REPORT

of

SUBCOMMITTEE ON LONG-TERM EFFECTS

OF IONIZING RADIATIONS FROM EXTERNAL SOURCES

COMMITTEE ON PATHOLOGIC EFFECTS OF ATOMIC RADIATION

NATIONAL ACADEMY OF SCIENCES

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JULY 1960

NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL
2101 CONSTITUTION AVENUE, WASHINGTON 25, D. C.

COMMITTEE ON BIOLOGICAL EFFECTS OF ATOMIC RADIATION

Address replies to
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October 7, 1960

TO: Members of Pathology Committee, Pathology Subcommittees, and Genetics Committee

FROM: Howard L. Andrews, Secretary, BEAR Committee

SUBJECT: Revised Report of Pathology Committee

In accordance with the plans for the revision of the 1956 report of the Committee on the Pathologic Effects of Atomic Radiation (Publ. 452), we are enclosing the last draft of the report of the Subcommittee on Long-Term Effects of Ionizing Radiations from External Sources for your information and review. This is the third of the four subcommittee reports being prepared for the new publication. Because this report contains a rather large genetics component, the draft is being sent to the members of the Genetics Committee for coordination and comment.

We would appreciate it very much if you would send your comments on this draft by October 20 to Dr. Blair, chairman of the subcommittee preparing this report, Dr. Shields Warren, and this office. Dr. Warren would also like to have any thoughts you may have on changes in the Pathology Committee Summary Report that might be necessitated by the new recommendations of this subcommittee.

We hope in a short time to distribute the draft report of the fourth subcommittee dealing with internal emitters.

MEMBERS OF SUBCOMMITTEE ON LONG-TERM EFFECTS

OF IONIZING RADIATIONS FROM EXTERNAL SOURCES

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I. INTRODUCTION

This report is a review of the permanent and delayed somatic effects of ionizing radiations from external sources. General nonleukemic hematologic effects and effects of prenatal irradiation are being considered by other groups and are not included here.

Emphasis is placed on radiation effects in the human. The data on long-term effects in man are so fragmentary, however, that results of animal experimentation must be used to illustrate principles and mechanisms relevant to these effects of radiation, and to provide bases for predictions of such effects in man.

This report is based on numerous studies, including experimental results in animals and observations on man; these are listed in the bibliography under major subdivisions of general radiation effects. The pertinent literature is so voluminous that it has not been feasible to include all of the papers in the field; however, many of the works listed are reviews or contain references to other related papers. Specific references are included in the report to some of the reports listed.

While it was recognized soon after their discovery that X-rays and the radiations from radioactive materials could cause acute functional and morphologic injury to living tissue, it did not become apparent until later that they could also result in more subtle permanent and delayed effects that could have serious consequences long after irradiation. These late effects are of prime importance in considering the problem of permissible human exposure.

Until recently, laboratory studies of long-term effects of irradiation have been relatively few; their importance was not appreciated earlier, and they are expensive and time consuming, requiring maintenance of large numbers of animals for all or most of their normal lifespan. In consequence, data on late effects in animals, although more plentiful than for man, are still limited in many respects. Nevertheless, knowledge of these effects has become sufficient recently to provide considerable insight into the problem. Such data as there are for man are sufficiently in agreement with those for other mammals so that fairly accurate extrapolation from lower mammals to man can eventually be expected.

II. THE QUESTION OF THRESHOLD DOSE

Definitive threshold-dose experiments on the long-term effects of small doses of radiation require so many animals that their performance is precluded by practical considerations; this has led to much speculation on whether or not there are threshold doses for various effects below which radiation has no effect.

There are two cogent reasons for avoiding reliance on the threshold concept in such situations; one theoretical and one practical:

(1) While certain effects of radiation may be interpreted as arising from the combined action of multiple quanta, each individual quantum is capable of producing an injurious effect. In consequence, all levels of radiation produce injury. Furthermore, the manifestations of radiation injury, for which threshold is often discussed, are not unique but arise normally from other, presumably additive and cumulative, causes. In view of the experimental evidence to be discussed, radiation injury seems to be additive to such causes. Thus, whether or not there is a threshold of injury for a given manifestation, the probability of the occurrence of this manifesta-

tion in a population will be increased above the so-called spontaneous rate by any increment of radiation exposure.

(2) A conservative policy is to concede the probability of a limited effect at a given low dose and not to rely on the unlikely and not practically verifiable hypothesis that such a dose may have no effect at all. An upper limit of effect not likely to be significantly exceeded at such a low dose can be estimated by extrapolation from the dose region in which quantitative data are available.

In the following discussion, the term threshold dose is used theoretically to describe the possible response to radiation alone of a single animal. It is not implied that it has any meaningful measurable counterpart with respect to a population.

III. PERMANENT AND DELAYED EFFECTS IN GENERAL

It is well established experimentally in mammals that shortening of lifespan is a general effect of whole-body or partial-body exposure to ionizing radiation in substantial doses. In the case of partial-body exposure, the life-shortening effect is variable in degree, depending on the kind and amount of tissue irradiated as well as the dose. Radiation may shorten lifespan by production of damage in a specific tissue (e.g., dermatitis followed by skin cancer) and by production of a specific disease (e.g., leukemia), as seen in humans and experimental animals; and by production of more generalized changes (e.g., lowered immunity, damage of vasculoconnective tissue, and the manifestations of premature aging), as seen in experimental animals.

A life-shortening effect in man as a result of substantial total-body irradiation can be expected on the basis of animal experimentation and the increased incidence of leukemia in humans from such exposures. However, there are as yet no data for man that provide a satisfactory basis for quantitative estimation of the overall lifespan effects of radiation or of the dependence of the effect on dose and dose fractionation.

Statistical studies of mortality rates of U. S. physicians, comparing radiologists with other physicians or with the general male population, indicate that occupational exposure of U. S. radiologists may have caused a small increase in age-specific mortality rates in past decades. The cumulative doses, although probably large on the average in earlier decades, are not known for individuals; it is, therefore, not possible to make quantitative determination of life shortening with respect to dose. A study of British radiologists suggests no increase in age-specific mortality rates among that group. There is no evidence as yet suggesting life shortening in man following small doses of radiation.

From experimental data, it is known that the survival time for given dose rates is generally shorter the more radiation energy absorbed. Life shortening is generally less, however, for a given total dose absorbed over a long period of time than over a short period.

There is some experimental evidence that radiation effects contributing to shortening of life may depend on genetic constitution and on the age and physical or clinical status at the time of exposure.

Animals irradiated with substantial but sublethal whole-body doses appear to recover from the acute early illness following irradiation, but tend to die prematurely. Such animals seem to deteriorate sooner or more rapidly than their nonirradiated controls, showing various physiologic and histopathologic changes suggestive of senescence and developing the diseases of their species earlier. To a first approximation, a comparison of the mortality curves of survivors of acute radiation mortality and their controls suggests that radiation causes premature aging in an actuarial sense.

There has been a tendency to attribute premature death resulting from radiation to the increased incidence of certain specific diseases, especially certain malignant neoplasms. While this may be justified for localized irradiation from external sources or from locally deposited radioactive materials, it may not be justified for whole-body irradiation. The number or variety of specific diseases arising after localized irradiation is limited compared with those arising after total-body irradiation.

There is evidence that, at their respective median death times, groups of animals showing life shortening as a result of single total-body irradiation and their nonirradiated control groups usually have approximately the same diseases, although not necessarily in the same incidence.

One could assume that irradiation separately induces each of the diseases of advanced age. It seems more reasonable, however, to regard such uniformity of response as evidence that total-body irradiation causes a nonspecific subclinical deterioration of the body tissues that advances the onset of most diseases to a roughly equal degree. According to experimental data, an unusually high susceptibility seems to exist in some experimental animal species or strains for certain diseases; e.g., ovarian tumors and lymphatic leukemia in mice and mammary tumors in rats.

In general, irradiation increases the incidence and/or the severity of clinically recognized diseases at given chronological ages. When these diseases appear only rarely or not at all in nonirradiated controls, or are thought to have pathogeneses different from those of similar diseases in the control, they are often regarded as having been induced completely by the radiation exposure. When certain diseases common to the population appear earlier in irradiated animals than in the controls, they are regarded as having been advanced by irradiation. In many experiments, both mechanisms may seem to operate together, with induction of disease of relatively greater importance in cases of intensive localized irradiation and advancement of disease of relatively greater importance in whole-body irradiation.

It is well known that the average lifespan of various experimental animals often falls far short of their potential averages because infectious diseases kill or damage large numbers well before senescence. In man, the counterparts of these lifespan-limiting diseases have been largely eliminated as major causes of death, at least in medically advanced countries; noninfectious diseases with long latent periods and associated with senescent deterioration are more prominent causes of death. In experimental animals, however, diseases of long latency may rarely or never develop spontaneously within the lifespan observed. Consequently, it is possible that some, if not all, of the diseases regarded as induced by irradiation may instead have been diseases of relatively long latency whose time of onset was advanced greatly. When intensive, highly localized irradiation causes a high incidence of certain diseases, whether induced or advanced, to the parts irradiated, the incidence depends greatly on the latent periods for the diseases in relation to temporal proximity of development of other terminal diseases to which the animals are susceptible. This, in turn, depends on the age of the animals.

The foregoing general considerations of the effects of irradiation on lifespan, mortality curves, cause of death, and time of onset of disease, together with available information on clinical, physiologic and histopathologic effects of irradiation, indicate a resemblance between pathologic events underlying radiologic life shortening and premature physiologic aging processes. To what extent the two processes are similar is not yet clear, and whether or not they are fundamentally identical cannot be determined until the fundamental causes of both radiologic life shortening and physiologic aging are better understood.

IV. PERMANENT AND DELAYED EFFECTS PARTICULARIZED

A. Shortening of Lifespan by Ionizing Radiations

Since there is experimental evidence that radiation effects depend on the genetic constitution of animals, their age, and their physical or clinical status at the time of exposure, some consideration of these factors is included in this section.

1. Life Shortening by Single Doses in Laboratory Animals

Many, but not all, existing data on rodents indicate that the effectiveness of single whole-body exposures to X- or gamma rays for life shortening, expressed as percent reduction of life per 100 rads, increases as dose increases. The relationship is such that for doses up to 300 rads, the reduction per 100 rads is constant or slowly increasing with dose, but increases rapidly for doses approaching the LD_{50} region. The reduction of life by doses approaching an LD_{50} is about 25 to 50% (5 to 10% per 100 rads). At doses from 200 to 500 rads (gamma), the reduction ranges from 2 to 4% per 100 rads, depending somewhat on dose.

Doses less than 200 rads do not usually yield a significant shortening of life with the number of rodents tested heretofore. An upper limit of approximately 1 to 1.5% per 100 rads can be assigned to the life-shortening effect of single doses below 200 rads, according to extrapolation of present data, on the assumption that effect remains proportional to dose down to the smallest doses. It is possible, however, that the effectiveness falls below this value when small doses (~10 rads or less) are concerned (see section IV.A.2.).

Female mice show more life shortening than males at all dose levels, presumably due to the general endocrine disturbances following radiation damage to the ovary. The extraordinary radiation sensitivity of the mouse ovary has no known parallel in other species, nor is there evidence of disproportionate life shortening in female rats or guinea pigs. There is no present basis for expecting a large sex differential in life shortening in man.

The effectiveness of fast neutrons for shortening life is about 2 to 3 times greater per rad in the LD_{50} region than gamma rays. This ratio of effectiveness (RBE) for life shortening is about the same as the RBE for acute lethality. Although survival data following a wide range of single neutron doses are not yet available, the accumulating evidence suggests that the life shortening by fast neutrons is nearly proportional to dose, instead of an accelerated function as in the case of X- and gamma rays. In consequence, the neutron RBE for the life-shortening effect increases as dose decreases. If the X- and gamma-ray effectiveness becomes proportional to dose at sufficiently small doses, the RBE for life shortening by fast neutrons will approach a limiting value on the order of 10.

2. Life Shortening by Multiple Doses or Protracted Irradiation in Laboratory Animals

Small laboratory animals irradiated with comparatively small daily doses of X- or gamma rays for periods of several months or more experience about 11% life shortening per 1000 rads. The effect is proportional to dose, or nearly so, for accumulated doses ranging from 500 to 2000 rads or more. This factor is consistent with the rough estimate given above for life shortening by small single doses.

If elapsed exposure time is decreased to less than 2 months or so, the effectiveness per rad begins to increase above the value characteristic of long protracted exposures, and approaches the value characteristic of the single dose. The dose-effect curve for exposures distributed over periods of days to weeks is intermediate between the curves for single doses and for highly fractionated exposure and becomes progressively less curved and less steep as elapsed exposure time increases. Although some data bear out this general conclusion, there are exceptions that need further investigation.

Two facts from animal data suggest that an indirect estimate of life shortening for man can be made for causes other than leukemia. First, the strain differences in irradiated mice are small (see section IV.A.4.); second, the more reliably estimated factors for percent life shortening per rad for different animal species fall within a factor of 3. The life-shortening parameter for man (expressed as percent per rad) is not likely to be much higher, if at all, than the high end of the estimates from animals (sections IV.A.1,2.); if it were, the amount of life shortening to be expected in occupationally exposed humans would be considerably greater than has been estimated. The consistency of these estimates suggests that the nonspecific life-shortening action may have a common basis in all mammalian forms, in cellular and subcellular mechanisms that are only slightly dependent

on genetic origin. Based on these considerations, the expected life shortening per rad from causes other than leukemia may be roughly similar for all human genetic stocks, and similar in magnitude to estimates for animal populations.

This indirect argument is of necessity a loose one. Even taken at face value, the argument still admits a factor of 3 for differences in life shortening effect among species studied. Furthermore, the similarity between individuals in experimental animal groups utilized heretofore, with respect to factors of age, genetics, physical circumstances, and environment, is in sharp contrast to an heterogeneous population such as the human one, in which large variations in these factors make for large variations among individuals in the existence and degree of nonradiation injuries contributing to the induction and development of diseases and to limitation in lifespan. Nevertheless, this argument gives us the best estimate of the present magnitude of the human problem.

3. Lethal Dose as a Function of Age

The average or median acute lethal dose (LD_{50} = 30 days) for young adult mammals is within approximately 300 to 900 rads for those species studied. While it is customary to refer to the LD_{50} of a given strain as a specific property independent of age, it is not justifiable when the entire age span is considered.

In the mouse, the susceptibility is maximal at age 30 days, then decreases rapidly to that seen in young adults, and is then maintained until advanced age when it increases rapidly. In the rat, also studied extensively, the LD_{50} at age 3 months is about double that at 3 weeks; beyond 3 months it diminishes approximately linearly with age as far as is known. More study of this relation is required, but it is now evident that the susceptibility of a whole population is not describable by a single LD_{50}. The published values

are usually obtained from the young adult and are therefore maximal or nearly so for the strain. This age dependence should be taken into consideration in attempts to estimate LD_{50} in man.

4. Role of Genetic Constitution and Physical Status

Information about the influence of genetic constitution on long-term survival following radiation exposure is meager, but sufficient to permit a preliminary discussion of its expected magnitude.

Most present research on the role of genetic constitution in the radiation-sensitivity of mammals is done by examining the differences in response between genetically homogeneous (inbred) mouse strains and their hybrids. Such work indicates that the susceptibility to early, acute death differs by somewhat less than a factor of 2 between the most sensitive and the most resistant strains. Resistance to acute death is apparently correlated with general vigor, for the most radiation-resistant strains tend to be longer-lived and less susceptible to spontaneous infectious disease. A short lifespan, if due to high susceptibility to leukemia, does not appear to influence susceptibility to acute death.

Lifetime follow-up of several inbred strains and their hybrids after irradiation indicates that the number of days lost per rad of exposure varies less between strains than does the acute sensitivity described above. A considerable part of this strain difference in life shortening is due to the strain difference in susceptibility to radiation-linked leukemia; when leukemia mortality is excluded, life shortening (expressed as days lost per rad) due to all other causes is found to vary comparatively little between strains and to be independent of the normal expectation of life. It would appear, therefore, that there is in the mouse a major nonspecific component of life shortening that is comparatively independent of genetic makeup, and a specific component, reflected particularly in susceptibility to leukemia

and ovarian tumor, that varies between strains. The contribution of these strain-specific diseases to the total mortality is greater in the mouse than in other species on which information is available; nevertheless, the range of variation in overall life shortening between strains is less than a factor of 2.

These results are only a partial answer, even for the mouse, because inbred mouse strains are already highly selected genetic material due to the selective elimination by breeding of many genes that would alter viability. These genes are maintained in wild populations by the various genetic mechanisms, some of which could make an additional contribution to life shortening by radiations. Furthermore, a number of the most widely used mouse strains are genetically related, and do not constitute a representative sample of the genetic potentialities of the species.

A typical human population, such as that of the United States, is genetically heterogeneous. There is as yet no way to determine the significance of this heterogeneity in terms of differences in radiation-sensitivity between members of the population. The evidence of ethnic differences in the incidence of spontaneous leukemia suggests that in man, as in the mouse, genetic constitution will play a role in the susceptibility to radiation-linked leukemia.

A fraction of the human population may have hereditary traits conferring extraordinary susceptibility to radiation-induced malignancies. The existence of such a trait, however, can only be established from data on familial tendency toward such susceptibility or from a demonstrated correlation between such malignancy and some other genetically determined trait. In either case, large numbers of presumptive radiation-linked cases would be required, and it is the hope of all mankind that they never become available.

It is probable that there is a correlation between vigor or fitness and acute radiation-sensitivity in man, as there is in experimental animals. The study of the influence of nutrition, exercise, disease, and other environmental and physiologic variables on radiation effects has only begun; present judgments about their influence must therefore be based almost entirely on incidental clinical and experimental observations.

A variety of stresses can have an activating effect on chronic or latent disease. Radiation can have such an effect on certain diseases; e.g., inactive tuberculosis in monkeys and humans, and diseases caused by Bartonella or Salmonella in rats. The nature of such activation is not known with certainty, but is probably due to the effect of stress imposed on the animal by irradiation and also to the impairment of specific immunologic and other defense mechanisms.

On the other hand, what seems to be a therapeutic or prophylactic effect of irradiation on certain infectious diseases can mask the life-shortening effect in experimental groups. In fact, the observed lifespan of such groups is sometimes greater with daily doses of 1 rad or so throughout adult life than that of their control groups (see discussion of oversurvival in section IV.A.5.).

It can be qualitatively concluded that humans harboring chronic or latent infectious disease, or debilitating disease of any kind, may suffer an increased risk from these diseases following radiation exposure. Since the biologic basis of the masking and oversurvival effects is still unknown, it is not possible to predict whether or not they can be expected in other species.

5. Oversurvival

The data on rodents exposed at low dose rate to small accumulated doses (about 100 to 400 rads per lifetime) were long considered equivocal because such exposed populations frequently survived longer on the average than controls. Although sampling errors and bias in experimental conditions may have played a role, some recent findings suggest that this may be a real effect. In many cases of increased aftersurvival, there was also considerable intercurrent mortality early in life in the control groups, presumably from infectious disease, whereas the groups receiving small exposures showed less mortality during the same periods. There is no evidence in these situations that the maximal span of life is extended, or that the incidence of cancer or degenerative disease is reduced. Since the biologic basis of the improved survival is not known, nothing can be said about its significance for man.

Such oversurvival is not to be confused with the existence of a threshold dose. The occasional occurrence of oversurvival actually makes it more difficult to determine the relation between dose and effect. Under the circumstances, the incidence of certain diseases may sometimes be a better criterion than mean lifespan for the effect of low doses. In view of known effects of environmental variations on lifespan and disease incidence, it is imperative that such variations be rigorously controlled in future studies of low dose effects.

6. Recovery and the Concept of Irreparable Injury

Radiation injury, like any other injury, immediately elicits the familiar series of coordinated physiologic reactions involved in homeostatic, defensive, regenerative, and reparative mechanisms, all of which tend to minimize the damage and reestablish the integrity of the body tissues and functions. To some extent, however, radiation can affect these reactions themselves.

Over a period of weeks following a single sublethal exposure, a gradual reduction occurs in the total damage, with disappearance of most of the functional disturbance and morphologic changes. Many, if not all, of the cells destroyed or lost as a result of radiation damage are replaced by regeneration from surviving cells. The irradiated organisms may return to normal or near normal appearance. This improvement is also manifest by the return toward normal levels of resistance to lethality from a second exposure to radiation.

These changes constitute the process of recovery from radiation injury and indicate that most of the radiation injury from X- and gamma rays is reparable. This is evidenced by the fact that animals will survive a widely protracted dose several-fold larger than the acute lethal dose. Despite the apparent recovery, however, the residual damage (e.g., incomplete regeneration or residual defects in cells and tissues) and the delayed effects observed after maximal recovery indicate that some of the injury or its consequent damage is irreparable.

To account for shortening of life as an aftereffect of irradiation, it may be supposed that radiation injury is in part reparable and in part irreparable. The irreparable component is equivalent to premature aging in an actuarial sense, for it ultimately deprives the animal of part of its expected lifespan, but whether or not it is identical with the cumulative injury of natural aging is not yet resolved. This view of irreparable injury does not prescribe whether it is equivalent to abrupt aging at the time of injury or to initiation of gradual aging processes. It is interesting that limited observations in rodents, dogs, and swine indicate that irreparable injury is measurable, after an interval of presumed complete repair, as a reduction in acute lethal dose. This suggests that irreparable injury is

at least partially sustained at the time of irradiation and is potentially observable as some form of persisting change in tissue, but this phenomenon has not yet been related definitively to cellular and tissue changes. (See section IV.F.)

7. Effect of Protracted Irradiation on Lifespan in Man

Three studies have been published on the mortality of radiologists as compared with other physicians or with the general male population.

Dublin and Spiegelman (476) investigated the mortality in various medical specialties in the U.S. over the period 1938-1942, finding a total of 2,029 deaths. The mortality in all specialist groups was lower than that for all physicians, but the mortality among radiologists and dermatologists was respectively 16 and 25% above that for all specialists combined. On the basis of their data, it is possible to show that the mortality of radiologists and dermatologists combined or as separate specialty groups differs from that of specialists who do not use radiation routinely by an amount bordering statistical significance. Dublin and Spiegelman did not express the occupational risk in terms of differences in life expectation, but on the basis of their mortality data and the life table for physicians, it can be estimated that the difference between radiologists or dermatologists and other specialists is about 1 to 3 years.

Warren (523) determined and compared the mean age at death for U.S. radiologists (60.5 yrs.) to that of specialists who do not routinely employ radiations (65.7 yrs.), finding that radiologists on the average died 5.2 years earlier. This study was based on deaths of 82,441 physicians reported from 1930 through 1954.

Court-Brown and Doll (471) examined and compared the mortality records of British radiologists from 1897 through 1957 with those of all physicians and of the nearest equivalent social class as defined by the Registrar-General. After taking appropriate account of age distribution and various biases in the vital statistics, they concluded that there was no excess mortality in male British radiologists, attributing this to early adoption of effective safety measures.

Each of these studies is subject to some uncertainty. The investigation of Dublin and Spiegelman was not intended to be an analysis of mortality in radiologists specifically, and for the present purpose suffers from the small size of the sample. Warren's analysis did not take due account of the differences in age distribution between the young and rapidly growing discipline of radiology and the other specialties. According to Seltzer and Sartwell (517), "the difference between radiologists and other physicians as to average age at death can be accounted for simply by differences in age composition between the two groups". It should be noted, however, that the differences found by Dublin and Spiegelman included consideration of age distributions.

These studies show that radiologists generally do not labor under any undue occupational risk but do not completely exclude the possibility that there is occupational mortality due specifically to the practice of radiology. To answer this question would require comparison of radiologists with non-exposed specialists in view of the differences between specialists and non-specialists reported by Dublin and Spiegelman.

A lower limit might be set for the life shortening in U. S. radiologists by consideration of the leukemia incidence. The excess of leukemia among these radiologists is statistically significant and has persisted from decade to decade, though at a decreasing rate in recent years (section IV.B.). This can be estimated to be equivalent to a contribution to life shortening of 3 to 12 months, depending on the assumptions made.

In conclusion, occupational exposure of radiologists in the United States may have caused an increase in mortality in past decades, but this increase was only of borderline significance. Since the cumulative occupational radiation exposure of the radiologists as a group or as individuals is not known, it is not possible to estimate the amount of life-shortening per unit of dose.

A life-shortening effect in man as a consequence of substantial total-body radiation exposure can be reasonably expected on the basis of animal experimentation. Moreover, there is evidence that such exposures increase the incidence of leukemia in human populations (section IV.B.). However, there are as yet no data for man that provide a satisfactory basis for quantitative estimation of the overall life-shortening effect or of its dependence on dose and dose fractionation.

B. Tumorigenic Effects of Radiation in Man

Experience with irradiated animals and humans indicates that a sufficient dose of localized irradiation to almost any part of the body may produce an increase in incidence of malignant neoplasia, the probability of development of a neoplasm being generally related to size of dose.

All types of induced and spontaneous tumors appear not to arise at once, but to pass through a series of preliminary stages. Radiation-induced tumors often take a particularly long time to develop, not beginning their development immediately after alteration of the cells. There is much evidence that malignant change ordinarily develops only after a series of precancerous changes or tissue disorder has taken place. This tissue disorder need not exist at the site of origin of the cancer; there are examples of experimental radiation-production of malignant disease through physiologic or hormonal mechanisms (e.g., ovarian, thymic, and pituitary tumors in mice) that are clearly indirect (i.e., where irradiation of the cells of origin of the neoplasm is not the critical factor).

Most animal experiments, usually employing relatively homogeneous populations, have demonstrated that there are dose levels that produce no detectable increase in incidence of certain neoplasms; in most instances, the dose-effect relationship is clearly not linear. Such data have been used by some investigators as evidence that there is a threshold dose of radiation below which certain neoplasms cannot be induced or their age-specific incidence increased.

On the other hand, a few experiments with relatively homogeneous populations of animals have shown that for some tumors in certain species or strains of animals, there are minimal effective dose levels so low that there may be practically no threshold for the production of an increased incidence of the tumors. In some of these rare instances, the dose-effect relationship seems to be linear and to permit extrapolation to zero so that extremely small doses are correlated theoretically with an increased incidence of the tumor. Such data have been used by some investigators as evidence of lack of radiation dose threshold for the effect.

Several recent reviewers have expressed the opinion that the incidence of radiation-induced tumors in a population may be directly proportional to dose, on the basis of a simple somatic mutation theory of tumorigenesis. They argued essentially that since the cancer cell is an altered type of normal tissue cell, cancer is the result of a mutation of a somatic cell, like a genetic mutation but arising in a tissue cell that perpetuates the character by reproduction.

Work on irradiated spermatozoa (fixed postmitotic cells having lost the ability to divide) has shown a linear dose-effect relationship down to low doses (about 25 r), which seems to permit extrapolation in linear fashion to an intercept on the vertical axis representing existing levels of mutation rate. This dose-effect relationship has been regarded as a single-hit process in radiation genetics, one in which the effect is proportional to dose and independent of dose rate, and therefore without dose threshold.

Some investigators interested in applying somatic mutation theories to various somatic radiation effects such as tumorigenesis, have assumed that the mechanisms in the production of effects and the dose-effect relationships for somatic mutations are the same as for these genetic mutations in spermatozoa. It should be pointed out that cells likely to become malignant are vegetative intermitotic, differentiating intermitotic, or reverting postmitotic cells, which have not completely lost the ability to divide. From histopathologic and cytologic studies, it is known that such cells made defective by irradiation may, to some extent, be selected out of the cell populations by death during the process of division. Supporting such observations are the recent data by Russell *et al* (678) on mice, from which a nonlinear dose-effect relationship could be drawn between dose and mutations due to irradiated spermatogonia (vegetative intermitotic cells). It was

also shown that protracted irradiation was significantly less effective than acute irradiation in inducing specific locus mutations in spermatogonia and ovocytes.

This work raises questions concerning the linearity of dose-effect relations for genetic mutations when gametogenic cells other than fixed postmitotic cells are concerned. It is therefore reasonable to question somatic mutation theories of tumorigenesis that are based on genetic mutation theories for fixed postmitotic gametogenic cells, when somatic cells capable of division are concerned. As the genetic concepts are altered, so must be altered the somatic mutation concepts based on the genetic concepts.

It has not been possible to test the simple somatic mutation theory of radiation tumorigenesis on human populations; in general, animal experiments have shown that radiation tumorigenesis, like chemical tumorigenesis, is an extremely complex process.

In the assessment of somatic radiation hazards to humans from small protracted doses of radiation, scientific opinion is divided on the existence of a dose threshold for malignant neoplasms. Since it is not possible at present to resolve this question by direct means, an indirect approach has been used by many investigators. This involves the determination or estimation of whether or not the dose-effect relationships for a malignancy, whose frequency increases with moderate and large doses, are linear and permit extrapolation to small doses or those delivered at greatly differing rates.

Determination of a linear or nonlinear dose-effect relationship for the process of radiation tumorigenesis, however, does not necessarily permit a conclusion regarding the involvement of somatic mutation or the existence of a threshold for the primary change involved, in view of the multiplicity of secondary or concomitant changes involved. Even if the primary or a

secondary change revealed a linear dose-effect relationship without threshold, the other events in the process may have a nonlinear dose-effect relationship. Furthermore, nonlinearity or linearity with one neoplasm cannot be applied to another neoplasm or system.

The first evidence of the tumorigenic effect of radiations in man was the development of skin cancers in radiologists and dermatology patients. Subsequently, radiation-induced tumors have been observed in other organs, such as hematopoietic organs, bone, and thyroid.

Today, an important malignant neoplasm caused by external radiation is leukemia, a relatively rare disease in man. Its increased incidence has been reported in U. S. radiologists, in Japanese atomic bomb survivors, in children irradiated in infancy for benign conditions (usually thymic enlargement), and in ankylosing spondylitis patients. Groups of children with leukemia and other malignancies have also been reported in certain retrospective studies to have had more X-ray exposure in utero than selected control groups without malignant disease.

The available data for man showing the association of leukemia with prior radiation exposure are convincing as to a cause and effect relationship. However, they do not indicate that the marked increase in recorded incidence of leukemia (largely chronic lymphatic leukemia) during the past 30 years is due entirely to the gradual increase in environmental radiation during this time. On the contrary, only a very small fraction of the increased incidence of leukemia can be ascribed definitely to radiation. The possibility that increased environmental radiation may account partly for the increased incidence of leukemia is based on the increased incidence among those persons exposed to large doses of radiation. As will be shown, the relationship between leukemia incidence and exposure to small radiation doses cannot be estimated accurately at the present time, nor can the degree of increased

risk of leukemia. In fact, the data available are not adequate to confirm any hypothesis regarding the quantitative expression of the entire dose-effect relationship (536). Furthermore, it seems clear that radiation is only one of many environmental agents that may influence the incidence of leukemia. Certainly, leukemia is not an inevitable result of exposure to radiation, even when the exposure is large, since only relatively small percentages of those receiving large doses of radiation develop this disease; to date only 226 instances of leukemia have been reported among the hundreds of thousands of people exposed to radiation (404).

The close association between radiation exposure and leukemia has been described under four different conditions of exposure. The first is that noted in U. S. radiologists exposed repeatedly in the course of their occupation, who show an incidence much higher than that noted in the general male population and in other physicians.

Reports on leukemia deaths as related to total deaths among U.S. physicians indicate that the ratio between radiologists and nonradiologists was 10.3 to 1 for the period 1929-1943 (427), 6.7 to 1 from 1944 to 1948 (429), and 3.6 to 1 from 1952 to 1955 (430). There has been a downward trend in incidence of leukemia among radiologists, perhaps reflecting greater safety precautions, and an upward trend among nonradiologists. From 1938 to 1952, there were 17 leukemic deaths in U. S. radiologists (35 to 74 years of age), constituting an average annual rate of 610 cases per million, as compared with an average annual rate of 121 per million for the general population after correction for age distribution((425). •It is clear, however, that the ratios will vary, depending upon the periods of time involved and corrections for age distribution.

Braestrup (468) estimates that a radiologist working with old-type X-ray equipment and few protective measures received as much as 100 rads per year, that the exposure before 1930 was considerably higher, and that at present it averages considerably less than 5 rads per year. His estimate of the accumulated total exposure of a radiologist using old-type X-ray units was about 2,000 rads during 40 years of practice. Lewis (425) estimated the average exposure of all radiologists to be 30 rads per year or 1200 rads in 40 years.

Except for showing that repeated intermittent partial-body exposure over many years is associated with an increased incidence of leukemia, the study of U. S. radiologists adds little to knowledge of the quantitative aspects of the relationship between X-ray exposure and the disease.

In contrast, excess cases of leukemia have not occurred in British radiologists who began practice after 1921, and only two known cases occurred among those in practice before this time (400). It has been suggested that the difference in leukemia frequency between British and U. S. radiologists is due to high British standards of radiation protection introduced in the early days of radiology.

The increased leukemia incidence in the Japanese exposed to the nuclear explosions in Hiroshima and Nagasaki is an example of this disease occurring after exposure at a very high dose rate to ionizing radiation and the various attendant circumstances of the bombings. In this case, there is a strong correlation between the incidence of the disease and the distance from the hypocenter. There is considerable uncertainty in the estimates of doses, however, even when the estimates are based on results of recent tests attempting to simulate an actual nuclear explosion.

The results of studies by the Atomic Bomb Casualty Commission since 1951 dealing with the increased leukemia incidence in the Hiroshima survivors of the atomic bomb explosion in 1945 have been summarized by Heyssel and his colleagues (419). Their data show the leukemia frequency in relation to calculated dose from gamma rays and neutrons combined in the open air at various distances from the hypocenter. In these calculations, a relative biological effectiveness (RBE) of 1 was used for neutrons. The authors estimated that 60% of the people were indoors at the time of the explosion, thereby reducing the air dose by 30 to 70%. Using only leukemia cases diagnosed between 1950 and 1958, they postulated a linear relationship between incidence and the calculated open air dose of 177 rads or more. The point representing the leukemia incidence of 3,605 persons receiving a mean dose of 77 rads falls almost on the line drawn through the points at higher doses. Although twice the spontaneous incidence, the increase at this dose is not significant. No cases of leukemia were observed in 3,512 and in 1,305 persons receiving an average dose of 34 and 19 rads, respectively.

The subcommittee agrees with the conclusion of the authors who state that there are insufficient data to permit a definitive analysis of the dose-response curve in the region below 77 rads.

In addition to the studies on leukemia incidence as a function of distance and dose, the authors present evidence showing that the latent period between exposure and development of the disease is a function of the size of the dose. They also report that nearly all cases in the exposed and nonexposed persons were either acute or were chronic myelocytic; chronic lymphocytic leukemia was rare in both groups.

The authors also estimate that radiation exposure caused an excess number of cases of leukemia rather than merely an advance in time of appearance of cases that would occur spontaneously. Only a fraction of the lifespan (about 14 years) of the exposed Japanese population has presently been studied, and assumptions must be made concerning future leukemia incidence in exposed and nonexposed groups; it is not yet possible to determine by more direct means whether or not this will prove to be true. In the Nagasaki and Hiroshima survivors, the incidence of leukemia seems to have reached a peak several years ago.

This recent report by Heyssel et al seems to provide the most reliable data on the subject of leukemia in the Japanese survivors, even though the leukemia cases occurring before 1950 are excluded. Although errors have undoubtedly been introduced by establishing the so-called "closed" population so long after the event, it is probably impossible to improve upon the samples. Rigorous definition of the sample in each exposure zone reduces the number of cases of leukemia that can be included in the study, particularly in the zones more than 1500 meters from the hypocenter. This makes the estimates of leukemia incidence at these distances subject to considerable error.

For a number of reasons, it is evident that there must be a considerable margin of error associated with the individual dose values. At least 200 persons survived in the exposure zone where the mean open air dose was calculated to be 2,620 rads (416). Even allowing for shielding and assuming that these persons were at the periphery of the exposure zone, the doses they received, according to these calculations, must have been well in excess of that considered to be 100 percent lethal. In the low dose region, the exactness of calculated doses may also be questioned. Many persons in the 2,000- to 2,499-meter zone, where the average estimated dose was 6 rads,

reported a history of severe radiation symptoms (epilation, oropharyngeal lesions, and purpura) (432). This dose is far below that associated with radiation sickness after total-body exposure. Since persons even farther away were said to have similar symptoms, it is the consensus of a number of observers (416) at the interviews with the patients that these symptoms were probably due to factors other than radiation.

Two examples illustrate the increased incidence of leukemia in persons who received therapeutic X-ray exposures to large portions of their bodies. One is that of ankylosing spondylitis patients who received intensive X-ray treatment to the entire length of their spines. Court-Brown and Doll (403) in Great Britain investigated 13,352 patients presumed to have ankylosing spondylitis and given X-ray treatment between January 1, 1935 and December 13, 1954. They reviewed the death certificates, studied the clinical and pathologic data of all patients suspected of dying of leukemia or aplastic anemia, and calculated from dose records the mean dose to the spinal marrow and the whole-body integral dose of a large sample of the cases. They concluded that 32 proved and 5 probable cases of leukemia, and 4 cases of aplastic anemia, occurred in this group. The number of certified deaths that would have been expected from the national vital statistics was estimated as 2.9 for leukemia and 0.3 for aplastic anemia, indicating a significant increase in mortality from these causes.

In this study, the annual incidence of leukemia for the general male population not therapeutically irradiated was estimated to be 50 per million. The annual incidence in men receiving a mean dose of over 1,750 rads to only the spinal marrow was between 1600 and 1700 per million. For all the patients as a group, regardless of anatomic site of exposure, the annual incidence was 7200 per million, with a mean dose to the spinal marrow of over 2,250 rads.

When the cases are separated according to mean spinal marrow dose and integral dose, there is a definite relationship between dose and leukemia incidence. The precise shape of the incidence-vs-dose curve depends upon whether the mean spinal marrow dose or the integral dose is used, and whether or not the cases receiving extraspinal radiation are excluded. The curve is possibly linear in the three middle dose groups expressed in terms of either mean spinal marrow dose or integral dose. The slope of the relationship curve between 750 and 1,250 rads (spinal marrow dose) is fairly constant. In the higher dose range (from 1,250 to 2,500 rads spinal marrow dose), the curve departs sharply upward from linearity, unless the incidence of all cases receiving more than 1,250 rads is averaged as a single point.

There is considerable uncertainty as to how the curve should be drawn below 500 rads or 7.5 megagram rads. In fact, the only point below 500 rads is based on 2 cases of lymphocytic leukemia, one chronic in type which developed after a mean marrow dose of 471 rads, and the other in which the spine received 113 rads but the extraspinal regions received additional larger doses.

After a single course of treatment, 10 cases of leukemia occurred in 5 years. Of the 37 leukemia cases found in this study, including those with multiple courses over a period of years and those with a single course in a month or so, 35 were diagnosed as leukemia within 5 years of the last treatment.

It is interesting to note that, of the 50 cases of leukemia in spondylitic patients treated with X-rays, including those reported by Court-Brown and Doll, 38 were acute and only 8 were chronic, with only one of the latter being chronic lymphatic leukemia. The data in the remaining cases were insufficient to establish clinical type.

Some of the leukemia cases showed a sequence of pathologic changes in which a persistent damaged or aplastic marrow was a precursor rather than a consequence of leukemia, and other cases of aplastic anemia were observed within the same range of doses.

In the attempted extrapolation of the incidence data to low doses, the use of the spontaneous leukemia incidence in the general population as a control point should be questioned. Since there appears to be a strong hereditary factor in ankylosing spondylitis (436), the leukemia incidence in the general population cannot be accepted as the incidence for the untreated patients. This is illustrated by the report of Abbott and Lea (393) showing an association between untreated rheumatism and leukemia. The only available control group of 399 spondylitic patients not treated with X-rays is too small to be of use in determining a control value for leukemia incidence.

In view of the limited data in the lower dose range and the lack of an appropriate control group, it seems reasonable to conclude that this study does not provide evidence to determine the true leukemia incidence in the dose range below 500 rads.

The second example of increased leukemia incidence in radiotherapy patients is found in children treated for benign conditions, usually thymic enlargement.

In studies by Simpson, Hempelmann, and Fuller (446), Simpson and Hempelmann (445), and Simpson (444), a composite group of 2,393 such cases in upstate New York was collected, and 87% were traced (416). In this group, 21 cases of malignancy were found instead of the 3.6 cases expected; and 9 confirmed and 1 unconfirmed leukemia deaths instead of the 1 expected. Thyroid carcinomas accounted for most of the other cases of malignancy. There was not a significant difference between the expected and observed cases of cancer or leukemia in 2,722 untreated siblings of the children in this study.

The exposures measured in air were known or calculated from the radiation factors for all but 299 children. Four of the known cases of leukemia occurred in 1,050 children with a cumulative exposure of less than 200 r, whereas 5 cases were found in 1,025 children exposed to more than 200 and usually less than 600 r. In contrast, all cases of other malignant neoplasia occurred in children exposed to 200 r or more. The average time between the exposures and death from leukemia was 5.3 years.

Since the state of the thymus gland is unknown for the sibling group and is, for the most part, normal by definition in children of the general population, it is clear that this study does not differentiate between the association of leukemia and (a) prior X-ray exposure, or (b) the medical condition diagnosed as thymic enlargement. Because it is impractical, if not impossible, to obtain an ideal control group (i.e., children with thymic enlargement at birth not treated with X-rays), children irradiated for other medical conditions must be studied in an effort to distinguish between the associated, and possibly leukemogenic, factors.

A group of 1,564 children treated with X-rays in Pittsburgh was studied in 1948 by Conti et al (397). Ninety-six percent of these children were shown to have thymus glands of normal size at birth. The radiation factors were uniform in the entire group. Eighty-eight percent of the children received 75 to 300 r (usually 150 r) to the region of the manubrium; the remainder received 200 to 450 r. Ninety percent of the children were studied again 11 to 18 years after therapy (398). Four cases of malignant disease, including 1 of leukemia, were expected to occur in this group, but none were found. There was no significant difference between the number of expected and observed cases of cancer and leukemia in the untreated siblings.

The failure to observe the 4 expected cases of neoplasia is not significant, particularly since one-tenth of the group was not located. One can conclude, however, that there was no evidence of an increased cancer rate in the treated children or of a greatly increased leukemia frequency.

To avoid complications introduced by considering only children given X-ray therapy to the mediastinal region, a study was made of 6,473 children in Rochester, New York, who were treated with X-rays for various benign conditions in the past 25 years (435). The difference between the 8 leukemia cases observed and the 2 expected is significant. Five leukemia deaths occurred in 2,750 children treated for thymic enlargement; 2 occurred in 75 children treated for pertussis; and 1 occurred in 1,073 children given X-rays to the head and neck region, mainly for lymphoid hyperplasia of the nasopharynx. No leukemia deaths were found in 2,460 children treated with superficial X-rays for benign skin lesions.

Similar surveys of children treated for thymic enlargement and other benign lesions are now being carried out in this country. Latourette and Hodges (424) reported the incidence of neoplasia in 861 children treated for thymic enlargement between 1932 and 1951. Most of these children were treated with 200 r or less, apparently through a large 10 x 10 cm port. The 2 cases of lymphoma (1 being leukemia) were more than was expected, but not significantly so. One child had a carcinoma of the thyroid and others had benign tumors of various sorts. Snegireff (447) observed 2 thyroid tumors in 148 children followed out of 1131 children treated for thymic enlargement; Moloney, in a discussion of Simpson's work (444), mentions 7 cases of thyroid neoplasia including two malignancies in 125 of 700 children so treated.

Saenger et al (442) reported a thorough study of 1,644 of a series of 2,230 children treated for various benign conditions. Of the 675 receiving treatments exclusively to the chest, mainly for thymic enlargement, only 124 are known to have received more than 200 r (Saenger, personal communication). Eighteen cases of thyroid neoplasia (11 diagnosed as malignant) and 1 case of leukemia were found in the entire group. They also report a striking incidence of morbidity of all types of nonfatal illnesses in these children indicating the selected nature of the group.

In evaluating the data obtained in these studies, it seems clear that an association has been established between radiation exposure and subsequent leukemia only in one group of children treated with X-rays for thymic enlargement. Further epidemiologic studies of a prospective nature must be undertaken to establish the true incidence of leukemia in children given thymic irradiation, and particularly the relation of incidence to dose, port size, and part of the body treated.

It should be noted that an increased incidence of thyroid neoplasia was found in numerous studies of children previously irradiated in the thymic region, whereas an increased leukemia incidence was found only in 1 study. It seems likely, therefore, that under certain exposure conditions, the thyroid gland of a child is more susceptible to the tumorigenic action of radiation than is the blood-forming tissue. The exposure conditions presumably involve dose, port size, and part of the body irradiated. The sensitivity of the child's thyroid is in marked contrast to the radiation-resistance of the adult thyroid.

In another type of study, Stewart et al (449) made an extensive retrospective interview survey of 1,399 children with leukemia or other malignant tumors. These children died before the age of 10 in England and Wales during 1954-1956. One of the findings was a higher frequence (13.7%) of diagnostic X-ray examinations of the mothers of children with malignant disease, almost double such examinations (7.2%) of mothers of the control children. The controls were matched with the study children for age, sex, and locality, but were otherwise chosen at random from the official birth register. The average number of X-ray films taken was 2.37 per child and the exposure was calculated to be of the order of 86 to 600 mr per film measured at the gonads of the fetus (375). If it is assumed, as proposed by the authors, that radiation was the etiologic factor in the additional 6 to 7% of the children with leukemia who received prenatal exposure, than 16 to 18 leukemia cases per year would have resulted from this diagnostic practice.

Four other such retrospective studies have been undertaken in different sections of the United States. Ford et al (409) studied 78 leukemic children and 74 children with other malignancies in New Orleans, compared with 306 dead controls matched for color, age, and place of death. Their findings confirm the observations of Stewart et al, with 26.9 and 28.4% of the children with leukemia and other forms of malignancy, respectively, irradiated in utero, as compared with only 18.3% of control children so exposed.

The three other studies, using alternative methods for selecting controls, do not show the same excess of fetal irradiation in leukemic children. Polhemus and Koch (440) found no significant difference in the history of prenatal irradiation in 251 diagnosed leukemia cases in the Children's Hospital of Los Angeles, compared with the same number of matched control children with nonorthopedic diseases on the surgical service of the same hospital. In a

current study of childhood leukemia in California, Kaplan and Moses (421) found that the number of children with leukemia having a history of prenatal irradiation exceeded that of the group of siblings used as controls; such an excess was not observed, however, when the leukemic children were compared with healthy playmates. Murray et al (435) found no significant difference in the history of prenatal exposure of 65 children with leukemia, 65 matched dead controls, and the 175 living siblings of both groups.

In retrospective studies of this kind, the choice of the control group may be crucial in reaching definitive conclusions. It would seem that the studies as presented do not differentiate clearly between the association of leukemia and (a) the effect of the medical condition which prompted the diagnostic examination, or (b) the effect of X-rays. More studies, preferably prospective and with more than one control group, are clearly needed to determine whether or not the small X-ray doses of the magnitude used in diagnostic radiology are leukemogenic to the human fetus.

Indeed, in a study in England by Court-Brown and Doll (399) involving about 40,000 children exposed prenatally to diagnostic procedures, 9 cases of leukemia were observed, whereas 10.5 were expected. This suggests that if a leukemogenic risk is incurred by such exposure, it is far smaller than that indicated by the study of Stewart et al.

Lewis (425) has compared the available data on leukemia incidence and radiation dose in the spondylitics, the Japanese survivors, the children with enlarged thymus, and the U. S. radiologists. He attempted to assess the probability of developing leukemia on the basis of the calculated radiation dose absorbed in the blood-forming tissues in individuals of the four groups. Using a number of assumptions concerning doses and correcting for the amount of tissue exposed, Lewis' best estimate of the leukemia probability per individual per rad per year was essentially the same in all groups,

namely, 1 to 2 x 10^{-6}.

Hempelmann (416), reconsidering the calculations of Lewis in the light of more recent information, found that the probability values for the different groups did not seem as close as Lewis'. Using the new estimates of leukemia frequency in Hiroshima, the probability varied from 0.3 to 1.2 x 10^{-6} in the different exposure zones. Lewis' calculated probability values for children with enlarged thymus and for U. S. radiologists were found to be based on incorrect estimates of the average dose to the entire blood-forming tissues. Since the average dose administered to each child was 250 r, and since less than one-fourth or one-fifth of the body was exposed, the probability in their cases should be at least 4 to 5 x 10^{-6} rather than 1 x 10^{-6}. With Lewis' estimates of the average exposure for the radiologists, but with the assumption that the soft X-rays irradiated only one-half to one-third of the blood-forming tissues, the probability becomes at least 4 to 6 x 10^{-6}. In the case of the children irradiated prenatally, not considered by Lewis, the probability becomes ~10 to 11 x 10^{-6}. It is probably not entirely justifiable to use this procedure for radiologists since the dose estimates represent nothing more reliable than a guess.

In conclusion, on the basis of present data it seems possible that the assumption of a linear dose-effect relationship for radiation production of leukemia and the attendant extrapolations, even if assumed to be valid, may be permissible only in the assessment of the leukemogenic risk for a single dose or small doses given over a relatively short time (e.g., in radiotherapy, where the dose rates are relatively high). Further extrapolation to background or environmental radiation over many years with dose rates that may be millionths smaller involves the assumption that such a difference in dose rate

does not alter the leukemogenic effect. This does not seem to be in accord with experimental data or even with the limited pertinent data on irradiated humans, which suggest some dose-rate dependence for the leukemogenic effect.

C. Radiation Cataract

Cataracts in humans have resulted from unwise exposure of the optic lens to X-rays, gamma rays, beta particles, and neutrons. Although changes in the optic lens have been detected following doses as low as 200 r, the minimal effective X-ray dose (200 kv) for the production of clinically significant cataract is thought to be between 600 and 1000 rads. There is some evidence that this dose may be lower for infants or children. On the basis of equivalent energy absorbed in the lens, neutrons are relatively more effective in cataract production than X-rays by a factor of 5 to 10.

The characteristic features of radiation cataract are found in the early stages of its development. An initial dot-like opacity occurs, usually at the posterior pole of the lens, and small granules and vacuoles develop around the opaque dot as it enlarges. As it becomes larger, the central opacity develops a relatively clear center, taking on a doughnut-shaped appearance by the time the opacity is 3 to 4 mm in diameter. At this time, granular opacities and vacuoles may develop in the anterior subcapsular region of the lens, usually in the pupillary area.

The opacity may remain stationary at any stage. Often it shows a slow progression for a long period of time to the point described above before it remains stationary. If the opacity continues to progress, it takes on a nonspecific appearance; i.e., it cannot be differentiated from cataracts from other causes.

Roughly 200 cases of radiation cataracts in humans due to X- or gamma radiation have been reported in the literature (30, 36, 56, 58, 63, 65, 66, 72, 73). Latent periods have been reported for most of the cases, but in many the latent period was not related to radiation variables such as quality, dose, or duration of treatment. Dose was not reported in many cases, nor were radiation factors that might permit calculation of dose.

The important problems of minimal cataractogenic dose — effect of dose and mode of exposure on incidence of stationary or progressive cataracts, influence of dose fractionation on cataractogenesis, influence of dose or duration of exposure on the latent period, effect of radiation quality, and influence of age on lens sensitivity – are still not solved for humans.

Based on experimental animal studies, radiation cataract seems to be the result of direct destructive actions of radiation on the anterior epithelium, which supplies the cells that differentiate into the fibers of the lens. Young animals exposed during the prenatal or early post-natal period show markedly greater lenticular radiation-sensitivity than do older animals.

A recent study of human clinical cases of radiation cataract by Merriam and Focht (65) has contributed much information on some of the problems mentioned. These investigators studied 100 cases of radiation cataract and 73 cases of irradiation to the head without development of lens opacities. They measured the X- or gamma-ray dose to the lens using a phantom to duplicate the radiation factors involved. In this study, a radiation cataract was regarded as any clinically recognizable opacity having the characteristic appearance described above, whether or not vision was affected.

The numerous uncontrollable variables in this kind of study made it impossible to determine accurately the absolute threshold for the effect. The minimal effective doses reported represented the smallest amount of radiation that produced any degree of lenticular opacity in any of the cases studied. It was also impossible to classify the cases according to dose and degree of lens opacities. The most that could be done was to classify according to whether the opacities were stationary or progressive, and to attempt to relate this to dose.

Ninety-seven of the radiation cataract cases and 70 without radiation cataract were divided according to temporal modes of treatment: single, fractionation over 3 weeks to 3 months, and fractionation over more than 3 months. The minimal doses for production of any lenticular opacity in any cases for each group were 200 r, 400 r, and 550 r, respectively. These figures suggest that the threshold dose increases with the duration of treatment.

Of 37 cases irradiated in a single treatment (with radium plaques), all 20 with doses from 200 to 1150 r developed lenticular opacities. The other 17 patients received doses from 40 to 175 r to the lens without developing lens changes. There were only 2 cases of stationary lens opacities of minimal degree at an estimated dose of 200 r, first seen 19 years and 22 years after treatment. In view of the small number of cases (4) with doses from 200 to 350 r, the fact that there were none without cataracts does not prove that the lens cannot tolerate higher single doses. Further information on the effects at these dose levels is necessary to determine more exactly the upper limit of tolerance. The maximal noncataractogenic dose in this treatment group was 175 r in a patient followed about 8-1/2 years.

Of the 87 cases receiving multiple treatments over periods from 3 weeks to 3 months, 49 developed lenticular opacities with X- or gamma-ray doses to the lens from 400 to 6,100 r. The lens opacity with the 400-r dose (1 case) was first seen about 2-1/2 years after treatment and was stationary. The maximal noncataractogenic dose in this treatment group was 1,000 r, with a treatment time of 2-1/2 months and a follow-up period of about 13-1/2 years. The following tabulation gives the incidences and types of lenticular opacities in patients following irradiation in various dose ranges for the 3-week to 3-month exposure period.

		Cataract Type		
Dose Range (r)	Cataract Incidence	Stationary	Progress.	Indeterm.
40 to 350	0 of 18 patients (0%)	-	-	-
351 to 550	4 of 9 patients (44%)	3	0	1
551 to 750	6 of 10 patients (60%)	5	1	0
751 to 950	16 of 26 patients (61%)	7	6	3
951 to 1,150	2 of 3 patients (67%)	1	1	0
1,151 to 1,399	no cases	-	-	-
1,400 to 6,100	21 of 21 patients (100%)	2	18	1

Of the 43 cases irradiated over a period longer than 3 months, 28 developed lenticular opacities with X- or gamma-ray doses to the lens ranging from 550 to 6,900 r. There were 2 cases of cataract with the 550-r dose, one progressive and one stationary, first seen 44 months and 4 years after treatment, respectively. The maximal noncataractogenic dose in this group was 1,100 r, with a treatment time of 1-1/2 years and a follow-up period of 22 years.

Regardless of the duration of treatment, all patients receiving a dose to the lens larger than 1,400 r developed lenticular opacity. The 100% incidence level occurred at the lowest dose level for the single treatment group (200 r) and at any greater dose. In the multiple treatment cases, the longer the duration of treatment, the lower the incidence at a given dose range below 1,150 r; the higher the dose for a given treatment, the shorter the time of appearance of the lens changes and the higher the incidence of progressive opacities with resulting decrease of vision. In general, fractionation of dose delays the time of onset of cataracts and decreases the incidence of severe opacities.

The lenses of children under one year of age seemed to be more sensitive to radiation than those of older children and adults.

It is known from experimental work that cataract production by fast neutrons relative to X-rays increases significantly with protracted exposure; i.e., the RBE is about 2 to 4 for high-intensity and 9 or greater for low-intensity radiation.

By December 1948, it was known that at least 5 nuclear physicists of mean age 31 had incipient cataracts as a result of cyclotron exposure (26). In January 1949, 10 of 11 cyclotron physicists examined were found to have cataracts. Three cases were severe with definitely impaired vision, 4 were moderately severe, and 3 were minimal. It was estimated that over periods of 10 to 250 weeks, these men had received total doses of fast neutrons to the region of the lens ranging from 10 n to 135 n with a median dose of 50 n [*]. At the time the cataractogenic exposures were received, periodic blood counts done on most of the men revealed no change in blood picture warning of overexposure to radiation.

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[*] One n = approximately 2 rads.

Following the finding of radiation cataracts in the physicists, Cogan et al (38, 39) found 10 heavily irradiated Japanese atomic bomb survivors with radiation cataracts. In studies by Kimura in 1949, as described by Fillmore (44), 98 cases of lenticular opacity were reported, 85 of which were among the 922 survivors in the high dose region 1000 meters or less from hypocenter. The severity of the lesions was not reported, but it is inferred that they were generally mild.

In 1955, Sinskey (79) reported an intensive investigation of 3,700 exposed and nonexposed Hiroshima Japanese from May 1951 to December 1953. In the total survey, there were 154 survivors with posterior subcapsular plaques in the lens large enough to be visible with the ophthalmoscope. Opacities not so visible in the greater percentage of survivors were not considered because they did not decrease visual acuity under standard test procedures. In view of the relatively negligible effect of the atomic bomb on visual loss 7 years after the bombing, the term cataract, which often connotates a severe loss of vision or blindness, was avoided in this survey.

The studies of Sinskey showed that of 425 survivors in Nagasaki between 400 and 1800 meters from ground zero, 47% experienced lens changes detected by slit-lamp examination, whether or not there was epilation and shielding. Although the opacities in the vast majority of cases were so insignificant as to be invisible with the ophthalmoscope, statistically significant lens changes were present in survivors with no other known early or late evidences of radiation damage.

Of the approximately 8,000 exposed survivors of Hiroshima and Nagasaki examined up to 1956 (11 years after the atomic bomb explosions), 10 cases of severe cataract have been found. The relationship between these cases and radiation alone is not clear.

D. Radiation Effects on Fertility

1. General Considerations

The gonads are among the most radiation-sensitive organs of the mammalian body, due to the high radiation-sensitivity of their gametogenic epithelia. Relatively small doses (25 rads or less) produce microscopically detectable changes of a temporary nature in these tissues.

Permanent pathologic effects of radiations on gonads consist chiefly of failure to recover completely after substantial radiation exposure and damage; with sufficient dose, complete and permanent atrophy of these organs may result.

Delayed pathologic effects in the gonads consist chiefly of a temporal advance in involutional changes with advancing chronologic age long after maximal recovery from initial radiation damage. In experimental animals, there is little evidence of the radiation-induction of testicular tumors, but the incidence of ovarian tumors has been increased by radiation.

Histologic sterility, by definition, is a complete absence of gametes and even gametogenic elements. It is a condition difficult to evaluate by histologic examination of biopsy or necropsy sections, particularly in terms of prediction of permanency. The production of permanent and complete histologic sterility requires very large doses to the gonads which would be lethal if given in a short time to the whole body or substantial volumes of vital tissue.

In a practical sense, a condition of effective or functional sterility can be produced by smaller doses of radiation and can be temporary or permanent depending upon magnitude and intensity of exposure. For example, this condition in the male requires only that the rate of production of sperm effective for fertilization and production of offspring be reduced to where there are insufficient numbers in semen at any particular time to be physiologically

effective for reproduction. The increased incidence of abnormal sperm in semen, caused by irradiation, also contributes to the reduction in number of effective sperm. Since the critical or minimal numbers of normal sperm per ejaculate necessary for reproduction are fairly large, practical sterility or subfertility may be associated with considerable but subnormal degrees of spermatogenesis. These conditions can be produced in many cases by doses of radiation to the gonads which would be sublethal if administered to the whole body.

2. Sterility Doses for Men and Women

There has been little study in humans of the long-term pathologic effects of radiation on the gonads, recovery processes, and the influence of these effects on fertility, especially where accurate estimates of doses could be made. On the basis of meager and fragmentary data, however, certain estimates are attempted here.

It seems probable that gonadal doses affecting fertility may be similar in magnitude for men and women. A single dose to the gonads of about 150 rads may produce brief, temporary subfertility or sterility in many men and women, especially in cases of borderline fertility. A single dose of 250 rads may produce temporary sterility for one or two years in most men and women. A single dose of 500 to 600 rads may produce permanent sterility in many persons, especially in cases of borderline fertility, and temporary sterility in others for several years. A single dose of 800 rads or more would probably cause permanent sterility in all but the relatively few most resistant men and women.

On this basis, gonadal doses that produce only temporary alterations in fertility or temporary sterility in fertile people, except for those with only borderline fertility before exposure, are likely to be sublethal if administered to the whole body. Gonadal doses that permanently sterilize most such fertile people are likely to be about equal to the total-body lethal dose.

Limited experience with the Marshallese, exposed Japanese, and certain accident cases suggest that substantial fractions of the midlethal dose for man (about 400 to 600 rads) do not have serious permanent effect on fertility. However, gonadal doses are not known with certainty in these cases and few such cases have been studied extensively for this purpose for a long period of time after exposure.

Men may be sterilized permanently without prominent changes in interstitial sex cells, hormone balance, or reduction in sexual potency or libido. Women sterilized by radiation, however, undergo greater physiologic disturbances, since the process by which the ovary produces sex hormones is more intimately related to the development and discharge of ova. When the production of ovarian follicles is terminated by irradiation, women tend to undergo an artificial menopause similar in most respects to the natural menopause, with amennorhea, "hot flashes", diminished sexual appetite, and sometimes severe psychic depression.

On the basis of experimental observations, protracted irradiation may be of serious consequence to fertility in animals with relatively poor gonadal regenerative capacity, such as humans.

3. Male Animals

Radiation effects on testes, as observed experimentally, are direct in that whole-body and localized irradiation produce essentially the same changes in the seminiferous epithelium; irradiation of other parts of the body has little influence.

According to some experimental evidence, certain modes of dose fractionation can reduce the total dose that will cause permanent sterility. Also certain modes of radiation protraction have been shown to more readily cause permanent sterility or more marked effects on spermatogenesis than equal total doses administered as a single dose.

The testicular effects of irradiation are in general qualitatively similar in all mammals studied, including man, but vary quantitatively among species according to differences in radiation-sensitivity and recovery capacity. Whether or not a radiation dose sterilizes permanently or temporarily depends at least as much on the natural capacity for regeneration of primitive spermatogenic cells as it does on the radiation-sensitivity of the spermatogenic cells per se.

The effects of X-rays, gamma rays, and neutrons on spermatogenesis and reproduction in the male animal are qualitatively similar, but neutrons have a greater biologic effectiveness.

Experimental reports on the efficiency of fractionated versus undivided doses of the same total size in producing testicular effects often appear contradictory, some indicating no difference, some indicating less effect with fractionation, and some indicating greater effect. In reality, these reports are largely complementary.

Protraction of the dose apparently has little influence on testicular effects unless the protraction is extreme. In such case, the effect of a given dose may be decreased, probably by virtue of a greater rate of biologic recovery than of production of injury.

The effects of dose fractionation on the testes depends upon the size of the dose fraction, the interval of time between fractions, and the total dose. In general, fractionation has less influence on the effect of small total doses than on the effect of large ones. Certain modes of fractionation of large doses appear to increase damage in the mechanisms responsible for regeneration of germinal epithelium.

For each species, there is probably a different dose-time relationship for divided doses, which is optimal for the efficient production of radiation injury. The empirical and experimental work done on the testis has already made this apparent. The most efficient mode of administration of radiation (per rad) to produce sterility in animals of a given species or strain would be that designed to take advantage of the biologic actions and reactions of the cells. In a tissue like the germinal epithelium, for example, in which stem cells are radiation-sensitive and capable of active division, one of the most efficient dose-time relationships in spaced irradiation would be one in which the dose fraction was small enough to permit attempts at division in the stem cells (e.g., spermatogonia) but large enough to injure many of these cells to the extent that they die when mitosis is attempted, and one in which the time interval between exposures is such that the following exposure is administered when the effect of the previous dose is diminishing. A change of this interdose time interval in either direction without appropriate change in size of dose fraction would decrease the efficiency of the irradiation with respect to utilization of mitotic-linked death of spermatogonia.

There has been little investigation on the effects of irradiation on gametogenesis and reproduction in mammals, except for the work on small rodents and some recent work on dogs. The single doses to the testes required to cause complete or nearly complete temporary atrophy of the seminiferous epithelium are similar in size in these small animals and in the dog and man as well, all being within the LD_{50} range. However, the regenerative capacity of the seminiferous epithelium of the small laboratory animals is so much greater and more rapid that very large single or divided doses, well above total-body LD_{100} doses, are required to prevent regeneration and permanently sterilize most or all of the animals of a group.

It would appear from data at hand that the dog, of all the animals investigated extensively, is most similar to the human in terms of radiation-sensitivity and regenerative capacity of seminiferous epithelium. The following table summarizes observations on male beagle dogs subjected to discontinuous daily exposure to X-rays from a 1000-kvp X-ray machine or to neutrons from a cyclotron, five or six days per week.

DOSE/WEEK	APPROX. TOTAL DOSE	DURATION OF EXPOSURE	OBSERVATIONS
0.3 r	125 r	8 yr	No significant change in sperm count
0.6 r	250 r	8 yr	No significant change in sperm count
0.6 r	62 r	2 yr	Little change in germinal epithelium
0.6 n*/	31 n	1 yr	Little change in germinal epithelium
3.0 r	156 r	1 yr	80% sterile, 20% reduced sperm count
3.0 r	312 r	2 yr	Substantial atrophy of germinal epithelium
6.0 r	312 r	1 yr	Aspermic
6.0 r	624 r	2 yr	Marked atrophy of germinal epithelium, 100% sterile
10.2 n	398-561 n	39-55 wk	Extreme atrophy of germinal epithelium, 100% sterile
15.4 r	477 r	31 wk	Aspermic after 375 r, still sterile 5 years post-irradiation
15.4 r	634 r	41 wk	Aspermic after 375 r, still sterile 5 years post-irradiation
15.0 r	375 r	25 wk	Still aspermic 1 year post-irradiation (to date)

*/ 1 n = approximately 2 rads.

In dogs, a single total-body dose of 300 or 375 r causes only partial and temporary reduction of spermatogenesis, with recovery to normal levels occurring within one year after irradiation. This is in contrast to the production of complete aspermia in dogs by 375 r administered over a period of 25 weeks at the rate of 15 r/wk, without any sign of beginning of recovery within a year after the end of the protracted exposure.

As shown in the dog, protracted irradiation results in a gradual reduction in number, motility, and viability of sperm. This is one of the most sensitive indicators of chronic damage so far observed, being measurable in dogs receiving 3.0 r/wk or ten times the permissible dose rate.

4. Female Animals

Irradiation of the mammalian ovary can cause profound atrophy of the organ with temporary or permanent sterility, depending upon the dose. Changes in the ovaries may be followed by secondary endocrine disturbances and atrophic changes in accessory genitalia in most mammals.

The ova and follicular cells are the most radiation-sensitive cells in the mammalian ovary; cells of the corpora lutea and interstitial cells are relatively resistant to radiation. The radiation-sensitivity of the ova and follicular cells varies with their functional states at the time of irradiation. There are also marked differences in radiation-sensitivity between species. In most laboratory mammals, the developing and mature follicles and ova appear to be more radiation-sensitive than the primordial follicles and ovocytes; some primary follicles persist after fairly large doses of radiation and may begin to develop long after irradiation.

Irradiation may sterilize the ovary by preventing the development of primary follicles of the ovary and by destroying the ova and follicular cells.

A radiation dose that destroys all developing follicles causes failure in development of corpora lutea. This may lead to decrease of interstitial gland cells in animals that have these glands, since new cells will fail to be developed from corpora lutea.

Care should be used in the extrapolation of ovary data from the mouse to humans since the mouse ovary is peculiar in many respects. Its primary follicles and ovocytes are exceptionally radiation-sensitive compared with developing and mature follicles. The mouse ovary also has the tendency to develop invaginated tubular downgrowths of germinal epithelium and ovarian tumors, and these changes are easily accelerated and increased by relatively low doses of radiation. The peculiar differences in the mouse ovary, or the underlying causative mechanisms, are probably responsible for the exceptional

radiation-sensitivity and the irreversibility of the effects of relatively low doses of radiation, compared with ovaries of other laboratory mammals and the human female. In the female mouse, a single X-ray dose of approximately 100 rads results in a high incidence of permanent sterility and ovarian tumors.

Total-body irradiation appears to produce greater effects on the ovary and on fertility in female animals than local irradiation of ovaries with equivalent doses, perhaps due to greater endocrine disturbances produced by the former.

5. Sexually Immature Animals

Some studies of rats, rabbits, and mice have shown that the germinal cells of prepubertal animals and the primordia of germinal cells in fetuses are considerably more radiation-sensitive than the germinal elements of sexually mature animals. In the mouse, irradiation of fetuses with relatively low fractionated doses (300 rads) results in subfertility and sterility of both sexes during postnatal life. It has also been shown in mice that the reaction of the fetal gonads to X-rays bears no relation to the relative radiation-sensitivity of the adult gonads. The fetal testis is more radiation-sensitive than adult testis and the fetal ovary is less radiation-sensitive than the adult ovary, as measured by subsequent fertility. In this respect, the mouse may represent a special case, as pointed out earlier.

E. Effects on Growth and Development

Regenerative and repair processes of the body appear to be fairly sensitive to radiation and their inhibition may be very persistent, especially if vascular integrity and patency are impaired. Much more quantitative investigation is needed, under circumstances of both total-body and localized irradiation.

Quantitative studies with rats seem to indicate that growth, as measured by body weight, is decreased by repeated whole-body exposure to 24 rads/wk. A significant decrease in body weight can be produced by repeated whole-body exposures without causing any decrease in hemoglobin levels or absolute neutrophils.

Localized irradiation of the epiphysis has been shown to cause measurable inhibition of bone growth and shortening of bones in humans and animals, with the greatest effect seen in the youngest animals. Localized irradiation of the jaws has been followed by decrease in tooth growth.

Studies on Japanese children exposed to the atomic bomb in 1945 indicate a statistically significant but very slight retardation of growth and maturation. However, the influence ot other nonradiation factors has not yet been adequately evaluated. Extensive measurements on 4800 children at 6, 7, and 8 years after exposure in Hiroshima revealed generally that growth was retarded and maturation delayed (234, 235). In another study of several hundred children in Hiroshima and Nagasaki, studied in the 2nd, 4th, and 5th years after irradiation, physical growth and development were reported to be adversely affected, and the resulting retardation of height, weight, and skeletal development was still evident at the end of 1950 (216). The investigators believed that factors other than radiation may have contributed to the effects described; e.g., malnutrition.

F. Degenerative Diseases and Histopathologic Changes

Some of the first delayed radiation injuries to be recognized were injuries of the skin (including atrophy, dermatitis, epilation, and epidermal neoplasia). In the human skin, doses of about 500 to 700 rads may result in permanent epilation. Somewhat smaller doses that cause temporary epilation may result in a decrease of pigmentation or graying of the new growth of

hair in the irradiated areas. Curiously enough, this effect has not been reported in exposed Japanese. Doses in the erythema dose range or somewhat higher may also cause increased pigmentation of the skin in the irradiated regions, some degree of epidermal atrophy, and some decrease in sebaceous and sweat glands. Hyperkeratotic areas in skin and vascular sclerosis are also late sequelae of skin irradiation. Surface doses of approximately 1600 rads may result in considerable permanent dilatation of capillaries (telangiectasia) in the region irradiated. Late changes were seen commonly at one time in the skin of the hands and faces of persons exposed repeatedly to irradiation in the course of their occupations; radiation dermatitis and the ulcers that often developed from this condition were frequently followed by epidermoid carcinomas.

It has been known for many years that nephrosclerosis is a complication of overexposure of the kidneys in radiation therapy. Renal hypertension may be produced in man within periods of months or a few years by single localized X-ray doses of about 3000 to 5000 rads or by fractionated doses of lesser size (e.g., a total dose of 2300 rads to both kidneys in 35 daily doses) (335). These conditions have been produced in experimental animals in a relatively short time by localized irradiation of the kidneys with large doses. More recently, it has been observed in experimental rats and mice that nephrosclerosis with renal hypertension and associated generalized arteriosclerosis are late effects of total-body irradiation with doses (sublethal or LD_{50} range) much lower than those given above. Although the pathogenesis of the nephrosclerosis, occurring as a greatly delayed effect, is not entirely clear, histopathologic data indicate that changes in fine vasculature play an important role in both its early and late initiation and development.

Nephrosclerosis and related hypertension may appear as a late radiation effect in experimental animals in which it has rarely or not been observed within the average lifespan (later periods not well studied) or its onset may be advanced in experimental animals in which the disease has occurred spontaneously to some extent.

Renal hypertension, once established and progressive, tends to increase the rate of vascular sclerosis in many regions of the body, and the progressive arteriosclerotic changes are often associated with progressive atrophy of parenchymatous organs in which the vascular changes are marked. Consequently, when irradiation has caused or advanced nephrosclerosis with related hypertension in animals or humans, there is a tendency toward increased incidence of death due to related causes (e.g., renal failure, cardiac failure, and cerebral hemorrhage) with corresponding reduction in probability of death from other unrelated causes or to diseases having longer induction times.

Irradiation of parts of the human brain or spinal cord with total doses of several thousand rads, given singly or in large fractions within a few weeks, may injure blood vessels, cause ischemic damage of the tissues, and cause progressive sclerosis of blood vessels, with subsequent secondary degeneration of brain or spinal cord tissue. Rupture of blood vessels may occur from one to several years after exposure.

Atrophic and fibrotic changes, often associated with arteriosclerosis, have been observed in human hemopoietic organs long after localized irradiation. Anemia has been observed after protracted irradiation of the bone marrow and also as a late complication of radiation therapy.

Radiation osteitis is a late degenerative effect of intensive irradiation of bone. The degenerative and destructive processes develop slowly, and after many years may lead to necrosis, pathologic fracture, and osteogenic sarcoma.

The gastrointestinal tract has revealed some permanent and delayed effects following fractionated doses of several thousand rads in the form of atrophic and fibrotic changes in the mucosa, sometimes late ulceration of the mucosa, and permanent reduction of secretion of acid and pepsin by the stomach.

Intensive irradiation of the lungs in radiation therapy has resulted in slowly developing progressive fibrosis, associated with vascular damage and arteriosclerotic changes. Malignant neoplasms of the lung have been observed in miners subject to inhalation of radioactive substances, and have been produced in experimental animals by means of intratracheal injection and implantation of radioactive substances.

Substantial doses of radiation to actively proliferating mammalian tissues have reduced their regenerative capacity. The failure of such tissues to regenerate parenchymal cells fully to normal numbers is often associated with increase in connective tissue and vascular changes. In general, the degree of this incomplete regeneration varies directly with the size of the single dose or with the dose rate in protracted irradiation; in some tissues such as testis, however, certain modes of fractionation may increase the dose efficiency in damaging reconstitution capacity of tissue. It is not clear to what extent the permanence of this effect is due to relatively direct biologic effects of radiation on the stem cells themselves in such tissues, or to damage of supporting tissue. Nor is it clear to what extent in each tissue this incomplete regeneration is due to (1) a decrease in the reproductive capacity of existing stem cells, (2) a decrease in the number

of stem cells surviving, (3) asynchrony in regeneration of histologic elements with increase in connective tissue, or (4) damage of fine vasculature, although any or all mechanisms may be involved to varying degrees depending upon dose factors. Little is known quantitatively about the reproductive capacity of individual stem cells or the numbers of primitive stem cells surviving in the post-recovery period after irradiation. It has been observed, however, that fibrosis of small blood vessels with general reduction in vascularity is often associated with subsequent reduction in number of parenchymatous cells and increase in connective tissue.

Changes in the blood vascular and lymphatic systems, together with the destruction of radiation-sensitive parenchymatous cells, are important features in the pathogenesis of many delayed radiation effects. Many of the delayed effects seem to come from metabolic and nutritional disturbances associated with impaired blood supply of organs, which leads to reduction of function and of reparative capacities, and to increased susceptibility to traumatic damage, infection, and disease in general.

G. Radiation Effects and Aging

In physiologic aging in all animals there occurs involution of many organs, which progresses with time, qualitatively but not quantitatively independent of disease. These involutional or atrophic changes consist generally of loss of parenchymal cells, increase in amount and density of connective tissue, and degenerative changes in the vasculature. Such changes are most prominent in the proliferating organs (e.g., thymus, lymph nodes, spleen, bone marrow, gonads, skin, and gastrointestinal tract), but are also observable in organs with reverting post-mitotic parenchymal cells (e.g., liver, kidney, pancreas, etc.), and those with fixed post-mitotic parenchymal cells (e.g., brain).

After the period of maximal regeneration (to normal or subnormal levels) of parenchymal cells lost, progressive involutional changes tend to be detectable earlier or to be more advanced at given chronological ages in animals irradiated with substantial total-body sublethal doses than in nonirradiated control animals.

There is some evidence of effects of this kind in human organs following localized irradiation. However, there has been no definitive study on effects of irradiation on aging processes of man, and the fragmentary data on delayed effects of localized irradiation in human tissues that are qualitatively similar to changes associated with aging are difficult to interpret in terms of premature aging since most of the human cases were complicated by malignancy or other serious disease processes.

Although the fundamental causes of the permanent and delayed effects of radiations are perhaps no better understood than those of physiologic aging, there are many parallels between the two. The findings discussed in foregoing sections of this report seem to indicate that animals dying prematurely as a result of total-body irradiation may do so as a result of a process resembling advanced or premature aging.

There may be some dissimilarities at present between physiologic aging and radiologic aging, particularly with respect to the radiation induction of particular diseases in certain strains of animals. In general, however, the premature mortality that occurs long after irradiation seems to result from the premature development of neoplasms and degenerative diseases, preceded by degenerative histopathologic changes resembling senescent changes; together they simulate the appearance of premature physiologic senescence.

The mortality curves for animal groups showing shortening of life after single radiation exposures have often been shown to be essentially similar to those for nonirradiated control groups of consistently greater age.

Although far from adequate, such comparisons between physiologic and radiologic senescence made from studies of tissue changes, physiologic changes, morbidity, and cause of death seem to indicate that animals dying prematurely as a result of irradiation have a pattern of physiologic and pathologic changes similar to that exhibited by nonirradiated control animals, and die largely of the same causes.

As in the case of life shortening, the quantitative dose-effect relationship at low dose levels for radiologic aging is not known.

V. MODIFICATION OF LONG-TERM EFFECTS OF RADIATION

A. Protection

Some of the agents that lower radiation-sensitivity have been found to reduce long-term as well as early effects of radiation. In general, these agents act by partially diminishing the effectiveness of a given amount of radiation. The extent of protection afforded varies with the tissue in question, with the ion density of the radiation, and with physiologic variables such as oxygen tension and temperature.

Mice have been protected to some extent against the life shortening and leukemogenic actions of X-rays by treatment before irradiation with mercaptoethylguanidine, a derivative of cysteamine. Similar effects have also been obtained in mice by combined protection with cysteine and anoxia. Cysteine has also inhibited the induction of cataracts in rabbits. Preliminary data suggest that these agents also protect other tissues such as the skin, intestine, and gonads.

Although these agents generally reduce the effectiveness of X-rays for acute effects by a factor as great as 3, the degree of protection they provide against late effects has yet to be accurately determined. The mechanism of their action and pharmacology are not fully understood. Experience to date with cysteine and some of its derivatives indicates that these compounds are too toxic for use on humans; however, newer derivatives are being tested which appear to offer greater promise of clinical applicability.

B. Enhancement of Recovery

Radiation-damaged hemopoietic tissue can be replaced by transplantation of nonirradiated isologous bone marrow or spleen cells. This measure not only promotes recovery of animals from otherwise acutely lethal radiation injury of the marrow, but it inhibits the subsequent development of lymphomas and facilitates restoration of the depressed immunological defenses of the irradiated animals. Whether this procedure affords protection against radiation injuries unrelated to hemopoietic damage appears doubtful, but there is some evidence that marrow-injected mice suffer less shortening of life than noninjected irradiated controls. When marrow is transplanted between animals that are antigenically different, the recipient frequently develops a fatal immunological reaction. Hence, the application of this procedure to man will be greatly limited unless means can be found to prevent or overcome this complication. If this can be accomplished, protection against late effects in various nonhemopoietic tissues may be feasible through replacement of damaged organs.

VI. COMMENTS AND RECOMMENDATIONS

Long-term effects of whole-body external radiation appear to be quite general, consisting of some degree of irreversible injury to all the organ systems. The organ pathology and the diseases occurring are not unique. The disease entities that develop are largely those, common to the population, that occur earlier in the life of irradiated animals than in their nonirradiated counterparts. Although not clearly established at low protracted dose levels, the syndrome resembling premature aging with shortening of lifespan appears to be common to all whole-body exposure. Because life shortening presumably occurs in all individuals in an irradiated population, its magnitude may provide a more valid criterion for exposure limits than increased incidence of certain diseases that affect only a limited number of individuals. Nevertheless, in both animals and man, it may often be more feasible to determine increased disease incidence than life shortening at low dose levels. We recommend increased effort toward the evaluation of the relative sensitivities of these two criteria.

Some quantitative experimental evidence has been obtained on the effects of partial-body irradiation on lifespan. More information is needed, however, about quantitative dose-effect relations with respect to exposure dose or integral dose, and with respect to irradiation of different regions or specific organs. With highly localized irradiation, local pathology is probably the best criterion for exposure limitation at the present time, since the increase in incidence of diseases related directly or indirectly to the parts exposed tend to exceed the increase in those related to nonexposed parts.

In the case of protracted irradiation, most pathologic studies have been made on animals dying or sacrificed during exposure rather than after exposure and repair. Consequently, the permanent after-effects have not been well separated from the total injury and related quantitatively to dose.

In general, the sequence of time-dependent histopathologic events following either brief or limited protracted sublethal exposures requires much additional study to permit evaluation of the progression of after-effects.

Animals prematurely aged by irradiation have not been studied sufficiently to determine those changes that presumably occurred in their physiologic efficiency. Investigations in this area are recommended.

Except for alterations in prenatal development, very little is known of the after-effects of either whole- or partial-body radiation in the young as compared to mature animals. Research on this question is needed.

In experimental work on late effects, as the dose is progressively reduced below levels associated with substantial early functional or morphologic changes, the appearance of the late effects seems to be increasingly delayed. Most of these delayed effects cannot be qualitatively distinguished from effects of other non-specific damaging agents or from effects occurring spontaneously. Some effects seem to be more cumulative than others. These conditions, together with species, sex, and individual differences, and the special sensitivities of different age groups (embryos, fetuses, children, and perhaps the aged), make it difficult to relate small radiation doses and the effects in individuals or large populations. Under these conditions, it is difficult to postulate the existence or the lack of dose thresholds.

On the basis of present information relating late effects with dose, it is not possible to evaluate accurately the possible somatic hazards of exposure to low dose levels. More accurate evaluation will require a better understanding of the fundamental mechanisms of the production and manifestations of radiation injury. One of the greatest obstacles is the lack of knowledge on the structure and function of cells and tissues, and on the mechanisms in the aging process and development of diseases and malignancies. Since radiation is a useful tool for the study of many of the fundamental cytologic, histopathologic, gerontologic, and pathologic problems, such fundamental radiobiologic studies should contribute greatly to the knowledge of life processes and the development of methods to detect subtle damage.

Since definitive information on man can probably be obtained only by extrapolation from animal results and comparison to meager human data, rigorously controlled animal studies on low doses should be widely extended, using greater numbers of experimental animals for increased accuracy of observation. Since radiation-sensitivity for different delayed effects varies widely among species and strains, experimental studies with a greater variety of species are needed to ascertain the generality of quantitative dose-effect relations.

Systematic recording of pertinent facts and observations on irradiated humans over longer periods of time would yield needed information on late effects of low radiation doses in humans, and the detection of effects presently observed only in experimental animals.

Except for the case of radiation cataracts, knowledge on delayed effects in man from radiation doses under 1000 rads has come largely from population studies. Many difficulties are involved in such studies; e.g., the control of variables other than radiation exposure, the development of rosters of radiation-exposed persons available for study, and the estimation of the sensitivity of such studies for detecting radiation-induced diseases. It is nevertheless urged that demographic and medical statistical studies of populations exposed to high natural or artificial radiation levels be given more emphasis in radiation research. A review of such studies may reveal unexplored sources of information.

Much experimental work is needed also on the mechanism of recovery and of chemical protection against radiation injury, particularly with respect to increasing the reversibility or reparability of injury thereby diminishing the late effects.

Increased attention should be given to detailed comparison of senescence in irradiated and nonirradiated experimental animals and humans. It should be noted that an accurate evaluation of the degree of advancement of senescent processes, as distinguished from changes more directly related to acute radiation injury, can be made in experimental animals only after maximal regeneration and repair of acute insults. Also, many tissues and organs possess reserve capacities, and senescence involves reduction of these capacities; physiologic changes related to senescence are better measured under conditions that challenge these reserves or challenge homeostasis rather than under resting conditions.

Since the dose-effect relationships for late somatic effects of low-level radiation are unsettled and subject to great uncertainty at present, it must be anticipated that increasing radiation exposure of human populations might result in a statistically detectable increment of somatic damage.

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