurring from natural causes) was found to be 0.6 deaths per thousand children (Ref. 4).

b) Mental Retardation and Abnormal Smallness of the Head (Microcephaly) - Studies of Japanese children who were exposed while in the womb to the atomic bomb radiation at Hiroshima and Nagasaki have shown evidence of both small head size and mental retardation. Most of the children were exposed to radiation doses in the range of 1 to 50 rad. The importance of the most recent study lies in the fact that investigators were able to show that the gestational age (age of the embryo/fetus after conception) at the time the children were exposed was a critical factor (Ref. 7). The approximate risk of small head size as a function of gestational age is shown in Table 2. For a radiation dose of 1,000 millirem at 4 to 7 weeks after conception, the number of excess cases of small head size was 5 per thousand; at 8 to 11 weeks, it was 9 per thousand (Ref. 7).

In another study, the highest risk of mental retardation occurred during the 8 to 15 week period after conception (Ref. 8). An EPA study (Ref. 16) has calculated that excess cases of mental retardation per live birth lie between 0.5 and 4 per thousand per rad.

c) Genetic Effects - Radiation-induced genetic effects have not been observed to date in humans. The largest source of material for genetic studies involves the survivors of Hiroshima and Nagasaki, but the 77,000 births that occurred among the survivors showed no evidence of genetic effects. For doses received by the pregnant worker in the course of employment considered in this guide, the dose received by the embryo/fetus apparently would have a negligible effect on descendants (Ref. 17 and 18).

2. Nonradiation Risks

a) Occupation - A study (Ref. 9) involving the birth records of 130,000 children in the State of Washington indicates that the risk of death to the unborn child is related to the occupation of the mother. Workers in the metal industry, the chemical industry, medical technology, the wood industry, the textile industry, and farms exhibited stillbirths or spontaneous abortions at a rate of 90 per thousand above that of workers in the control group, which consisted of workers in several other industries.

b) Alcohol - Exposure of the embryo/fetus to alcohol can result in a range of disorders, known as fetal alcohol spectrum disorders (FASDs), which includes fetal alcohol syndrome (FAS). FAS causes physical and mental disabilities and is characterized by abnormal facial features, growth deficiencies, and problems with the central nervous system. People with FAS might have problems with learning, memory, attention span, communication, vision, hearing, or a combination of these. FAS is one of the leading known preventable causes of mental retardation and birth defects. There is a syndrome that has the same symptoms as full-blown FAS that occurs in children born to mothers who have not consumed alcohol. This naturally occurring syndrome occurs in about 1 to 2 cases per thousand (Ref. 10).

For mothers who consume 2 to 4 drinks per day, the excess occurrences number about 100 per thousand and for those who consume more than 4 drinks per day, excess occurrences number 200 per thousand. The most sensitive period for this effect of alcohol appears to be the first few weeks after conception, before the mother-to-be realizes she is pregnant (Refs. 10 and 11). Also, 17% or 170 per thousand, of the embryos/fetuses of chronic alcoholics develop FAS and die before birth (Ref. 15).

c) Smoking - Smoking during pregnancy causes reduced birth weights in babies amounting to 5 to 9 ounces on the average. In addition, there is an increased risk of 5 infant deaths per thousand for mothers who smoke less than one pack per day and 10 infant deaths per thousand for mothers who smoke one or more packs per day (Ref. 13).

d) Miscellaneous - Numerous other risks affect the embryo/fetus, only a few of which are touched upon here. Most people are familiar with the drug thalidomide (a sedative given to some pregnant women until it was withdrawn in 1961), which caused children to be born with missing limbs. Another drug, diethylstilbestrol (DES), was given to some women in the 1950's and 1960's to prevent miscarriages, but was found to produce vaginal and cervical cancer, reproductive tract structural differences, pregnancy complications, infertility, and auto-immune disorders in the daughters born to women who took the drug. Living at high altitudes also gives rise to an increase in the number of low-birth-weight children born, while an increase in Down Syndrome occurs in children born to mothers who are over 35 years of age.

E. Advice For The Employee And Employer

During pregnancy, the employee should be aware of things in her surroundings that could affect the unborn child. Employees who work or visit areas designated as Restricted Areas (where access is controlled to protect individuals from being exposed to radiation and radioactive materials) should understand the biological risks of radiation to the embryo/fetus.

Although the risks to the unborn child are small under normal working conditions, it is still advisable to limit the radiation dose from occupational exposure to no more than 500 millirem (5 mSv) for the total pregnancy. The employee, Principle Investigator and Radiation Control Office should work together to decide the best method for minimizing exposure and accomplishing this goal. Some methods include reducing time spent in radiation areas, wearing some shielding over the abdominal area, and maximizing the distance from radiation sources. The medical/health physicist will be able to estimate the probable dose to the unborn child during the normal nine-month pregnancy period and to inform the employee of the amount. If the predicted dose exceeds 50 millirem (0.5 mSv) per month, work schedules or procedures shall be modified to limit the dose to the 500 millirem recommended limit. It is important that the employee inform her Principal Investigator and the Radiation Control Officer of her condition as soon as she realizes she is pregnant, so that the exposure to the unborn child can be minimized.

Table 2: Effects Of Risk Factors On Pregnancy Outcome

Effect	Number Occurring from Natural Causes	Risk Factor	Excess Occurrence from Risk Factor
		RADIATION RISKS	
		Childhood Cancer	
Cancer death in children	1.4 per thousand (Ref. 5)	Radiation dose of 1000 millirem received before birth	0.6 per thousand (Ref. 4)
		Abnormalities	
		Radiation dose of 1000 millirad received during specific periods after conception:	
Small head size	40 per thousand (Ref. 6)	4-7 weeks after conception	5 per thousand (Ref. 7)
Small head size	40 per thousand (Ref. 6)	8-11 weeks after conception	9 per thousand (Ref. 7)
Mental retardation	4 per thousand (Ref. 8)	Radiation dose of 1000 millirad received 8 to 15 weeks after conception	.05-4 per thousand (Ref. 8)
		NONRADIATION RISK	
		Occupation	
Stillbirth or spontaneous abortion	200 per thousand (Ref. 9)	Work in high-risk occupations (see text)	90 per thousand (Ref. 9)
		Alcohol Consumption (see text)	
Fetal Alcohol Syndrome	1 to 2 per thousand (Ref. 10)	2-4 drinks per day	100 per thousand (Ref. 11)
Fetal Alcohol Syndrome	1 to 2 per thousand (Ref. 10)	More than 4 drinks per day	200 per thousand (Ref. 11)
Fetal Alcohol Syndrome	1 to 2 per thousand (Ref. 10)	Chronic alcoholic (more than 10 drinks per day)	350 per thousand (Ref. 12)
Prenatal infant death (around the time of birth)	23 per thousand (Refs. 13, 14)	Chronic alcoholic (more than 10 drinks per day)	170 per thousand (Ref. 15)
		Smoking	
Perinatal infant death	23 per thousand (Refs. 13, 14)	Less than 1 pack per day	5 per thousand (Ref. 13)
Perinatal infant death	23 per thousand (Refs. 13, 14)	One pack or more per day	10 per thousand (Ref. 13)

F. Internal Hazards Pertaining to Prenatal Exposure

Most of the previous discussion related to sources of radiation external to the body, but workers must also be aware of the risk of radioactive material entering the body in workplaces where unsealed radioactive material is used. Nuclear medicine clinics, research laboratories, and certain manufacturers use radioactive material in bulk form, often as a liquid or a gas. General precautions[1] might include the following:

1. Do not smoke, eat, drink, or apply cosmetics around radioactive material.
2. Do not pipette solutions by mouth.
3. Use disposable gloves while handling radioactive material.
4. Wash hands after working around radioactive material.
5. Wear lab coats or other protective clothing whenever there is a possibility of spills.

(Refer to Chapter 6 for further precautions).

The Principal Investigator is required to have demonstrated that he/she will have safe procedures and practices before the Radiation Control Office will authorize his/her approval to use radioactive material under one of the University's licenses. Workers are urged to follow established procedures and consult the Radiation Control Office or medical/health physicist whenever problems or questions arise.

Biological data has been collected for a set of radionuclides which are expected to be of greatest significance for prenatal exposure in the work environment. These materials are: tritium, as gas and water; tritium and carbon in three typical organic forms - glucose, amino acid, and thymidine; and iodine.

1. <u>Tritium</u>

   Trace amounts of inorganic tritium in gaseous form or when incorporated into water are readily absorbed from the lungs or gastrointestinal (GI) tract. In air, most tritium will form water, as will some small amount of that which is absorbed, so that little tritium actually enters the body as a gas. Physiological studies demonstrate that water crosses the placenta in both directions. The percentage water content of the embryonic and fetal tissues is measurably greater than that of the corresponding tissues in adults, so the relative tritium concentrations in those tissues may be slightly greater, as well. For practical purposes, however, it may be assumed that the concentration of tritium in the embryo/fetus is the same as that of the pregnant woman, and that it would be readily excreted in parallel with its loss from her body.

[1]Specific precautions are made on a case-by-case basis for specific radionuclide of interest.

Tritium in the form of tritiated water is assumed to be uniformly distributed throughout the maternal and embryonic/fetal soft tissues. It is assumed that tritiated water has a biological half-life of 10 days. (Ref. 23).

2. Organically Bound Tritium and Carbon

a) Glucose

Glucose is actively transported from maternal to fetal blood across the placenta. Fetal brain, liver, kidney and skeletal muscle are the major organs that utilize glucose, and the overall glucose utilization rate is higher in the fetus than in the pregnant female.

Glycolysis of tritium-labeled glucose produces tritiated water, which then can exchange and distribute throughout the intracellular and extracellular water pools in both maternal and fetal compartments. A limited fraction of the tritiated water may subsequently become incorporated into lipid via lipogenesis, but this is sufficiently small that it can be ignored for dosimetry purposes. Catabolism of ^{14}C-labeled glucose results in $^{14}CO_2$ production in the fetus, but this does not accumulate in the fetus; rather it is randomly excreted to the mother via the placenta, and then exhaled. There are essentially no available concentration data for ^{3}H-glucose or ^{14}C-glucose applicable to radiation dosimetry (Ref. 23).

b) Amino Acids

In general, the concentrations of free amino acids in fetal tissues are similar to those in maternal tissues. Significant amounts of labeled amino acids are incorporated in protein during organogenesis or the growth phases of gestation. Concentration would be reduced through dilution by further incorporation of amino acids during fetal growth, so that consistently major deviations from maternal concentrations would not be expected (Ref. 23).

c) Thymidine

The biological behavior of radiolabeled thymidine under conditions of accidental or environmental exposure is not clear. There do not appear to be any major differences between the metabolic behavior of ^{3}H- or ^{14}C-labeled thymidine, and both precursors are incorporated into the DNA of proliferating cells. Only a fraction (10%) of that which enters the adult is incorporated; most of the remainder is catabolized rapidly and excreted. There is long-term retention of incorporated thymidine; it remains in the DNA until the cell divides, where it is partitioned between the daughter cells, and some may be re-utilized when the cell

dies. The processes by which thymidine crosses the placenta have not been established (Ref. 23).

3. Iodine

The fetal thyroid begins to concentrate iodine at about 90 days of age and continues to accumulate iodine throughout gestation. Inorganic iodine in the blood readily crosses the placenta and is accessible to the embryo or fetus. Depending on which iodine radionuclides are involved, their decay schemes and half-lifes, and whether exposure is chronic or acute, the thyroid concentration in the last months of pregnancy has been estimated to be as much as three to ninefold greater in the human fetus that in the adult.

The thyroid begins to secrete iodine shortly after it starts to concentrate iodine, and this secretion continues throughout gestation resulting in an organic iodine concentration of about 75% of that in maternal blood. The concentrations of individual species of organic iodine (in particular triiodothyronine (T_3) and thyroxine (T_4)) in fetal and maternal blood are not well correlated, which suggests that there is little, if any, placental transfer of organic iodine. Concentrations of T_3 and T_4 change abruptly at birth, and within about a week, reach values comparable to adults (Ref. 23).

X. BACKGROUND RADIATION

Everyone is exposed daily to various kinds of radiation: heat, light, ultraviolet, microwave, ionizing, and so on. For the purposes of this section, only the ionizing radiation (such as x-rays, gamma rays, neutrons, and other high-speed atomic particles) is considered. Actually, all human activities involve exposure to radiation. People are exposed to different amounts of natural "background" ionizing radiation depending on where they live. Radon gas in homes is a problem of growing concern. Background radiation comes from the four following sources:

	Average Annual Dose
Terrestrial: radiation from soil and rocks	21 millirem (0.21 mSv)
Cosmic: radiation from out space	33 millirem (0.33 mSv)
Radioactivity normally found within the human body	29 millirem (0.29 mSv)
Radon	228 millirem (2.28 mSv)
	311 millirem (3.11 mSv)
Dosage range (geographic and other factors)	75 to 5,000 millirem (0.75 mSv to 50.0 mSv)

The first two of these sources expose the body from the outside and the last two exposes it from the inside. The average person is thus exposed to a total dose of about 311 millirem per year from natural background radiation.

In addition to exposure from normal background radiation, radiation exposure can result from man-made materials and devices. Some consumer products such as smoke detectors, static eliminators and building materials contain radioactive materials. The following lists the average annual dose from man-made radiation.

	Average Annual Dose
Medical	300 millirem (3.00 mSv)
Consumer products	13 millirem (0.13 mSv)
Occupational	0.5 millirem (0.005 mSv)
Industrial, security, educational, research, military, power generation	0.3 millirem (0.003 mSv)

Medical procedures may also contribute to the dose people receive. The following table lists the average doses received by the bone marrow (the blood-forming cells) from different medical applications.

X-Ray Procedure	Average Dose*
Normal dental examination	0.5 millirem (0.005 mSv)
Normal chest examination	10 millirem (0.1 mSv)
Pelvic examination	60 millirem (0.6 mSv)
Barium enema examination	800 millirem (8.0 mSv)
Abdominal CT	800 millirem (8.0 mSv)
Three-phase liver CT	1500 millirem (15.0 mSv)
Coronary angioplasty	1500 millirem (15.0 mSv)
Pelvic vein embolization	6000 millirem (60.0 mSv)

*Variations by a factor of 2 (above and below) are not unusual.

In summary, the average person is exposed to radiation daily, receiving a radiation dose of approximately 620 mrem/year (6.2 mSv/year). A dose of about 311 millirem/year (3.11 mSv/year) is from natural background radiation, while medical radiation exposure and consumer products contribute the rest (Refs 4, 19, 20, 29). This is illustrated in Figure 3, below.

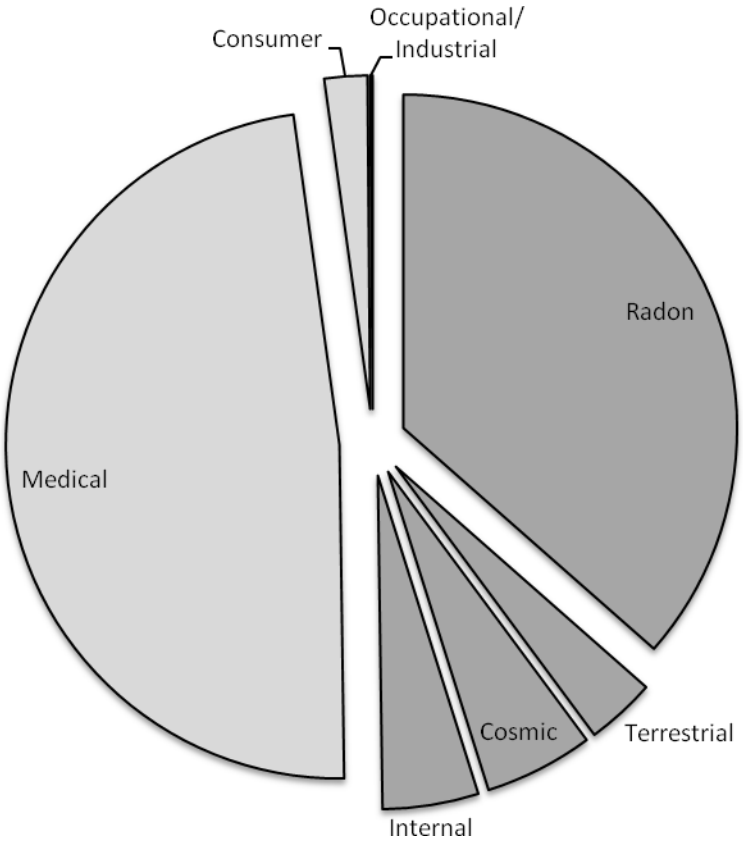

Figure 4: Contribution of Radiation Sources to Population Exposure. Light gray wedges indicated man-made sources of exposure, while dark gray wedges indicate natural sources of exposure.

XI. REFERENCES

1. *Federal Radiation Protection Guidance for Occupational Exposure*, Federal Register, p. 2822, January 27, 1987.

2. National Council on Radiation Protection and Measurements, *Protection in Nuclear Medicine and Ultrasound Diagnostic Procedures in Children*, NCRP Report No. 73, 1983.

3. International Commission on Radiological Protection, *Recommendation of the International Commission on Radiological Protection*, ICRP Publication No. 60, 1991.

4. National Academy of Sciences, *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR V)*, National Academy Press, Washington, DC, 1990.

5. J.L. Young and R.W. Miller, *Incidence of Malignant Tumors in U.S. Children*, Journal of Pediatrics, pp. 254-258, 1975.

6. W.J. Blot, *Growth and Development Following Prenatal and Childhood Exposure to Atomic Radiation*, Journal of Radiation Research (Supplement), pp. 82-85, 1975.

7. R.W. Miller and J.J. Mulvihill, *Small Head Size After Atomic Radiation*, Teratology, Vol. 14, pp. 355-358, 1976.

8. M. Otake and W.J. Schull, *In Utero Exposure to A-bomb Radiation and Mental Retardation; a Reassessment*, The British Journal of Radiology, Vol. 57, pp. 409-414, 1984.

9. T.L. Vaughan et al., *Fetal Death and Maternal Occupation*, Journal of Occupational Medicine, Vol. 26, No. 9, pp. 676-678, 1984.

10. J.W. Hanson, A.P. Streissguth, and D.W. Smith, *The Effects of Moderate Alcohol Consumption During Pregnancy on Fetal Growth and Morphogenesis*, Journal of Pediatrics, Vol. 92, pp. 457-460, 1978.

11. D.W. Smith, *Alcohol Effects on the Fetus*, Progress in Clinical and Biological Research, Vol. 36, pp. 73-82, 1980.

12. L.B. Robe, *Alcohol and Pregnancy*, The American Medical Association , Box 10946, Chicago, 1984.

13. M.B. Meyer and J.A. Tonascia, *Maternal Smoking, Pregnancy Complications, and Perinatal Mortality*, American Journal of Obstetrics and Gynecology, Vol. 128, No. 5, pp. 494-502, 1977.

14. R.H. Mole, *Radiation Effects on Pre-Natal Development and Their Radiological Significance*, The British Journal of Radiology, Vol. 52, No. 614, pp. 89-101, February 1979.

15. D.A. Roe, *Alcohol and the Diet*, AVI Publishing Company Inc., Westport, Connecticut, 1979.

16. Environmental Protection Agency, *Radionuclides*, Background Information Document
EPA: 520/1-84-002-1, pp. 8-56 to 8-63.

17. G.W. Beebe, *The Atomic Bomb Survivors and the Problem of Low-Dose Radiation Effects*, American Journal of Epidemiology, Vol. 114, No. 6, pp. 761-783, 1981.

18. W.J. Blot et al., *Reproductive Potential of Males Exposed in Utero or Prepubertally to Atomic Radiation*, in Atomic Bomb Casualty Commission Technical Report TR-39-72, Radiation Effects Research Foundation, Hiroshima, Japan, 1972.

19. National Council on Radiation Protection and Measurements, *Ionizing Radiation Exposure of the Population of the United States*, NCRP Report No. 93, 1987.

20. Nuclear Regulatory Commission Regulatory Guide 8.13, *Instructions Concerning Prenatal Radiation Exposure*, Revised July 1986.

21. University of California, Davis, *Pregnant Worker's Guide*.

22. F. Witter and T.M. King, *Cigarettes and Pregnancy*, Progress in Clinical and Biological Research, Vol. 36, pp. 83-92, 1980.

23. NUREG/CR-5631, *Contribution of Maternal Radionuclide Burdens to Prenantal Radiation Doses*, October 1990.

24. J.R. Johnson, *Fetal Thyroid Dose from Intakes of radioiodine by the Mother*, Health Physics Journal, Vol. 43, No. 4, pp. 573-582, 1982.

25. 10CFR20, *Standards for Protection Against Radiation*

26. FAC 64E-5, *Control of Radiation Hazard Regulations*

27. Merck Research Laboratories, Rahway NJ, *Pregnant Worker's Guide*

28. Department of Energy, *Radiological Control Manual*, Document DOE/EH-0256T, pp. 205,2-6,6-8,G-3,G-6, June 1992.

29. National Council on Radiation Protection and Measurements, *Ionizing Radiation Exposure of the Population of the United States*, NCRP Report No. 160, 2009.