

**PATHOLOGIC EFFECTS OF
ATOMIC RADIATION**

National Academy of Sciences—

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**REPORT OF THE
COMMITTEE ON
PATHOLOGIC EFFECTS OF ATOMIC
RADIATION**

**FROM A STUDY
OF THE
BIOLOGICAL EFFECTS OF ATOMIC RADIATION**

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PREFACE

The National Academy of Sciences is carrying on a study of the biological effects of atomic radiations of which the report of the Committee on Pathologic Effects is a part. Five other committees have been at work preparing similar reports concerning the problem from the point of view of genetics, meteorology, oceanography and fisheries, agriculture and food supplies, and the disposal and dispersal of radioactive wastes. Brief summary reports by each of the committees were published in a single volume by the Academy on June 13, 1956, and these are available on request.

The Committee on Pathologic Effects met three times as a group -- on December 18, 19, and 20 at the Princeton Inn, on January 22 and 23, and again on March 7 at the Academy. To permit more detailed consideration of certain aspects of the problem subcommittees were appointed under chairmanship of members of the committee but with membership beyond that of the committee. The reports of these groups were considered by the committee, approved, and incorporated in the report. In addition several members of the committee prepared detailed reports on matters with which they have been particularly concerned, and these are also appended.

The work of the committee has been facilitated by the cooperation of the U. S. Atomic Energy Commission and the Department of Defense. Financial support of the Academy's study of the biological effects of atomic radiations is provided by the Rockefeller Foundation.

Shields Warren, MD
Chairman of the Committee
on Pathologic Effects

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SUMMARY REPORT

of the

COMMITTEE ON PATHOLOGIC EFFECTS

Appreciation of the pathologic effects of radiation on man has required of this Committee and its subcommittees, consideration of voluminous experimental work on animals, as well as such direct data on human beings as are available. When the results of controlled experimental studies are considered in the light of the human data, it is found that the sequence of pathological changes is indeed quite similar in man and in animals, although man has certain definable peculiarities of response.

The human data include:

Results of excessive exposure to X-rays and radium in the early days;

Results of more moderate exposure to different forms of radiation, as experienced by cyclotron workers;

Results of introduction of naturally occurring radioelements into the body, notably radium preparations and thorotrast;

Effects of exposure at Hiroshima and Nagasaki;

Observations on populations irradiated by fallout;

Additional observations from clinical radiotherapy, use of artificial isotopes in therapy, a very limited number of accidents in atomic energy work, and certain statistical surveys of large groups.

Experimental work covers the whole field and includes studies of acute and chronic effects on many species of animals.

Certain human effects have to be assumed from consideration of experimental knowledge: for example, early effects of high doses to the central nervous system, and results of absorption of most of the artificially produced isotopes, and it is fair to say that the lethal dosage of penetrating radiation for man is less well known than for many other species.

Radiation has been added to the means of production of casualties in warfare. Not only can radiation cause death or immediate or delayed injury by itself, but exposure to it intensifies the seriousness of burns or other injuries. The acute lethal dose for half of a given population is in the range of 400 to 600 r.

Despite the existing gaps in our knowledge, it is abundantly clear that radiation is by far the best understood environmental hazard. The increasing contamination of the atmosphere with potential carcinogens, the widespread use of many new and powerful drugs in medicine and chemical agents in industry, emphasize the need for vigilance over the entire environment. Only with regard to radiation has there been determination to minimize the risk at any cost.

It appears, however, that a fairly clear general picture of human radiation effects can be presented. Members of this group and of its subpanels, while recommending various points of departure for greater consideration and further research, were in no case of the opinion that any sort of "crash program" would be desirable or profitable.

The various means whereby persons may be overexposed to radiation will have a great deal of influence on the over-all effects. For example, the exposures at Hiroshima and Nagasaki and a few exposures in accidents in atomic energy plants, involved radiation to the whole body in which the clinical effects reflected mainly injury to the blood-forming tissues and intestinal tract. These tissues are very sensitive to radiation but have a great power of recovery.

Where, on the other hand, exposure has been suffered at a relatively low level from time to time over a period of years, a variety of injurious effects may be encountered, such as leukemia and skin cancer. Among those who have adhered to present permissible dose levels, none of these effects have been detected.

Shortening of life span may result from exposure to radiation not only as a consequence of damage to a specific tissue, as seen in the development of skin cancer and leukemia, but also as a result of such general factors as lowered immunity, damage to connective tissue, or premature aging. Older members of the populations seem to be more sensitive to this nonspecific damage. The shortening of life correlates roughly with dose of radiation, but has not yet been demonstrated at low doses. The following table indicates life shortening in radiologists, who may well have received doses in the course of their occupation ranging from very slight to about 1000 r.

AVERAGE AGE AT DEATH

Physicians having no known contact with radiation.	65.7 years
Specialists having some exposure to radiation (dermatologists, urologists, etc.)	63.3 years
Radiologists	60.5 years
U.S. population over 25 years of age	65.6 years

Shielding of even a portion of the body from radiation lessens the effect out of proportion to the relative amount of tissue protected. Therapeutic radiation to a single portion usually is much greater than the lethal level of total body radiation.

Radiation may have its prominent effects in particular parts of the body when it is applied locally, and this may take place in two ways. First, an external source may be so handled as to direct its radiation to a particular part; in this way many of the early radiologists suffered acute or chronic injury to the hands, which has also occurred in more recent atomic energy accidents.

In the second instance, a radioactive substance may be taken into the body and deposited where it is a source of constant local irradiation until it is eliminated. Bone disease in radium workers and lung disease in miners of radioactive ores (both leading to cancer as a late development) are well-known examples of this mode of exposure. It is worth noting that the atomic energy industry, through diligence, has apparently avoided exposures leading to this type of injury.

It is thus characteristic of the radiations that their effects may manifest themselves not only immediately, but perhaps only after a long period of intermittent radiation, or may even be long delayed after a single exposure. One of the particular tasks of the panel has been to see all of these effects in a common perspective. They will be discussed here in terms of the effects of radiation on the important organs and tissues of the body, since it is a well known fact that some are more readily injured by radiation than others, and that injury to some has more serious consequences than to others.

Among the more serious effects of radiation are those on the blood, since the vital blood forming organs are particularly sensitive to radiation injury. The white blood cells are decreased in number

soon after radiation, and in fatal cases they almost disappear before death. Other acute changes in the blood give rise to disorders in the clotting mechanism and a bleeding tendency, and the formation of antibodies against infections is impaired. These changes lead to acute illness in the second week (perhaps a little later in man), heralded by decrease in the white cells.

In the next few weeks anemias may occur due to deficiencies in red blood cell formation and survival. Those victims living through the first month usually recover, but in certain individuals, or where radiation is continued, there is a further serious breakdown of blood cell formation.

Some late effects of radiation appear as leukemias, which are found to arise a few years after radiation. This disease, relatively rare in man, may show manifold increase in persons subjected to a nearly fatal single dose (Hiroshima data) or in those whose professional work has exposed them to higher than acceptable permissible dose rates.

Effects on the intestinal tract are also critical in the early period. Vomiting and diarrhea occur within a few hours. This is a common complication of X-ray treatment to the abdomen, but is not fatal. It seems to be mediated through the vegetative nervous system and is probably not related to later damage.

Within a few days (usually four or five) after radiation, more serious effects occur. Failure of the cells lining the intestine to replace themselves results in denudation of the surface, with intractable loss of fluid and salts; complicated by ulcerations, spread of infection, and bleeding.

Late effects are seen after heavy radiation therapy, and resemble those seen in some other heavily irradiated tissues: overgrowth of connective tissue (fibrosis) and decrease in the number of functioning epithelial cells. Cancer has occurred in animals given overwhelmingly large doses of isotopes in insoluble form by mouth.

Effects of radiation on skin have been widely observed. On the first day an erythema, resembling that of sunburn, appears but is transitory. A few days later a somewhat more persistent erythema occurs which may be associated with pigmentation. Ulceration may occur in this period after high doses. Much later, atrophic changes are seen, with marked deficiency of the blood supply and intractable ulceration; such a chronically damaged skin is a fertile bed for cancer

development. The Marshall Island group, while receiving total body radiation insufficient to produce serious changes, had rather marked secondary skin lesions from direct contact with fallout material. Slight local vascular changes have been observed after two years, but serious after effects are not anticipated. Falling of hair was temporary in these persons; heavy dosages are required to make it permanent. In animals, destruction of the pigment cells causes regrown hair to be white, but such loss of pigment seems not to take place in men under comparable conditions.

Bone: Early radiation effects are not of note, except that retardation of growth of epiphyses of immature bones occurs and may produce serious results in children given local radiation therapy. Late effects are seen in radium poisoning, where we see repeated destruction and repair, culminating in widespread destructive changes in which bone sarcoma is likely to appear.

Lung: Early after large doses we see congestion and increased secretion. Here, again, the late-appearing changes are of greatest importance: fibrosis, and development of cancer, which has been very common in mining areas where large concentrations of radon gas were inhaled.

Thyroid: An early and persistent effect is depression in secretory activity, which is used as the basis of the radioiodine therapy of hyperthyroidism. No serious late local effects of thyroid radiation in adults have been recorded, although some leukemias have followed heavy radioiodine treatment. A small proportion of children treated with X-ray to the upper part of the body, however, develop thyroid cancer later on, suggesting a specially high sensitivity of the child's thyroid.

Eye: The only noteworthy lesion is cataract of the lens, which is a late response. It is much more readily produced by neutrons than by X-rays, therefore, has been most prominently observed in cyclotron workers.

Gonads: A single sublethal radiation dose to a male may result in sterility after two to three weeks, followed by a slow recovery. Chronic treatment results in a gradual reduction in number, motility and viability of sperm. This is the most sensitive indicator of chronic damage so far observed, being measurable in dogs at ten times the permissible dose rate. Larger doses (about equal to the total-body lethal dose) permanently sterilize males and females. Experience with the Marshall Islanders, the exposed Japanese, and certain accident cases

indicate that total body doses up to about 40 - 50% of the lethal have no permanent effect on human fertility.

Central Nervous System: Observations in man are quite limited. Very high doses given to animals result in loss of coordination and excitement soon after irradiation. At later stages, various effects are seen which indicate sensitivity of particular cells and areas.

Effects on Embryos: Treatment of embryos at various stages of development may lead to highly specific malformations depending on the exact developmental stage at the time of irradiation. At critical stages, relatively low dosages (those permitting survival of the mother) may cause serious malformations. These changes must be distinguished from genetic mutations, as one is often tempted to call abnormal offspring mutations. The type of malformation discussed here would not perpetuate itself genetically, and would result from radiation during gestation.

It must also be remembered that there are various other agents causing malformations during development, of which German measles is a well-known example.

A few factors influencing sensitivity might be mentioned. Very young or very old animals have increased sensitivity to lethal effects. Growing tissues are generally more readily damaged. States like hibernation delay the appearance of radiation damage but do not prevent it. Moderate stresses seem not to effect sensitivity but severe ones such as burns or exhausting exercise, have a deleterious influence, augmenting sensitivity.

Local radiation in sufficient amount to almost any part of the body may produce cancer, the chance of tumor development being somewhat related to dose. Since the cancer cell is an altered type of a normal tissue cell, it has often been suggested that cancer is a somatic mutation, like a genetic mutation but arising in a tissue cell which perpetuates the character by its growth.

All types of induced and spontaneous tumors appear not to arise at once, but to pass through a series of preliminary stages; and radiation induced tumors take a particularly long time to develop. Radiation induced cancer occurs in the absence of a generally abnormal state of the tissue of origin. Mouse experiments show that shielding of a part of the body will prevent radiation leukemia and that shielding of one ovary will prevent a tumor from developing in the other; and several of the tumors appearing late after irradiation seem to be produced in response to indirect mechanisms. If somatic mutation is a necessary

part of the induction of cancer, it would seem to play a minor role.

We have so far considered effects of overdosage of radiation in various forms. The question must necessarily be considered, as to whether much smaller amounts of radiation harmless to individuals, might be deleterious to large populations. Because of the striking difference of germinal and somatic cells the former carrying on from generation to generation injuries received, the Genetics Committee has recommended for large populations permissible dose levels of radiation lower than those which are safe for any one generation. As the permissible dose level which they have hypothesized as desirable for large populations were to be applied there would be no demonstrable somatic effect, although a theoretical minor shortening of life span could not be ruled out.

As regards internal contamination, independent data on Rongelap inhabitants and Japanese fishermen indicate that a considerable proportion of the lethal dose of external radiation was received by individuals who barely exceeded, and only for a short period, the permissible internal burden.

The only situation worth considering in relation to large-scale pathologic effects would then be widespread contamination with Strontium-90, which is a long-lived (half life 10,000 days) readily absorbed, bone-seeking isotope which tends to fall out generally over the earth rather than in accordance with the usual close or intermediate fallout pattern. It has already been found that some young individuals have retained 0.001 microcuries or one-thousandth of the permissible dose. This amount if maintained through life would yield 0.2 rep (equivalent r) to the skeleton.

In developing an unequivocally safe amount, we can recall that a certain degree of radiation exposure has always been with us, even excluding X-rays, in the form of gamma radiation from minerals, cosmic rays, and radioelements normally in the body. These levels vary greatly from one location or altitude to another and are not considered to produce harmful effects.

There seems no reason to hesitate to allow a universal human strontium (very similar chemically to calcium) burden of 1/10 of the permissible, yielding 20 rep in a lifetime, since this dose falls close to the range of values for natural radiation background. Visible changes in the skeleton have been reported only after hundreds of rep were accumulated and tumors only after 1500 or more.

In relation to world-wide contamination, food chains are important. Fallout contaminates plants through ground and leaf deposition; animals eat these plants. Therefore milk and cheese are human sources of radiostrontium, being high in calcium. Throughout this chain, strontium is discriminated against relative to calcium, which reduces the hazard somewhat. It must be remembered that in regions where soil and water are low in calcium, calcium and strontium will be more readily taken up.

As to therapy of radiation injury: while treatment is difficult, some success has been achieved with antibiotics and properly timed blood transfusions. Shielding of a portion of the body appears to give a degree of protection disproportionately large for the mass shielded. Experiments set up to explain this fact may help in developing a rational treatment. Also, various forms of treatment given immediately before radiation have been devised, but do not appear in any sense practical. Studies of this sort may, however, provide a basis for future discoveries.

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APPENDIX I

REPORT OF THE SUBCOMMITTEE ON
ACUTE AND LONG TERM HEMATOLOGICAL EFFECTS
OF ATOMIC RADIATION

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ACUTE AND LONG TERM HEMATOLOGICAL EFFECTS

On January 7 and 8, 1956, the Subcommittee met at the National Academy of Sciences in Washington, D. C. with all members present. A preliminary report was written by Dr's. Bond and Cronkite and distributed to Subcommittee members. The comments of the members have been incorporated into this report.

INTRODUCTORY COMMENTS BY THE CHAIRMAN

Mankind has always lived in an environment suffused with radioactivity from natural and unavoidable sources such as radioactive minerals and cosmic rays. Natural radioactivity varies greatly in degree throughout the world. Intensities tend to be much lower at sea level and on most small islands, with the exception of Baltic islands, throughout the world. At high altitudes cosmic ray activity increases significantly. Similarly natural radioactivity from minerals increases significantly in some mines, and in the water supplies of some areas. For example, water in the Joliet area in Illinois contains relatively large quantities of radium and its daughter products. Since the discovery of x-rays by Konrad Roentgen and natural radioisotopes by Becquerel and the Curies, there has been a steady increase in the amounts of radiation to which segments of mankind are being exposed. With the development of nuclear weapons and the spread of atomic energy by industrial activities, the levels of world wide radiation will unquestionably continue to increase.

At the present time there is confidence that the increment to the naturally existing radioactivity is but a small fraction of that believed to exist prior to the testing of atomic weapons and the presently developed atomic energy industry. However, when one specifies the diverse sources of radiation to which large numbers of mankind are being exposed, it is quite evident that serious concern must be felt by physicians and scientists for the possible influence of such radiation upon individuals, selected groups, and whole populations. In the course of the deliberation of this panel attention was called to the existence of the following types of exposure to radiation to which human beings were exposed, voluntarily and involuntarily:

1. Natural sources
2. World wide low-level fallout
3. Roentgenographic surveys of large segments of the population for tuberculosis and cancer
4. Dental x-rays
5. Industrial fluoroscopy and radiography
6. Fluoroscopy of infants
7. Fluoroscopy for shoe fitting
8. Diagnostic x-rays

9. Medical and scientific use of tracers in human beings
10. Therapeutic use of radioisotopes and x-ray
11. Tracer radioisotopes in agriculture and industry
12. Research and power reactors
13. Ionizing radiations for food sterilization
14. Experimental accelerators

During the early years when the diagnostic and therapeutic uses of x-ray were being developed, heavy and repeated exposure to physicians, physicists, nurses and technicians resulted in serious injuries. Historically, the occurrence of leukemia and aplastic anemia as late sequelae of exposure to x-ray and radioactive substances was well documented in the medical literature prior to 1937. Presumably Madame Curie died from an aplastic anemia. In recent years, while great care has been taken to avoid heavy radiation exposure, there is little knowledge on the hazards of repeated smaller doses, especially in regard to late effects on the blood forming organs.

The record of the atomic energy development, which involved the handling of large amounts of dangerously radioactive material is an example of the effectiveness of a controlled environment.

Dose dependence and correlation of other effects with hematologic effects:

In order to set the acute and chronic hemopoietic effects of radiation into the proper perspective with regard to overall radiation effects, the whole body radiation syndromes as a function of dose of radiation are summarized:

After very large doses of radiation delivered in a short time, a typical clinical syndrome is produced in animals. On the basis of observed symptomatology, it has been useful to name this symptom complex the central nervous syndrome (CNS). In animals, doses in excess of many thousands of r, are necessary to produce this complex. There are species variations. The "threshold" for this syndrome in man is not known and this syndrome has not been observed in man. Symptoms referable to the nervous system and GI tract appear promptly. Death may occur "under the beam" or within a few hours. In laboratory animals this syndrome invariably results in death either promptly, or later as a result of the next clinical syndrome which results in death at a later time. If the nervous symptom complex subsides, or if the dose has been smaller (in the region of 900 - 5,000 r for laboratory animals; dose for man not known), a symptom complex termed the gastrointestinal syndrome (GIS) appears. Nausea and vomiting appear shortly after exposure. Diarrhea and tenesmus become severe. The GI symptoms may be intractable

or may subside for a variable period. Fluid and electrolyte loss from the GI tract progressively produce dehydration and eventual vascular collapse, and death that may occur during the 1st and 2nd weeks. This picture was observed in the Japanese casualties and has been well studied in laboratory animals. Death from this syndrome has been prevented experimentally in some dogs by adequate fluid and electrolyte replacement; in addition spontaneous recovery may occur after the lower doses in this range. However, the survivors then experienced another symptom complex that may result in death. It is this third symptom complex characterized by signs and symptoms referable to bone marrow depression which characterizes the lethal dose range*. By custom, the mortality from this syndrome has been tabulated as of 30 days after exposure. There are reasons, to be discussed later, why a 30 day tabulation may be too short for human beings.

A fourth phase of deaths was observed during the 2nd and 3rd months after exposure in the Japanese casualties in which in some instances the causes of death were not clear; however, pancytopenic sequelae were still present. Hemopoietic recovery was in progress but defects in proliferation and maturation were observed in the pathologic sections of marrow. Following the third month, deaths are infrequent and it becomes increasingly difficult to ascribe deaths to the effects of radiation since phenomena observed are those which may result in death in any non-irradiated population. In some instances cause of death was uncertain although pancytopenia was prominent.

There is evidence that large single doses, or repeated small doses of radiation can produce diverse neoplasia, genetic defects, and shortened life span in select controlled animal populations. However, attempts to ascribe a specific role to irradiation in neoplasia in human populations becomes an exceptionally complex biometric study because of the increasing contamination of the atmosphere by industry with potential carcinogens, and the introduction and widespread use of an array of clinically useful drugs, whose long term effects in man are imperfectly understood, but which in some cases have produced severe blood dyscrasias. Accordingly, in all of the discussions on the long term

*Sublethal refers to the lower doses of radiation that will produce no deaths within a given period of time, usually taken as 30 days in animals. The lethal range extends from the threshold dose at which only rare deaths occur in this time interval, to the level at which virtually all exposed will die (the LD 1 to LD 99 range). Doses above the LD 99 level are termed supralethal. In all ranges, however, ultimate longevity is reduced to some degree.

effects of single doses of radiation on man, and the effect of repeated or low level exposure, one must be especially cognizant of the fact that the "effects" are deduced by statistical correlations, and cannot be proved by controlled experimentation, nor can other causative factors be eliminated. In this era of awakened public interest to the hazards of radiation, it is especially important that preoccupation with the hazards of ionizing radiation does not becloud the searching mind of the scientist or the responsible citizen to the presence of other hazards of equal importance. This is not an attempt to minimize the hazards of ionizing radiation with respect to the development of blood dyscrasias and other late effects. It is most important to bear in mind that the incidence of bone marrow failure* and leukemia has increased significantly in the United States in groups in whom there is no known overexposure to ionizing radiations. Today no informed physician believes that exposure to ionizing radiation has either a beneficial or stimulating effect on the blood.

In the course of the deliberation of this Subcommittee, attention was focused upon the known effects of nuclear explosions, the immediate and long term effects of single exposures from all causes, and the long term effects of intermittent and continuous exposure to radiation of diverse types. In the latter category, the Subcommittee felt that a reasoned judgment could not be made because of the paucity of realistic quantitative data on the degree of exposure.

ACUTE HEMATOLOGICAL RESPONSE TO SINGLE DOSES OF PENETRATING RADIATION

Although the available sources of hematological data on human beings exposed to total body external radiation have serious limitations, they were considered to be reasonably consistent among themselves to allow characterization of the time course of change in peripheral elements following exposure. The sources of data included the reports of the Japanese exposed to immediate radiation from atomic weapons, the account of the human beings accidentally exposed to fallout radiations at the Pacific Proving Grounds in March, 1954, the reports of human beings exposed to reactor accidents in the laboratory, and data on patients with incurable neoplastic disease exposed to therapeutic total body

*Synonymous with aplastic anemia, refractory anemia, hypoplastic anemia. Aplastic anemia has been observed to terminate in leukemia. The occurrence of aplastic anemia after use of diverse drugs is common clinical knowledge.

irradiation. The pattern of response of the peripheral blood elements changes with increasing radiation dose. In the following description, changes are divided into those that occur in the sublethal range, and those that occur in the lethal range (doses that result in some mortality within 60 days of exposure). This division is arbitrary, since the patterns of change merge imperceptibly, and each category covers a range of doses and thus degree of effect. When the dose is increased from sublethal levels to lethal levels, the lag period between exposure and depression is progressively shortened.

Response after sublethal doses:

The neutrophil count shows an initial rise in the first 12 to 48 hours followed by a sharp drop, to or below, the pre-exposure level. The count then fluctuates around or slightly below the pre-exposure level until the 3rd or 4th week, following which definite depression is observed. The time of maximum depression occurs during the 5th or 6th week or even later, and is followed by a gradual return to pre-exposure levels. Complete recovery may require several months or more.

The drop in lymphocytes is early and profound. Little or no evidence of recovery in the high sublethal range may be apparent several months after exposure, and return to former levels may not occur for months or years. The total white count parallels closely the change in neutrophil count.

The platelet count shows little or no change over the first three weeks following exposure. At approximately the end of the 3rd week the platelet count falls. The time of maximum depression is remarkably constant at sublethal dose levels, and occurs on the 28th to the 32nd day of post-exposure.

No trend in eosinophile, basophile, or monocyte counts can be definitely ascertained. This may result in part from the larger errors inherent in counts of these cells. In the absence of hemorrhage, the hematocrit may show slight depression. This effect is probably due to a combination of inhibition of erythropoiesis and shortened life span of the red cell.

Response after doses in the lethal range:

The neutrophil count may rise during the first two days following exposure. The count then falls steadily to reach values below 1,000/mm³ by the 5th to the 10th post-exposure day, depending on dose. In survivors,

recovery begins during the 5th week, but may not be complete for several months.

The lymphocyte count drops to vanishing levels within 12 to 24 hours of exposure; recovery is not apparent for several weeks; and it may not be complete for several months, or for a year. The total white count parallels the neutrophil count.

The platelet count in the lethal range, in marked contrast to that at lower doses, may drop precipitously, starting approximately on the 4th day, and platelets may virtually disappear from the peripheral blood by the 10th day.

Changes in the eosinophiles, basophiles, and monocytes counts cannot be characterized definitely at this time. The hematocrit* is not appreciably affected until hemorrhage occurs, severe gross external or occult internal bleeding may occur as early as the 9th day, depending primarily on the time at which the platelet count reaches dangerously low levels. This may occur from the second to the fifth week, with peak incidence in the 4th week in the low and mid-lethal dose ranges. The degree of response as a function of dose varies for the several blood elements. The platelet and lymphocyte counts are affected by very small doses of radiation, and are reduced to minimal levels before the lethal dose range is reached. The neutrophil count, however, does not reach minimal values until the lethal range is reached.

Comparison of man and other mammals:

The time course of changes in the leucocyte and platelet counts in human beings is definitely different from that observed in lower animals. In man, severe depression of these elements occurs later, and recovery is more delayed. Similarly, the time of deaths in man resulting principally from hematological depression differs from that of laboratory animals. In most laboratory species, essentially all animals alive on the 30th post-exposure day will remain alive for several months, although the life span is shortened. In man, however, the peak incidence of death from marrow depression occurs during the 4th and 5th post-exposure week (Hiroshima and Nagasaki data). Thus an LD 50, 30 day consideration is inadequate to characterize the acute lethal dose response

*Admittedly the hematocrit can be misleading since it represents both changes in plasma volume and red cell mass. However, in general decreases in hematocrit represent a diminution in red cell mass for one reason or another (loss, hemolysis, or no new production).

of man, and an LD 50, 60 days would be preferable*. The extensive serial blood counts obtained in human beings exposed to fallout gamma radiations were relied on heavily in characterizing the hematological responses of human beings exposed to external radiation. Admittedly the dose rate with fallout was much lower than with prompt radiation and may have reduced the effectiveness somewhat. These individuals received, in addition to gamma radiations, beta radiations of the skin, and probably a minimal degree of internal contamination. It was the consensus of the Subcommittee that neither the beta lesions nor the low level of internal contamination significantly contributed to the pattern of change observed. This view was supported by the general agreement of these data with other less extensive data on human beings who did not receive additional skin lesions or internal contamination; and the lack of correlation between the severity of hematological change and the extent of beta lesions in those exposed to fallout radiation. The reservation was held, however, that data are inadequate to establish this view with certainty, and that synergistic effects cannot be ruled out.

Mortality and morbidity from whole-body radiation:

The pan-hemopoietic depression contributes in large measure to morbidity and mortality following total body irradiation. In the sub-lethal and low lethal ranges, the response observed is consistent with other clinical pancytopenic states. Neutrophil depression increases the susceptibility to infection and platelet depression contributes to the bleeding tendency. Correction or treatment of these defects during the first few weeks may permit survival in some individuals who might otherwise have succumbed. The concept of total body x-radiation as primarily a pancytopenic state, while useful, is probably an oversimplification, particularly in low and high lethal ranges.

Susceptibility to infection is well established and the pathogenesis may well involve interference with specific immune mechanisms, phagocytosis, and migration of leukocytes in addition to simple neutrophil depression.

Susceptibility to bleeding is well correlated with platelet

*The reservation must be made here that the exposed Japanese population were heterogenous with respect to age, sex, physical condition and degree of added trauma from burns or blast. The extent to which these factors affected survival time has not been determined. In studies on laboratory animals the converse is true--homogeneous populations are studied.

depression. However, additional factors may be involved such as lipid antithromboplastins (Tocantins) or disturbances in the β lipoprotein transport mechanism (Nickson and Bane). In some instances, the latter changes are similar to changes induced by heparin administration to rabbits. The relation of these alterations to the bleeding tendency has not been established. It was the consensus that frank heparinemia is not a contributing cause of bleeding.

After higher doses, death ensues even if hemorrhage and infection are corrected. Germ free rats die at dose levels moderately higher than the lethal dose for rats in the natural state. These animals die later with severe hemorrhage and anemia. At dose levels in excess of the LD 100, 60 day level, individuals die within the first week presumably from fluid imbalance and vascular collapse correlated with marked damage to the intestinal epithelium. It is clear that at all dose levels, poorly known and little understood biochemical changes* occur which may contribute to mortality in the exposed individual. Our knowledge is inadequate to determine at the present time to what extent such biochemical changes may prove lethal in themselves even when infection and hemorrhage can be treated adequately.

Lethal dose for man:

No data are available to allow adequate characterization of the LD 50 value for man. The degree of hematological depression observed in patients receiving total body x-radiation indicates that the current estimate of 450 r is a reasonable estimate for x-radiation as employed in the clinic. A recent re-evaluation of the data from Hiroshima and Nagasaki indicated a value higher than this for immediate gamma radiation from the bomb. Geometrical and depth-dose considerations can be interpreted to indicate that the LD 50 for man exposed to immediate gamma radiation and fallout gamma radiation from the atomic bomb may be lower than this figure. A large degree of uncertainty exists in both approaches, and more biological and physical data are required to settle the issue. The situation is complex, and it became evident that it is not possible to extrapolate with confidence from one condition of radiation exposure to another, or from animal data to man.

*Apparently decreased respiratory quotient (RQ) in animals, increased excretion of amino acids in irradiated human beings, etc.

Threshold dose for detectible effects:

There appears to be no threshold* dose for changes in the peripheral platelet count and possibly for other elements of the blood. Changes at very low dose levels, however, can be detected only in a relatively large population. Nothing is known about subtle changes in the blood forming organs at dose levels so small that changes in the blood picture cannot be detected.

Diagnosis of radiation exposure and its severity:

The diagnosis of exposure to radiation and its severity is made on the basis of the history and physical and laboratory examinations, as with any disease. Available estimates of air roentgen dose received obtained by physical means should be considered in evaluating the degree of exposure, but should never in themselves be taken as an index for disposition or treatment since tissue dose and distribution of absorbed energy ultimately determines effect not dose in air. Any degree of radiation exposure should be avoided if possible. If exposure is necessary under emergency conditions, severe hematological depression may be expected at doses of 100 r or more measured in air, from immediate radiation from the bomb or from the gamma radiation from fallout material. With human exposure a wide spectrum of ages and of state of health is likely to be involved. Thus it is not possible to predict accurately the severity of response that might be expected for a population exposed at various dose levels. There is evidence from the human beings exposed to fallout radiation that children may be more severely affected than are young adults. Whether this is due to inherently greater sensitivity or to an increased depth dose due to smaller size is not known. From animal data, it has been postulated that elderly individuals may be more seriously affected than young adults.

Therapy of Radiation Injury:

Recommendations for therapy are given for 1) conditions where exposed individuals can be carefully and individually handled because they are limited in number and adequate facilities exist for taking care of them, and 2) exposures at the catastrophic level where adequate

*The threshold concept may be incorrect since inability to detect effects at lower doses may only be a manifestation of inadequate criteria for effect. For practical purposes a threshold might be classified as that dose where statistically significant differences are detected. For many effects this may necessitate extremely large samples.

medical observation and care are impossible. In the first category, of cardinal importance in therapy is careful observation, good nursing care, and treatment on an individual basis of any condition that may arise. Antibiotics in general should not be given prophylactically, and should be administered only if infectious processes develop that would be treated with antibiotics in the absence of radiation. Prophylactic use of antibiotics may be considered if the neutrophil count drops below $1,000/\text{mm}^3$. Prophylactic use of antibiotics may be considered particularly where severe wounds or other complications may be present. If antibiotics are used, they should be given in large doses and the broad-spectrum drugs should be employed. Fluids should be given as indicated clinically. Blood should not be given prophylactically, but only as indicated from clinical and laboratory findings. Fresh whole blood by direct silicone multiple syringes without anticoagulant or collected in plastic bags or platelet transfusions may be of some value in controlling purpura and other hemorrhagic manifestations. The use of drugs without clear indication is discouraged because of their unknown and possibly harmful effects on the irradiated individual whose metabolism is deranged. Parenteral administration of drugs should be held to a minimum because of the added trauma in an individual susceptible to purpura and infection. At present there are no specific prophylactic or therapeutic agents* that should be stock-piled for use in the hematological depression and the resulting disease state following exposure to total body irradiation.

Under catastrophic conditions it of course will not be possible to adhere to the above regimen. The principles of therapy remain the same, except that here there is a much better potential case for widespread and empirical antibiotic dispensation, particularly to individuals in which burns, mechanical wounds or other added trauma exist.

LONG TERM EFFECTS ON THE BLOOD OF A SINGLE EXPOSURE TO IONIZING RADIATION

The best single source of information on this subject is the Japanese survivors exposed at Hiroshima and Nagasaki in August, 1945. Of necessity, data on the immediate radiation effects are fragmentary

*Antibiotics of great value in the therapy of infection in the exposed individual are not considered here as specific drugs. Such prophylactic agents known to this panel such as sulfhydryl compounds, hypoxia inducing drugs, spleen or bone marrow preparations, etc., claimed or shown to favorably modify acute radiation injury in animals, have no place as yet in the treatment of human radiation injury.

and data on the exposed individuals between the 16th week and the 2nd year are not available. In 1954 a statistical analysis of the hematological data obtained by studies on Hiroshima survivors and a control population, carried out from 1950-1953 (ABCC Program ME SS) showed that there was no evidence for an increase in leukopenia, leukocytosis or anemia in the exposed as compared to the control population. During this period several cases of aplastic anemia were encountered among the Nagasaki survivors. However, it cannot be definitely stated that these cases were due to atomic radiation. Up to late 1953, no cases of aplastic anemia had been found in the Hiroshima survivors. It should be noted that "aplastic" anemia is not an uncommon blood dyscrasia in the Japanese.

Incidence of leukemia:

In contrast, an increased incidence of leukemia among survivors has been clearly established. It has long been known that repeated or single doses of radiation could increase the incidence of leukemia under controlled experimental conditions in laboratory animals. Accordingly, an intensive investigation of the incidence of leukemia in the irradiated survivors in Hiroshima has been carried out by the ABCC. This study is continuing and a statistical analysis, based on the verified cases of leukemia occurring in the Hiroshima survivors, establishes beyond reasonable doubt that the incidence of leukemia was significantly increased in exposed individuals.

The following graphs and tables are based on the 1947-1953 incidence of leukemia in Japan and have been supplied by the Committee on Atomic Casualties of the National Research Council.

LEUKEMIA IN EXPOSED PERSONS - NUMBER AND RATE
BY PRESENCE OF
RADIATION SYMPTOMS AND DISTANCE FROM HYPOCENTER

Distance from hypocenter- meters	Hiroshima Population ¹			Number of Cases of leukemia ²			Incidence		
	SRC ³	NRC ⁴	Total	SRC	NRC	Total	SRC	NRC	Total
Under 1000	750	450	1,200	14	2	16	246.2	58.6	175.8
1000-1499	2,250	8,250	10,500	15	13	28	87.9	20.8	35.2
1500-1999	1,750	16,950	18,700	2	4	6	15.1	3.1	4.2
2000-2499	950	16,250	17,200	1	1	2	13.9	0.8	1.5
2500 over	850	49,650	50,500	0	8	8	--	2.1	2.1
Total	6,550	91,550	98,100	32	28	60	64.4	4.0	8.1

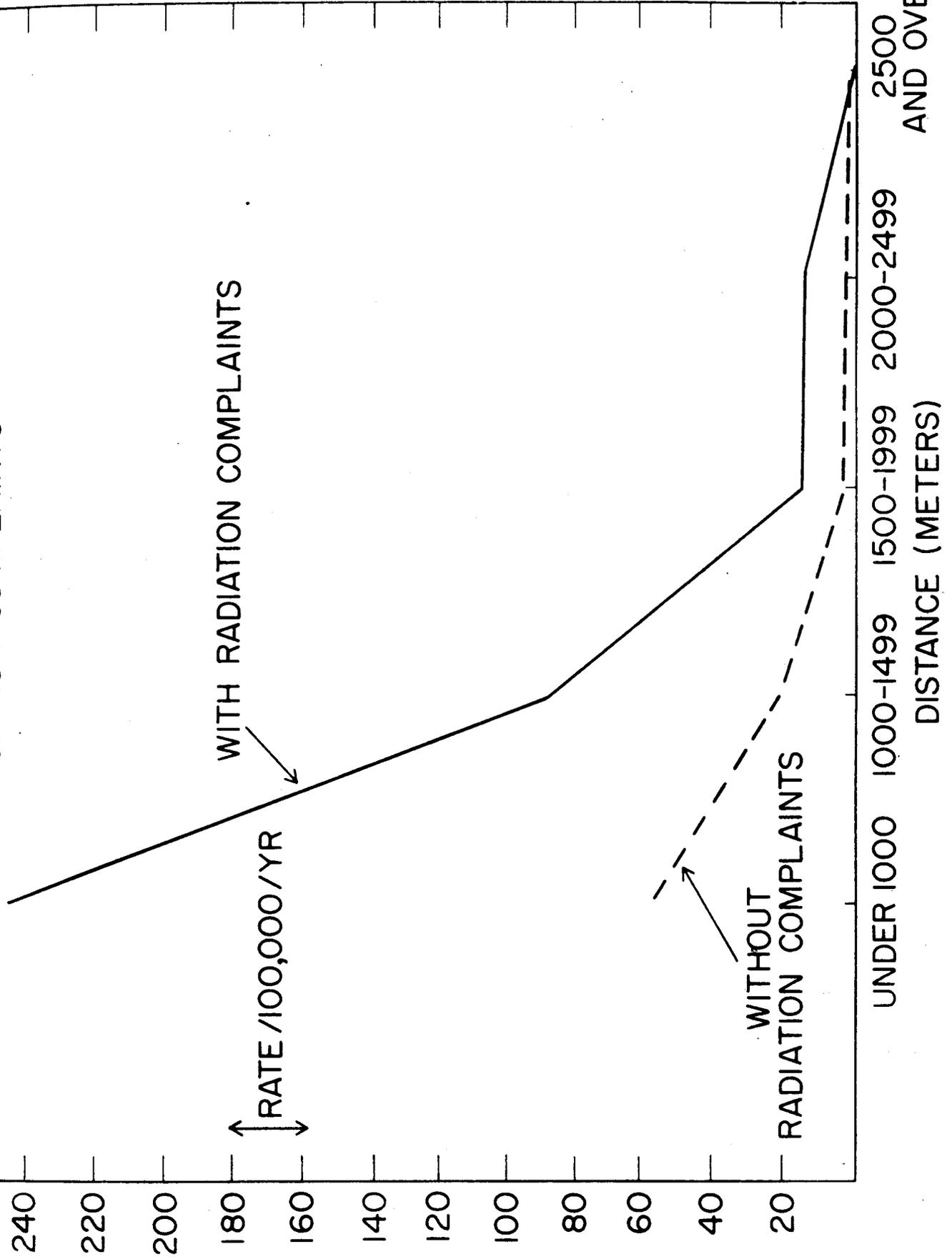
¹Source: Population estimated and rounded off to the nearest 50 persons. These population figures were based on the Commission's 1949 Radiation census and the Japanese national census (1950). Numbers of survivors with severe radiation complaints were estimated from observations made by the Commission's genetics department on 19,675 Hiroshima survivors of childbearing age.

²Source: Listing of Leukemia Cases in Hiroshima and Nagasaki, Sept. 1955. Cases are restricted to those in persons resident in Hiroshima at the time of diagnosis, and described in the listing under the heading, Diagnosis Acceptable.

³SRC: Significant radiation complaints - Epilation or purpura on history not confirmed by competent physical examination or medical records.

⁴NRC: No radiation complaints.

LEUKEMIA RATES BY DISTANCE FROM HYPOCENTER AND RADIATION COMPLAINTS



LEUKEMIA IN PERSONS EXPOSED WITHIN 1500 METERS OF THE
HYPOCENTER - NUMBER AND RATE, BY SEX AND AGE ATB

Age ATB	Hiroshima Population 1950		Number of ² cases of Leukemia		Incidence Annual rate per 100,000	
	Male	Female	Male	Female	Male	Female
0-9	839	878	6	6	94.3	90.1
10-19	995	1490	7	2	92.8	17.7
20-29	458	1352	3	6	86.4	58.5
30-39	713	1118	3	2	55.5	23.6
40-49	902	1016	3	2	43.9	26.0
50-59	606	572	1	2	21.8	46.1
60-69	236	278	-	1	--	47.4
Total	4749	6704	23	21	63.8	41.3

¹Source: "Estimated Number of Survivors in Hiroshima City in 1950",
Preliminary Report, Death Certificate Survey.

²Source: Listing of Leukemia Cases in Hiroshima and Nagasaki, Septem-
ber 1955. Cases are restricted to those in persons resident
in Hiroshima at the time of diagnosis, and described in the
listing under the heading, Diagnosis Acceptable.

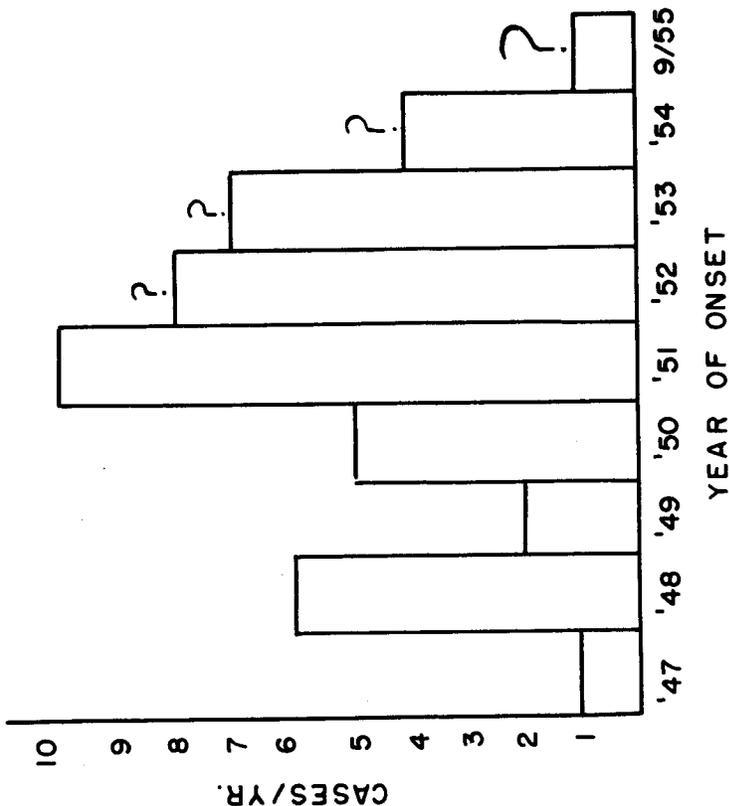
* * * * *

Leukemia rates in USA as listed on the
1951 record of Vital Statistics

	Male	Female	Over-all rate
White	7.6	5.3	6.1
Non-white	4.0	2.7	

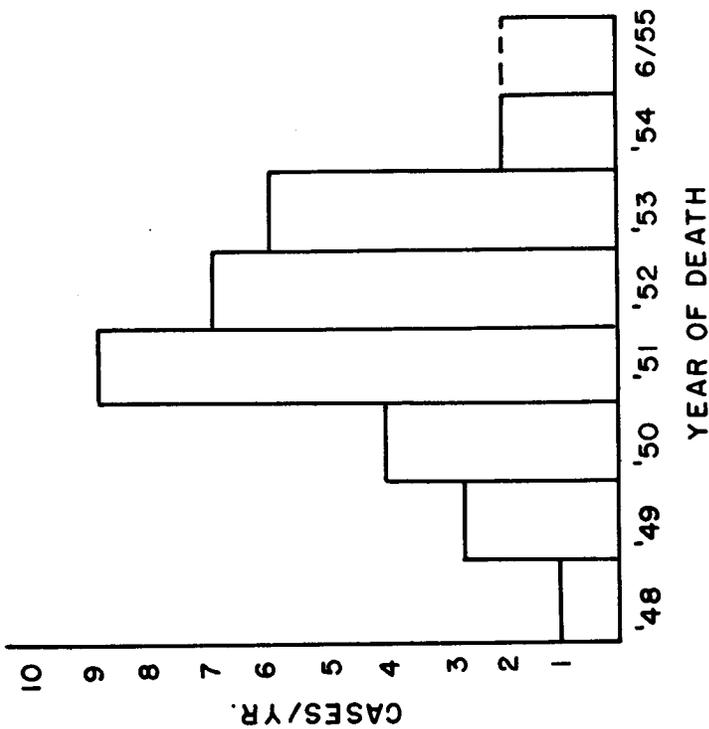
LEUKEMIA CASES FROM LISTING OF SEPTEMBER 1955
 (Diagnosis acceptable - patients resident in Hiroshima at time of diagnosis)

ONSET OF LEUKEMIA



Note: Patients' histories not equally reliable. New data more likely to change totals for more recent years.

DEATH FROM LEUKEMIA



Note: 10 patients still alive. Their deaths may form another peak in next year or two.

The preceding tables and graphs clearly indicate that the incidence of leukemia increases with the dose of radiation. The incidence of radiation complaints at 2000 to 2500 meters is open to question since the dose received at these distances was between 8 and 35 r according to the best source of information*. It is noteworthy that radiation complaints are based on late interrogation and not on medical records by competent observers at the time of the bombing and as such are prone to subjective error in memory by the individuals interrogated. At closer distances this possible error is probably negligible because of the unquestioned and recorded histories of radiation injury. The peak incidence of onset appears to have been passed in 1951; however, scattered cases are still being observed, but relationship to confirmed previous exposure to radiation injury is obscure.

Since precise data on the radiation doses received at Hiroshima and Nagasaki have not been made available to the ABCC it is not possible to set a "Dose threshold" for induction of leukemia in man by whole body radiation. Such information is vital to the future welfare of human beings who may be forced to live in contaminated areas. In addition, with the growing belief that there may not be threshold levels for radiation effects, it becomes absolutely essential to obtain the most reliable estimate of the exposure wherever observable effects have been detected.

In Japanese atom bomb survivors the leukemias have been predominantly myeloid. However, Dr. Furth of the committee emphasizes that radiation induced lymphatic leukemias in Europeans have been observed. In this connection it is of interest that lymphatic leukemia is a rarity in Japan suggesting that radiation is prone to induce the type of leukemia that might occur spontaneously.

Hematologic changes preceding development of obvious leukemia:

In the course of studies on Japanese atomic bomb survivors, observations on hematologic changes preceding development of overt chronic myelogenous leukemia were made in a number of cases. In routine surveys, blood studies revealed evidence of a generalized proliferative effort by the bone marrow, many months before obvious evidence of leukemia. These manifestations were the presence of a small per cent of myelocytes and metamyelocytes, and a very striking increase in absolute numbers of basophils, in the peripheral blood. These changes were accompanied by increased numbers of platelets and occasional

*The Effects of Atomic Weapons, U. S. Government Printing Office, Washington, D. C., 1950.

normoblasts. Beginning in November, 1952, biochemical studies on the separated leukocytes demonstrated that in these early pre-clinical cases of leukemia, the polymorphonuclear leukocytes contained very little alkaline phosphatase. These alkaline phosphatase values were similar to those reported by Valentine et al. for neutrophils in well established cases of chronic myelogenous leukemia.

Subsequent studies in chronic myelogenous leukemia, employing histo-chemical as well as biochemical methods, have shown that 2 per cent or less of segmented polys contain even small amounts of alkaline phosphatase. In contrast, in other conditions with increased polymorphonuclear leukocytes, such as infection and myeloid metaplasia, the alkaline phosphatase values are high and practically all segmented neutrophils contain large amounts of alkaline phosphatase.

It has been postulated that the leukemic cell is deficient and in the precursor stage of development of leukemia, two populations of cells are present with the leukemic type increasing in number until a typical leukemic blood picture is evident. It has been the experience of some of the Subcommittee members that cases of "bone marrow failure" may terminate in leukemia.

EFFECTS OF REPEATED LOW LEVEL EXPOSURE

Increasing numbers of human beings are exposed to repeated doses of radiation frequently at very low dose levels. Thus in industry and in AEC installations, in radiologists and radiological technicians, public health surveys and particularly those using fluoroscopy, and in repeated roentgenograms in medical and dental diagnosis, large populations are exposed to radiation at levels well in excess of background.

There are several studies on radiologists and radiological technicians, indicating that statistically the blood counts of such individuals may be altered. Similarly from the vast number of counts on individuals exposed to low level radiations at AEC installations, there is evidence that the so-called maximum permissible dose may result in statistical alteration in the blood count. The possible significance of these small changes is not clear. The slight decrease in neutrophils or lymphocytes count has little or no significance in itself. It would appear that its significance in relation to the later development of leukemia or other disease that shortens life span should be investigated. Recommendations to this effect are given below. Data are available on the hematological effects of exposure to radiation up to 10 times background. The drinking water of prisoners at Joliet prison in Illinois

contains 20 times the radium content of the drinking water of neighboring communities. Extensive study has failed to detect differences ascribable to the increased radium content of the drinking water. In the course of radiotherapy for relatively benign conditions, it seems clear that serious late effects can result from a single exposure or a series of exposures to x- or isotopic radiations. Thus thyroid cancer has resulted in children given x-radiation for thymic enlargement. Similarly, leukemia has been reported in individuals receiving repeated x-radiation therapy for spondylitis, and in patients receiving repeated I-131 for thyroid cancer.

USEFULNESS OF HEMATOLOGIC STUDIES IN CONTROL OF RADIATION INJURY

A large effort at great expense was made by the AEC during the development of atomic energy to determine if routine hematologic studies would detect low level exposure to radiation. It was the consensus that frequent routine studies on personnel exposed to low levels of radiation have a limited value that does not justify the expense. Physical control of the environment by radiation monitoring is an effective means of maintaining a safe environment, and nothing is gained by widespread hematologic studies on personnel. However, it would not be wise to dispense completely with hematologic studies since it is important to have pre-exposure levels in the individuals who may be exposed to radiation such as with those accidentally exposed to fallout radiation. Had base line studies been available relative depression and recovery time as a function of dose could have been more precisely determined. Accordingly it is believed that periodic, perhaps annual hematologic studies should continue on limited groups of individuals who run a greater risk of accidental over-exposure. Certainly, all individuals who have been exposed so accidentally at dose levels of 25 r or more of essentially whole body radiation (single exposure) should have periodic systematic studies to determine the degree of hematologic depression and the recovery rate. These individuals should remain away from an environment where further overexposure is likely until the dose received has been amortized at the rate of 0.3 r/week. The latter is suggested because clinical radiation therapy experience indicates that individuals who have been exposed previously as a result of local therapy or whole body exposure show greater hematologic depression following further whole body radiation. A more fruitful field of hematologic study in relation to chronic radiation exposure would appear to be the periodic study of phosphatase content of the neutrophils and number of basophils, on limited populations, who are known to be exposed chronically, such as radiologists, urologists, orthopedists, x-ray technicians, and dentists.

RECOMMENDATIONS FOR RESEARCH

A. Recommendations With Respect to the Acute Hematological Response of Human Beings to Radiation.

1) The Japanese data from the Hiroshima and Nagasaki bombings should be further analyzed in respect to:

- a) Duration of depression of leukocytes as a function of distance and shielding (dose).
- b) Leukocyte counts at various intervals in relation to ultimate survival.
- c) Survival time as a function of distance and shielding (dose), and of age.
- d) The degree of initial blood count depression in relation to the later development of leukemia and other late disease.

2) Additional and intensive studies should be initiated on human beings receiving radiation to the whole body or large portions of the body in the therapy of malignant disease. Particular attention should be given to the time course of peripheral blood counts for several weeks following exposure to different doses, and the nature of the clotting defect*.

3) Initiate studies on the cause of death in animals in which death from hemorrhage and infection have been prevented. This refers to deaths within the first few weeks, as opposed to the much later deaths from nephritis, neoplasia, etc.

4) Although nothing of practical value is now available for the specific therapy of acute radiation injury, it is urged that further research be pursued on the fundamental defects produced by ionizing radiation on mammalian systems. Medical experience has shown that rational therapy is only developed when the basic physiologic defects are understood. With this in mind further research is needed. However, it

*One member of the panel reactivated the heparinemia concept of radiation hemorrhage by describing the cessation of bleeding in an irradiated individual with thrombopenia following injection of protamine, an antiheparin agent.

would be unfair to the public to imply that effective therapy can be expected in the near future or indeed that overwhelming doses are ever likely to yield to therapy.

B. Recommendations With Respect to Long Term Effects of a Single Exposure to Ionizing Radiation.

1) Periodic hematologic surveys should be performed on the Marshallese and Americans exposed to fallout radiation in March, 1954. Careful study for cytological changes mentioned above, especially basophilcytosis and immature leukocytes, and routine histochemical studies for alkaline phosphatase (using peripheral blood smears and either Gomori's Cobalt technique or the azo dye method) should be carried out. In suspicious cases, biochemical determinations for alkaline phosphatase on separated leukocytes should be done. In view of the long "latent period", studies for many years after exposure if not for life, are essential.

2) The cytologic and histochemical-biochemical studies might well be employed in surveys of radiologists and other chronically exposed groups.

3) The present concepts of leukemoid reactions and myeloid metaplasia, and the relationship of these disorders to leukemia are obscure. Further studies on the enzyme and metabolic activities of leukocytes in these disorders may lead to a better understanding of radiation effects on myeloid cells and the role of irradiation in leukemogenesis.

4) It is generally recognized that routine hematologic studies of potentially exposed individuals are wasteful and unproductive. However, studies on select groups by routine and newer techniques are highly desirable, e. g., radiologists, physicist.

5) It was the consensus that it would be desirable to know the incidence of leukemia in WW I soldiers who were exposed significantly to mustard gas.

6) Pediatricians have fluoroscoped newborn babies, and a considerable dose of whole body radiation may have been received. A long term follow-up on these exposed children is needed.

C. Recommendations With Respect to Effects of Repeated Low Level Exposure.

1) Since there are geographical locations in which the known radiation intensities vary considerably, it is felt that the incidence of leukemia should be established in:

- a) Island populations (low background except Baltic Islands)
- b) Andes (high background)
- c) Prison and civil population in Joliet (radium content in water higher than normal)

2) It was the consensus that a ceaseless search should be continuously made for other harmful agents in the atmosphere and our modern diet. It is genuinely felt that preoccupation with radiation may obscure other equally hazardous factors in man's environment.

CONCLUSIONS

At the commencement of the deliberations there was some question in the minds of the Subcommittee as to the objectives and the reasons for establishing it. However, in the course of the discussions it became apparent that in addition to the confusion in the minds of the public there also exists some large gaps in knowledge essential for the understanding and quantification of radiation hazards in the world of today let alone the world of the future. The immediate effects of direct exposure to high intensity radiation are well documented and the relation of dose to effect is known with some degree of confidence, even though certain hiatuses exist that are listed in the general discussion and recommendations. In the realm of chronic exposure it was recognized that the unavoidable background level of radiation was known to vary with seasons of the year, geographic location, and altitude above sea level. However, world-wide levels do not seem to be known with sufficient accuracy to determine when a rise in atmospheric level of radiation is definitely occurring. Since there is little quantitative information on the relation of dose to effect under conditions where harmful effects were observed it becomes vital to ascertain natural levels of radioactivity and to try to establish the level of atmospheric radioactivity at which detectable chronic effects might conceivably occur. However, with all of the recommendations contained in this report, it is believed that a "crash-type" research program to obtain needed information is not indicated.

Bibliography
Radiation Effects on Blood and Blood-forming
Tissues of Man - 1900 - March 1956

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Introduction

The literature was searched for references relating to the effects of radiation on blood and blood-forming tissues of man. In this bibliography, radiation includes radiation from neutrons, alpha, beta, gamma rays, A-bomb, x-rays and internally deposited radioisotopes. References relating to ultra-violet, infra-red, microwaves, thermal radiation and visible light have been omitted.

The following sources were checked:-

Chemical Abstracts (CA) v. 1(1907) - v. 48(1954)
Chemische Zentralblatt (CZ) 1897 - 1906
Current List of Medical Literature (CLML) v. 19(1950) - v. 29
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Nuclear Science Abstracts (NSA) v. 1(1948) - v. 10(March 15, 1956)
Quarterly Cumulative Index Medicus (QCIM) v. 1(1927) - v. 53(1953)
Quarterly Cumulative Index to Current Medical Literature (QCI)
v. 1(1916) - v. 12(1926)
Library Files

In addition to the above sources, Zentralblatt für die gesamte Radiologie was also used to check references. References are available in the Research Library unless otherwise indicated. The secondary source, abbreviated as above in parenthesis, is given when possible for references not available at the Laboratory. Journals have been abbreviated according to the Chemical Abstracts list as far as possible. In some cases where the authors initials were known, they have been added in parenthesis although they did not appear either in the original article or in the abstract.

An effort has been made to check references for pertinency. This could not be done for some of the earlier references due to the lack of abstract journals covering the subject. It was necessary to rely solely on the title for many of these entries.

Every effort has been made to make this bibliography complete. However, there is no way of knowing whether or not this has been accomplished.

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APPENDIX II

REPORT OF THE SUBCOMMITTEE ON

TOXICITY OF INTERNAL EMITTERS

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TOXICITY OF INTERNAL EMITTERS

The Subcommittee on Toxicity of Internal Emitters met on January 10 and 11 at Argonne National Laboratory. They discussed the subject from many aspects including a certain amount of classified literature which is not referred to in this report but which it is believed would not alter the conclusions. The agenda were not followed literally in order to promote free discussion, so this report contains a somewhat rearranged version of the discussion.

Statement of the Problem: The question of safe working exposure levels for industrial and laboratory practice has been intensively studied and is presented in the National Bureau of Standards Handbook 52. (Several members of the Subcommittee agreed that while this represents the best body of data and opinion, it is not the last word, in the matters of use of the biological half-life for all isotopes and the high relative biological effectiveness of alpha rays, in particular. It is thought that the Handbook will probably undergo some changes and that these changes will in general be in the direction of withdrawing a little from the conservatism with which the figures were originally reached.)

Important matters of public concern are: (1) radio-elements (that is, fission or activation products) close to a ground burst of an atomic bomb; (2) more remote fallout; (3) gradual world-wide fallout, especially of strontium-90; (4) consequences of a nuclear reactor accident near a populated center. Other problems of course exist, but most of the answers will be encompassed in a consideration of these.

The categories of data to be considered include: (1) acute and sub-acute radio-element toxicity and its relation to external radiation damage in an area of heavy contamination; (2) nature and dosage requirements of chronic radiation damage from various radio-elements; (3) physical, ecological, and physiological conditions determining absorption of radio-elements; (4) metabolic handling of radio-elements after their absorption; (5) therapy.

Problems requiring special consideration were: (6) realistic appraisal of absorption from the gut and retention in and absorption from lung; (7) influence of particulate or "hot spot" irradiation, especially in lung and skeleton; and (8) permissible dosage to a large "innocent" population in relation to that to industrially exposed persons for which the present levels are drawn.

The nuclides considered in particular fall in the following groups:

(1) Radium, strontium, barium, calcium; readily absorbed with long-term retention in the skeleton.

(2) Iodine; readily absorbed, of short physical half-life but highly concentrated in the thyroid.

(3) The rare earths, yttrium, and plutonium and other actinides; nearly insoluble and poorly absorbed.

(4) Ruthenium; absorbability ambiguous due to multiplicity of chemical forms.

(5) Cesium; in all probability readily absorbable.

(6) Activation products, various and unpredictable, generally considered unimportant.

Of the above, strontium and iodine received the most consideration. The background of natural radioactivity was also given consideration because of its relation to large population exposure.

Fallout Conditions: The larger particulates fall out first and smaller ones at a greater distance, for obvious physical reasons. Fission products are plated on the larger, near-in particulates, probably reducing their absorbability. The strontium isotopes, since they exist for a short period after fission as krypton isotopes, escape to some extent from entrapment in larger particles; accordingly, they appear in a smaller ratio than their fission yield in the near fallout and are somewhat enriched at a distance: also, they appear as smaller particles and are more readily absorbed. Rabbits analyzed in Nevada showed a higher skeletal concentration at 133 miles from the test than at greater or less distances.

A detailed study of the effects of the fallout from the thermonuclear explosion of March 1, 1954 on the Marshall Island inhabitants, which is to be published soon (see Cronkite et. al. in the references) discusses the body burden from material absorbed into the human body under the conditions of exposure encountered there. Estimates based on excretion rates indicate an initial body burden of Sr^{89} of about the permissible amount, while the I^{131} retained is estimated to have delivered a thyroid dose of the order of 100 rep. Other radio-elements (including Ca^{45} and fissile material) are relatively negligible. The opinion of the Subcommittee, that products of neutron activation would be unimportant beside fission product activities, is borne out by this. Data in Table I, from a Japanese publication, are essentially confirmatory, and include autopsy findings which bear out the inferences from measurements on human excreta. It is noted that these low levels of internal contamination existed in persons who received a significant fraction of the human external lethal dose from gamma radiation.

The chemical nature of fallout elements has apparently not been well enough studied to yield many useful inferences about absorbability.

Acute Toxicity: This would be encountered in pure form only in the event of absorption of specific products. In exposure to large amounts of mixed fission products or by inhalation in a fission cloud, external gamma and beta radiation would be expected to be by far the predominant source of injury.

Acute toxicity from a variety of isotopes generally manifests itself as acute radiation sickness. In combination, bone-seeking and colloidal isotopes act synergistically, due in large part to the fact that spleen and bone marrow are both irradiated in the combined treatment. Feeding of insoluble beta emitters may cause intestinal death, but only after enormous doses, because of the rapidity of their passage through the intestinal tract and because in those places where they remain the longest most of the energy is absorbed by the fecal material which is present there.

Subacute changes depend on the distribution of the element in the body. Hematologic effects are, of course, seen where bone marrow or total body irradiation predominate, and it might be mentioned that strontium-89 or 90, although they produce marked hematologic changes and acute radiation syndrome, produce no or almost no leukemia in mice. The doses required for these subacute changes may be an order of magnitude below those giving acute toxic symptoms. Premature aging, greying of hair, retinal changes, reduced blood volume, and changes in the blood colloids have been observed in dogs given radium and plutonium but not with strontium-90. No explanation of this is available, but these are animals run in parallel experiments. Arterial calcification also occurs in rats after they are given radium in subacute doses, but has not been seen with other nuclides.

Chronic Toxicity: Site of Injury. It may be stated generally that the more important nuclides will act quite differently depending on the route of administration and their absorbability through the lung or gut, it being generally assumed that these will run parallel.

Materials such as yttrium, the rare earths, and plutonium are very little absorbed by either route, and the predominant hazard will therefore be to the lung. Those with experience in this agree on a general picture of the fate of inhaled, optimal-size particles (those most likely to gain access to the alveoli) in the range of 0.1 to 2.0 microns in diameter. About 25 per cent of this material is exhaled at once; 50 per cent is trapped in the bronchi and is carried up and swallowed

within a short time (the half-time being about 9 hours); 25 per cent is deposited in the alveoli and, of this, three-fifths reaches the gut, by way of respiratory passages, leaving a 10 per cent deposition in the lungs. That fraction disappears in cases of inhaled radium sulfate in human cases which have been followed, with a half-time between 100 and 200 days, a very small amount being absorbed.

Absorption of these insoluble materials from the intestine is taken as 0.003 per cent. That was a consensus and obviously may not refer to all possible circumstances. Speaking generally, 10^{-4} is about the highest figure for intestinal absorption which would be found under most conditions. There appears, however, to be an exception in very young animals. Mice before 16 days of age absorb 2 to 3 per cent of plutonium administered either as the citrate by stomach tube or in milk from a plutonium-poisoned animal. From milk it continues to be absorbed in the ratio of 1:300 by young adult mice, although when it is present as the citrate it is not. Parenthetically, one suspects that this reflects an ability of the very young animal to absorb particulate material from the intestinal tract, for example, the milk factor. No data are available on other species so far as is known. Citrate does not promote absorption of plutonium in post-suckling animals but versene does.

Soluble materials are presumed to be absorbed both from alveoli and intestinal tract. Thus the route of entry becomes a matter of indifference. Absorption of specific elements will be discussed later.

As to whether any insoluble materials may be handled by plants in such a way as to promote their absorption, there is no positive information. They are generally not taken up by plants as well as by animals. It is reported, however, that for some reason hickory concentrates yttrium from the soil.

Effects on the Lung: One microgram of plutonium (or 0.06 microcuries) introduced into the mouse lung as an "optimal" aerosol has proved toxic after a few months resulting in bronchial metaplasia, cellular infiltrations, and fibrosis, and carcinomas appeared after a year. The retained amount at that time has gone down to about one-twentieth of the dose administered, which is about what one would infer from the calculations stated above. Ruthenium administered in a similar way also produces pathologic changes, but data are not sufficient to indicate effective dose comparisons. It may be added that fibrotic changes occur in the human lung after 2,000 r of x-ray and rather regularly after 3,000 r. The Subcommittee on the respiratory tract headed by Dr. Wager has reported in greater detail on this topic.

Ruthenium: The chloride of ruthenium is absorbed from the rat intestine to the extent of 3 per cent. This value is probably higher than for most of the chemical forms, except of course the tetroxide vapor which, if it were encountered (which is unlikely) would be well absorbed from the lung; this has been shown experimentally.

After absorption of ruthenium the chronic effects would most likely be in the skeleton, based on tracer work and some medium level toxicity work. While ruthenium was found in animals after the Australian test, it is generally considered to be much less important than strontium.

Cesium: The gamma ray of the cesium isotope 137 has been seen in normal individuals in the last year but in an amount of radioactivity far below that of body potassium. It was encountered as a deformation in the gamma spectrum of total body potassium and radium. No additional information is available, except that it appears to be somewhat variable and it may be correlated with the intake of milk, which apparently is, relatively speaking, a fairly rich source of radioactive cesium.

Activation Products: Calcium was mentioned as a component of the Bikini ash, but toxicologically speaking would be a very minor contaminant of strontium. Activation of usual environmental elements would also yield correspondingly minor amounts of insoluble material (rare earths and silicon) plus P^{32} and Na^{24} . It was reported that Zinc⁶⁵ was formed in high concentration in muscles of post-test Pacific fish, and it is recognized that other unexpected nuclides might turn up under specialized conditions.

The Alkaline Earths: Strontium has quite properly received major attention. It is a bone-seeker like the others of the series, and there is ample experimental evidence of its carcinogenicity in both masses 89 and 90. Since the best available human data regarding absorption and toxicity are from radium cases, this occupies first attention.

Metabolism: Human radium retention in the age range 20 to 35, based on a 24-year follow-up, is described approximately by a power function of time with an exponent near -0.5; that is, retention varies as the inverse square root of time, being about 50 per cent of the injected dose at the end of one day and following this function thereafter.

It may be remarked that indeed the retention of most absorbed materials of whatever nature can best be described by a power function unless one wants to construct a series of exponentials, although it may

actually be a series of many exponentials. In all instances that have been carefully studied, even that of the retention of tritium oxide in the form of water, several exponentials exist. The rare earths and actinides show a much less steep slope than the alkaline earths.

There is also a species difference; the dog has a slope of -0.2 to -0.3 , depending on age, which makes a great deal of difference in the accumulated dose in this animal.

Integrating this function in man, the cumulative radiation dose, assumed after a very brief period to be limited to the skeleton, goes up as the square root of time, and the rate of loss by excretion relative to the amount retained (specific loss), varies inversely with time. This gives one a way of determining when an exposure took place. It has been pointed out that this function gives a quantitative picture very different from that assuming an exponential half-life (which based on loss by chronic patients, where the loss is very low after 20 years, becomes very long).

It is clear, if this expression is correct, that throughout a human lifetime a man would accumulate little more than 100 days' intake. Observations on adolescent boys indicate that the accumulation to age 17 represents about 40 days' intake.

Evidence now being accumulated in at least two clinics indicate that strontium-85, which is given because it is less toxic than the beta emitting isotopes, is handled by men in a nearly identical manner to radium. The initial loss varies considerably with age, being least in the younger individuals.

Toxicity: The best available data on radium toxicity brought to our attention deal with a series of patients that received known amounts of pure radium chloride 24 years ago and were followed. The assumed minimum burden producing serious disease after this period has been taken as 1 microgram, but this has been questioned because of the fact that other preparations were in many cases contaminated with mesothorium and, perhaps more seriously, with radiothorium. One bone tumor has appeared in one of these patients having 3 micrograms pure radium. The patient with the lowest burden in the series, that is, 0.4 microgram, shows diffuse minimal changes by x-ray, whereas other patients at higher doses from 0.6 to 1.0 microgram do not show detectable changes at this time. It can be assumed that the belief that the lowest effective burden is 1.0 microgram of pure radium is probably not in error by more than a factor of 2 from the standpoint of effects at 20 to 25 years.

Assuming the power function of -0.5 cited above, it can be shown that the total radiation dose accumulated at any time is equal to twice the time multiplied by the burden. Taking the mass of the skeleton as 7 kilograms, some accumulated dosages are given in Table II.

Strontium 90 - Radium Comparison: Data on late toxicities of strontium and radium in small animals have indicated that a factor of 10 on an energy basis is roughly correct. This would suggest that alpha and beta radiations are relatively equivalent in terms of energy. This may be approximately correct, although the relative biological effectiveness of alpha radiation to x-ray of 10 is presently assumed in calculating permissible doses where experimental data are lacking.

Relative Biological Effectiveness (RBE), Alpha and Beta Rays: Alpha rays from slow neutron absorption in animals containing boron, have indicated that a factor of 1.4 relative to X rays is roughly correct. Experiments with inhaled radon and injected radon show factors of 1.4 to 1.5 for acute effects, and 3.0 for chronic effects. The RBE for mice seems to pass through a maximum around the ionization density of fast neutrons. Observations on yeast also show a maximum in the intermediate range. The consensus is that a radium to strontium-90 factor of 10 may be a little low but not as low as it was formerly assumed. It was agreed by the Subcommittee to calculate radium and strontium both in roentgen equivalents for the present, although this may give strontium a small additional factor of safety over radium.

Absorption of Strontium: There are considerable variations in the degree of absorption of strontium depending on the contents of the gastrointestinal tract and the demand for calcium. Absorption of radiostrontium by plants has been investigated, and it appears that the uptake is relatively independent of the concentration of carrier; in other words, it is taken up as a contaminant of the water absorbed. This breaks down only at high levels, where radiation effects on the physiology of the plant enter in. Under fallout conditions, it may also be deposited on leaves. Experiments have indicated that, under a variety of conditions, between one and ten per cent of the strontium-90 in the soil is available to a crop of plants. About five per cent of the strontium taken up by the plants is then retained by animals foraging on them after two to four weeks.

Data on the actual strontium-90 content of biological materials and human beings as a result of past and present fallout have indicated that human bones have now reached an amount equal to one-thousandth of a microcurie (that is, of presently accepted permissible human skeletal content) in young children, declining to approximately zero in

persons above 40 years of age. Such calcium-rich sources of the isotope as cheese and milk yield values which are higher in respect to the Sr⁹⁰:calcium ratio.

Another way of looking at the same question is to consider uptake. When this is done, it appears that the strontium retention in man from the diet is 0.3 to 0.6 times what it would be if strontium were an ideal tracer for calcium.

Radioiodine: Under existing fallout conditions, cattle in Tennessee have shown up to 10^{-3} $\mu\text{c}/\text{gm}$ of thyroid, but human thyroids have not shown more than 1/100 of this concentration. External counts on monitors in the Nevada test areas have shown not more than 10^{-4} $\mu\text{c}/\text{gm}$ of thyroid, with all probabilities in favor of a smaller concentration. In view of the short half-life of I-131 it can be concluded that the hazard of bomb tests from this standpoint is negligible.

It has been suggested that the human thyroid is less radio-sensitive than other tissues, such as bone, since after many years of treatment of Graves' disease with radioactive iodine, no cases of resulting carcinoma have been reported. The customary dosages of I¹³¹ in such cases yield at least 4000 rep to the gland. On the other hand, carcinoma of the thyroid found in children and young adults has almost invariably been preceded by x-ray treatment to the upper part of the body, in amounts such as to yield as little as 200 r to the infant thyroid. It has been estimated that less than 3% of such treated cases yield carcinoma; nevertheless, the data suggest that 200 r is a potentially carcinogenic dose to the infant thyroid. While the possibility exists that the carcinogenic action may be an indirect, hormonal one, it must still be recognized that this, like leukemia, is an instance of significant carcinogenesis by less than 1000 rep. It seems likely that the infant thyroid is unduly susceptible, but that the adult thyroid is not.

Radiation from Particles and Hot-Spots: One matter which has caused some concern is the effect of intense radiation of a few cells from particulate sources of radiation.

The only available experimental evidence that bears on this question is an experiment in which the skin was irradiated with beta rays, diffusely over the surface, and by point sources yielding the same amount of radioactivity. It was shown that the point sources were considerably less efficient.

In the case of the skeleton in chronic radium or radiostrontium poisoning, a large part of the dose is from the hot-spots due to

concentration of the radioactive material in a few haversian systems that were forming at the time the radioelement was administered. All of the integrated skeletal dosages shown in table 2 (except from X rays, where the bone dose is about four times the air dose given) must therefore be looked at with the consideration that the maximal dose in these hot areas is about ten times as great as the average.

Permissible dosage to Large Populations: This is a matter on which no complete agreement was reached by the Subcommittee. First responses to this question ranged all the way from the permissible industrial level down to no radiation at all. The uncertainty existing here stems from our ignorance as to whether there is a true threshold for such late effects as malignant tumors, and as to the degree of variation in response of equally exposed individuals.

It was agreed that the only rational approach must take into account the natural radiation background to which the population is exposed. Figures on this, from various sources, are given in table II. It is noteworthy that considerable differences exist from place to place, due mainly to differences in gamma radiation from the environment, and in part to variations in radium content of individuals. Since these existing variations have not given rise to any changes in incidences of tumors or other pathologic states sufficient to attract attention, it was felt that an amount of internal radiation sufficient to double the large population background could certainly be considered safe.

Part B of table II shows integrated skeletal radiation dosages which have given rise to various degrees of pathologic change. Two patients from the Elgin Hospital series are included, since it is known that pure radium was administered and the retention curve has been determined. It is noted that tumors require dosages in the thousands of rep; that observable pathologic changes have required a few hundred; that the natural background (including skeletal radium) varies from 7 to 30 in a lifetime (higher in isolated areas, perhaps); that large populations in high radium areas approach 5 rep in a lifetime from natural skeletal radium alone; while 1/1000 of the permissible strontium burden yields 0.2 rep in a lifetime. Exceeding this latter burden by fifty times would yield 10 rep in 70 years. This would not more than double the usual low skeletal background radiation and leave it well within the range of values; the highest backgrounds encountered in any large areas would be raised about one-third. The general belief of the Subcommittee is that this would produce no perceptible effect.

It is noted that the International Commission on Radiological Protection, using a somewhat more arbitrary procedure, has adopted a figure twice as great for the large population (one tenth of the

industrial permissible level) so that there is a large measure of agreement.

Therapy by Removal of Radioelements: This subject was not discussed by the Subcommittee, but was treated thoroughly at a meeting in October, 1955, the transactions of which will be published by Argonne National Laboratory. A summary of the present status follows:

Clinical and experimental evidence to date shows that there are two effective methods of removing radioelements from the body or prophylactically minimizing their deposition. These are the use of zirconium citrate and of chelating agents, particularly ethylenediamine tetraacetic acid (EDTA). Both of these have their optimum effectiveness if given immediately after exposure. The use of the two methods in combination, at least experimentally, appears to be more effective than either one alone.

The chelating agents are mainly effective in removing radioelements from the soft tissues and causing their excretion. Under optimal conditions (that is, large doses administered early) they reduce bone deposition by a factor of two. They are effective on the transuranic elements and rare earth fission products, but for known chemical reasons they are not effective on the alkaline earths such as strontium and radium.

Zirconium citrate appears to be effective as therapy for almost all types of fission products, as is to be expected from the postulated modes of its action. It is particularly useful in minimizing bone deposition of radioelements and if given early, at least in the dog, it has been shown to remove almost all the plutonium from all the tissues.

No method has yet been developed for the removal of significant amounts of strontium. From the chemical standpoint the only promising approach to date appears to be one using agents which pick up the radioelement by cation exchange, such as zirconium citrate. Other experimental approaches, particularly involving dietary and hormone therapy with known influence on skeletal metabolism, are under investigation without clear clinical implications at present.

Treatment of individual situations will necessarily be influenced by consideration of route of entry (e. g. lung or in a wound) and the isotopes involved, bearing in mind that most of the experimental work has dealt with intravenous administration and that clinical experience to date has been severely limited.

Table I. Data on Fallout (calculated from Tsuzuki, loc. cit.)

A. Analysis of "ash" from test of March 1, 1954, made on March 26.

Isotope	Half-life	% of total activity on March 26.		relative atomic yield	fission yield
		measured	as of Mar. 1		
<u>Fission products:</u>					
Sr ⁸⁹	53 d.	1.0	1.4	74	4.6%
Sr ⁹⁰ -Y ⁹⁰	27 y.	0.04	0.04	200	5
Zr ⁹⁵ -Nb ⁹⁵	65 d.	8.0	10.5	(500)	6.4
Y ⁹¹	61 d.	8.0	10.8	660	5.9
Ru ^{103, 106;} Te ^{129, 132;} I ^{131, 132.})		15.0	?	?	13.5
Ba ¹⁴⁰ -La ¹⁴⁰	12 d.	11.0	50	300	6.1
Ce ¹⁴¹	33 d.	7.0	12.3	410	6.0
Ce ¹⁴⁴ -Pr ¹⁴⁴	282 d.	4.0	4.3	610	5.3
Pr ¹⁴³	14 d.	16.0	59	830	6.0
Nd ¹⁴⁷	11 d.	9.0	46	510	2.6
<u>Activation Products:</u>					
				(relative to fission yield)	
S ³⁵	87 d.	0.05	0.06	5.2	0.05%
Ca ⁴⁵	152 d.	0.2	0.22	34	0.3%
<u>Other:</u>					
U ²³⁷	7 d.	20	260	1820	18%
Pu ²³⁹	24,000 y.	0.0004	0.0004	3500	35%

Note: After extrapolating activity back to March 1, relative yield is obtained multiplying by the half-life in days. Where 2 isotopes were measured, half of this value is taken for the parent; an intermediate value was taken for Zr⁹⁵ since the daughter has a 35-day half-life.

Table I. Data on Fallout (calculated from Tsuzuki, loc. cit.)

B. Analysis of autopsy material 207 days after the fallout
(figures in $\mu\text{C} \times 10^{-3}$ per kilo wet weight)

	liver	kidney	lung	muscle	bone
Ru and Te		0.9		0.2	2
corrected for decay (as Ru ¹⁰⁶)		1.3		0.3	3
Zr and Nb	1	1	0.4	0.3	2
corrected for decay	9	9	3.6	2.7	18
Ce and Pr	2	1	0.5	0.5	20
corrected for decay	3.4	1.7	0.8	0.8	34
Sr	0.6	0.4	0.1		1
Sr ⁸⁹ (lf 97%)	9.0	6.0	1.5		15
Sr ⁹⁰ (lf 3%)	0.27	0.18	0.05		0.45

Note: this indicates that internal radiation was well within permissible limits throughout, amounting to a few mrep/day. In the event the figures for skeletal Ce and Sr were transposed in the report, the Sr⁸⁹ burden appears to be at the permissible level.

TABLE II

BACKGROUND AND EFFECTIVE RADIATION DOSAGESA. Natural Background Radiation, mrep/year

	<u>Libby</u>	<u>Burch & Spiers</u>	<u>Sievert</u>	<u>Other</u>
Cosmic, sea level	35	16		
5,000 feet	50			(Lea gives 730,
10,000 feet	100			which is probably
15,000 feet	170			in error)
20,000 feet	375			
Earth gamma		58	94-296	(Sievert gives one
" , granite	110			value of 520)
" , sedimentary	43			
Over ocean	20			
Body K ⁴⁰	19	18.2		
Body C ¹⁴	1.5	1.0		
Body Radium (dose to skeleton)	6.7 - 67			(Rochester, N. Y. value 16)
	(Extremes in Illinois)			

Note: This emphasizes the variability in background, even at sea level. In various localities the value might vary from 100 to 420 mr/year; the latter might be taken as the maximum which any large population receives.

B. Various levels of Skeletal Irradiation (in rep)

Patient* with sarcoma (pure radium) at 24 years -	6,000
1.0 μ c radium retained 24 years after dosage -	2,000
Patient* with minimal skeletal changes, 24 years -	800
Permissible burden (0.1 μ c) sustained 24 years -	100
Minimum dose of x-ray reported to induce tumor -	1,500
Normal range of background radiation, external and internal, 70 years -	7 to 30
High large-population Illinois radium level, 70 years -	4.7
1/1000 permissible Sr ⁹⁰ level, 70 years -	0.2

Note: patients cited are known to have received pure radium injections. In other reported instances where the thorium chain may have been included in the dose, the radium dose would be calculated as low as 300 rep.

Recommendations: The Subcommittee made the following suggestions in relation to its study:

Attention should be given to the physiological state of the animal in relation to absorption and toxicity of radioelements, particularly in the case of absorption through the usual routes (lung and gastrointestinal tract). Present information is partial and is practically limited to the alkaline earths and iodine.

Further information on the retention of alkaline earths as a function of age and species and other variables, is needed.

The relation of experimental data on life shortening to the probable picture in man needs clarification, and further verification of the apparent lengthening of life at low doses. These problems are of importance in the isotope toxicity field as well as in relation to external radiations.

The past work on distribution of various radioelements which have not received intensive study should be extended, since unusual radiochemical toxius may be expected to appear occasionally.

Account should be taken of the applicability of the power function to the retention of radioelements, since it would appear that in some cases the present intake levels are much too stringent owing to our past reliance on the half-life concept. Further critical evaluations of the RBE, particularly for alpha radiation, is very desirable for similar reasons. The RBE should be evaluated separately for the several modes of damage.

It is believed that there may be a considerable number of persons who have received radium in the past, who are alive and not seeking medical help. Any means which could be found to obtain an unbiased group of individuals would be extremely desirable, since only in this way can the degree of variability in human response be estimated. For similar reasons, any promising environmental study involving areas of different natural background should be encouraged.

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APPENDIX III

REPORT OF THE SUBCOMMITTEE ON
ACUTE AND CHRONIC EFFECTS OF RADIOACTIVE
PARTICLES ON THE RESPIRATORY TRACT

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ACUTE AND CHRONIC EFFECTS OF RADIOACTIVE PARTICLES IN THE PULMONARY TRACT

I Introduction

The Subcommittee held its first meeting in San Francisco February 20-23, 1956, and a second meeting took place at Stanford Research Institute, Menlo Park, California, to evaluate further and to summarize briefly the available information on the effects of inhaled radioactive particles on the respiratory tract. Consideration was given to the sources and nature of such particles and to the numerous physical and biological factors involved. An attempt was made to define known parameters, to determine gaps in existing knowledge, and to formulate recommendations for needed research. Although the primary emphasis was on radioactive particles, it was found necessary to consider also the general problem of the effects of radiation on the lung, whether the source was external or internal.

II Sources and Nature of Airborne Radioactive Particles

Radioactive particles containing the daughter products of radon and thoron* are a normal constituent of our atmosphere and are continually being inhaled by man. Most of the daughter products have short half-lives and thus decay rapidly to insignificant levels. The concentration of the radon and thoron products in the atmosphere does not normally exceed one-thousandth of that level presently considered to be safe for man. (Exceptions occur in some mines and in locations where quantities of radium or thorium are stored.) Mankind is therefore able to breathe continuously air containing small numbers of radioactive particles with no significant harm to health.

With the recent increase in the quantities of artificial radioactive substances produced, the possible sources of airborne radioactive particles have greatly increased. Significant sources include nuclear explosions, nuclear production and power plants, experimental reactors, and industrial and research applications of radioisotopes. The contamination resulting from these sources can be divided into two categories, (1) the world-wide distribution from nuclear explosions, and (2) the essentially local distribution from the other sources.

A. Nuclear Detonations

The characteristics of the radioactive particles from a nuclear detonation and their distribution in the atmosphere are determined by

*Radon and thoron gases produced from radium and thorium in the earth's crust.

many physical factors, including the type of device, the altitude of the detonation, and the meteorological conditions. The more powerful devices result in the transport of radioactive particles into the stratosphere with subsequent distribution over the face of the earth (1). The small particles, carried to great heights, fall back into our atmosphere months and years after the detonation. In addition to the world-wide distribution produced by all large-yield devices, low bursts (surface and sub-surface) also create inhalation hazards over local areas (up to 10,000 square miles).

These radioactive particles contain fission products, nonconsumed fissionable material, and activated materials from the environment. This debris is produced in various particle sizes ranging from submicron to millimeter sizes, with the larger particles deposited in the local area of the detonation. Atmospheric contamination at distances of hundreds of miles or more consists largely of particles in the respirable range, although some particles as large as 1000 microns in diameter may be transported similar distances (1). Particles of the order of 1 micron may remain suspended in the stratosphere for years, gradually falling into man's environment, where they may be inhaled.

The rate of radioactive decay of these substances decreases with their age with the initial rate being extremely rapid. Table I illustrates the percentages of fission products remaining at various times following a detonation. In spite of these rapid decay rates, at the end of one year the residual activity of a 20-kiloton device will still be on the order of 100,000 curies (2). The quantities of unconsumed fissionable substances are small in comparison with the fission products but they provide a possible source of very long-lived, alpha-emitting materials. The activated products of a nuclear detonation depend upon the environment of the detonation. In general they consist of both short-lived and long-lived materials, with their qualitative behavior with time similar to that of the fission products.

Table I

PERCENT OF ACTIVITY REMAINING FOLLOWING THE DETONATION
OF A NUCLEAR DEVICE (3)

Time Since Formation (t)	% of Activity Present at 1 Minute that Remains at Time, t
1 day	0.016
1 month	0.00028
1 year	0.000014

Because of the immense dilution that occurs in the atmosphere, the probability of inhaling significant amounts of such particles is still exceedingly slight, except in the vicinity of nuclear detonations.

B. Other Sources

The other sources of airborne radioactive particles present a potential hazard to small numbers of people working in and near the area where the operations take place. These particles arise from handling radioactive materials in reactors, nuclear processing plants, research laboratories, and other radioisotope applications.

The particles may contain any of the hundreds of individual radioisotopes either alone or in combination. In many cases these radioactive isotopes have long half-lives, may have high specific activities, and may vary in size from less than one micron to several millimeters. Although normal control practices protect the workers under most circumstances, the probability of exposure from an accident remains significant. The most spectacular hazard would be the accidental release of large quantities of radioisotopes from a nuclear reactor.

III Description of the Respiratory Tract, Anatomy and Physiology

The descriptive and functional information given below is limited to that pertinent to inhalation of particulate material, and its fate once it enters the respiratory system. The function of the respiratory tract is to convey air to the pulmonary alveoli for oxygen and carbon dioxide exchange. During the passage of the air from the outside to the alveoli, moisture is added to the air and much of the extraneous material present in air, such as dust particles and pollens, which are of no importance in gas exchange, is removed before the air reaches the alveoli.

The nasal passages, trachea, and bronchi through which air passes are lined by a membrane, which constantly secretes mucus and is lined throughout most of its course with ciliated cells which constantly move the mucus away from the terminal bronchi, in the case of the nasal passages toward the throat and in case of the trachea and bronchi toward the pharynx where it is either expectorated or swallowed. The nasal air passages are tortuous and are so constructed that the air must pass over a large surface of this mucus-covered membrane which acts as an effective filter for particles larger than 5 microns. Mouth breathing does not have this protective function.

The trachea is a moderately rigid, cartilaginous structure approximately 2 cm in diameter in the adult male; it extends from the

pharynx into the thorax, where it divides into two major bronchi which convey air to the lungs. These bronchi penetrate the lungs, repeatedly divide, and with each division decrease in size until they enter the pulmonary lobule, at which point they are 0.15 to 0.20 mm in diameter. The bronchi and bronchioli, except the "respiratory bronchioli," are lined with ciliated and mucus-secreting cells.

In the normal healthy respiratory tract foreign particulate material that penetrates no farther than the terminal bronchi is moved out of the lung by ciliary action, but that which passes beyond the terminal bronchi is handled by a different mechanism.

The primary lobule of the lung consists of a terminal bronchus surrounded by alveoli (air sacs) in which exchange of gases between the air and blood takes place. The alveoli consist of capillaries lined with endothelium, which is in contact with the blood, and epithelium, which is in contact with air. Also within the alveoli there are phagocytic cells (septal cells).

The lymphatics consist of a closed, endothelial tubular structure, somewhat resembling a vascular system; it collects interstitial fluid (lymph) and cells, passes through lymph nodes and finally into the vena cava. The lymph nodes function as a filtering structure and remove from the lymph phagocytic cells containing foreign or endogenous particulate material. The alveoli probably do not contain lymph vessels, the smallest and first lymph vessels being found in the walls of the terminal bronchi. From this point the vessels pass either along the pulmonary arteries and bronchi or to the surface of the lung and form the pleural plexus. In either case the lymph ultimately passes through the plexuses about the large bronchi and trachea. Surrounding the bronchi there are a large number of lymph nodes through which the lymph must pass before it reaches the thoracic duct.

Particulate material which reaches the alveoli may be engulfed by phagocytic cells. These cells migrate to the lymphatic vessels and are carried with the lymph to the nodes at the hilum of the lungs. Some phagocytic cells may migrate to the bronchi and be carried upward in the bronchi by ciliary action. Small amounts of particulate material become lodged free in the interstitial tissue usually at points of bifurcation of bronchi and blood vessels and about the lymphatics of the pleura. Particulate material may remain in the lung for some period of time, depending on the chemical and physical properties of the material.

IV Fate of Inhaled Particles

A. General Statement

Evaluation of the potential hazard from inhaling radioactive airborne materials requires careful consideration of numerous physical factors and of the physiological functions of the respiratory system. Among the physical factors the more important are: (1) particle size, (2) solubility, (3) density, (4) aggregation of particles, (5) the relative amount of radioactivity in particles of the respirable size range, (6) duration of exposure, and (7) the chemical and physical nature of the radioactive particles. The more important physiological factors concerned in the removal and absorption of inhaled particles include: (1) mouth versus nose breathing, (2) minute volume, (3) filtering effect of the upper respiratory passages, (4) various clearance mechanisms, and (5) vascularity of capillary beds in the respiratory mucosa.

Most particles larger than five microns in diameter adhere to the mucous membranes of the nose and larger bronchi, especially at the points of angulation or branching of the respiratory tree, and do not penetrate to the deeper air passages. As the particle size decreases, a larger and larger fraction of the inhaled material reaches the alveolar ducts and sacs. Much of this is exhaled again, but appreciable fractions may be retained. The amount finally retained in the lung is determined in part by the shapes of the particles (e. g. a long, thin asbestos fiber may be retained while spherical or cuboidal silica particles may not) and their density, but is largely dependent on chemical factors. Readily soluble materials enter the circulation and are carried to other organs by the blood stream, whereas insoluble materials may remain in the lung for long periods. The removal of the latter depends on the physiological mechanisms for removal of foreign bodies from the respiratory system. These include (1) reflex coughing and sneezing, (2) the constant activity of cilia in the bronchiolar epithelium, which brings material from the deeper respiratory passages to the mouth where they are either expectorated or swallowed, (3) engulfment by phagocytic cells with subsequent movement either up the respiratory tract as in (2) or to the lymphatic system with possible concentration in lymph nodes or other sections of the lymph drainage system, (4) entanglement and dilution in mucus lining the respiratory tree and propulsion with the mucus as above, and (5) possible direct entry into the lymphatic system without the mediation of phagocytic cells.

Since the upper respiratory passages act as a filtering mechanism for larger particle sizes, they may accumulate appreciable quantities of inhaled material if the mean particle size is large (greater

than 5 microns). On the other hand, the lung itself may be exposed to the highest concentrations of a material of a smaller size, especially if it is also insoluble. Other organs of the body will receive material from lungs or upper respiratory passages if it is (1) soluble or (2) brought to them as a result of the lung clearance activities described above. If exposure is repeated, both the lung and other organs may contain appreciable amounts simultaneously. Also, on repeated exposure to insoluble substances the amount permanently retained in the lower respiratory passages may increase considerably with time.

The general relationships described above are documented specifically in the following sections, but mention should be made here of the compendia and reviews by Dalla Valle (4), Davies (5), Drinker and Hatch (6) and Eisenbud (7), and to the studies of Drinker and colleagues (8), Landahl and Hermann (9), etc.

The radioactive elements formed in nuclear fission are predominantly oxides which have a limited solubility in body fluids. Further, the airborne particles with which radioactivity is associated are for the most part considerably larger than the optimum size for deposition and retention in the alveolar tissue of the lung. Thus, the probability of long-term retention of significant amounts of inhaled fallout material in the lower respiratory passages is not appreciable following an acute exposure. However, the amount of inhaled radioactive material which can produce injurious effects may be minute because of the close proximity of the particles to the tissue which they irradiate and their high specific activities. There is, in fact, some preliminary evidence that single active particles of plutonium lodged in the mouse lung can induce epidermoid carcinoma (10).

B. Clinical Experience

A considerable body of clinical data has been gathered on human inhalation of various particulate materials. Some of these agents produce diseases which have a fairly characteristic clinical course and pathological structure. Examples of these are silica and asbestos, causing pulmonary fibrosis; beryllium, causing granulomatosis; and chromiumates, nickel carbonyl, and asbestos, leading to carcinoma of the lung. Many particulates, such as non-crystalline silica, carbon, and iron, have been demonstrated to be biologically inert and not to lead to disease in the respiratory system.

Investigations of dust hazards in industry have yielded some information on the fate of the inhaled particles in the human respiratory tract. The majority of these investigations pertain to the total quantity

of dust retained under a very generally defined set of conditions. Very divergent results have been obtained, as is summarized by Davies (5). Properties such as particle size distribution and the physical properties of particles which determine their impaction and settling rates are important, and the breathing characteristics of the subject may exert a modifying influence. Although we have gained a general picture of the fate of inhaled materials in the respiratory tract from such work, quantitative information is not in general available. The impression is always that individual substances pose individual problems and that simplifying generalizations have not been possible.

Because of the greater ease of measurement, especially in the presence of an energetic gamma component, the fate of radioactive dust may be followed somewhat more easily in man than that of non-radioactive materials. However, work is just starting in this field. Marinelli, Norris, et al. (11), could follow the clearance of radium sulfate from the lungs of six persons who suffered accidental exposure to radium sulfate dust. They used a gamma-ray scanning device. There was an early rapid elimination from the lung followed by a progressively slower loss. The half-time for retention varied from 32 days initially to 140 days within six months after exposure. Albert and Arnett (12), measured rates of loss from the lungs of thoron daughter products absorbed on kaolin and of a radioactive iron dust. These substances left the lung much more rapidly than the radium sulfate cited above. The retention half-time was about 9 hours. Two distinct phases appeared in this early bronchiolar clearance, a very rapid one ending in 2 to 4 hours, and a second phase ending in about 30 hours. Their relative importance varied with the average particle size.

Recently, interest has developed in the possibility of bringing therapeutically effective radiation dosages to regional lymph nodes by administering radioactive colloids intratracheally. Hahn, et al. (13), have shown that such colloidal suspensions may remain fixed locally for long periods. This is in line with earlier information obtained with colloids of thorium (e. g. thorostrast) which have been found to remain in situ for period of years. Finally, preliminary studies of the rate of transfer of insoluble plutonium deposited in the lungs of humans indicate movement with half-times of the order of two years (14).

Thus, the information on deposition and retention in human lungs is scanty in many particulars and permits few generalizations. Indeed, in all probability each substance represents a separate situation, and generalizations to a broad evaluation of the hazard of inhaling radioactive materials cannot be made at present.

C. Experimental Observations in Animals

Obviously, much detailed information regarding the deposition, retention, and clearance of inhaled materials that cannot be obtained from clinical observations can be obtained from experimental work with animals. Although the difficulties of transfer of experimental information from animals to man are recognized, a short summary of the current status of information in this field may be useful.

1. Non-Radioactive Materials

Exposure of animals to dusts of the type important in industrial medicine has yielded valuable basic information on the fate of various substances (Gardner (15) and Lanza (16)). Clearance mechanisms previously discussed provide important physiological safety factors in respect to the potential radiation damage to the respiratory system. The efficiency of these mechanisms varies, as stated above, with the physical and chemical properties of the particulate material and the components of the respiratory system. This has been reviewed adequately by Eisenbud (7). In general, foreign particles are rapidly removed from the nasal passages and bronchial tree during the first few hours or days by ciliary action and mucus secretion. Materials initially deposited in lung parenchyma distal to the ciliated air passages remain in these areas for a longer period (weeks or months) and are removed more slowly and less efficiently by phagocytosis. They may be subsequently translocated to organs of the reticulo-endothelial system by way of the pulmonary lymphatics (17). Insoluble materials of unit density, such as bacterial spores (18), india ink, and prodigiosin (19), are more rapidly and effectively removed from both major compartments of the respiratory system than are similar particulate materials of greater density (20) such as silica and beryllium sulfate. With unit density materials, the upper passages are cleared within a few hours and the lower passages within a few days. With the higher density materials, although the upper passages are still cleared in hours, removal from the lung parenchyma requires much longer periods. The most important aspect is that in these cases a small percentage of the material initially deposited in the distal part of the pulmonary tree is retained for very long periods. Furthermore, on repeated inhalation exposures, there is a gradual increase in the amount permanently retained (21).

A clear demonstration of the importance of particle size to toxicity is found in the studies of Wilson, et al., on uranium dioxide dust (22). Using lung damage, lung weight, body weight loss, and evidence of kidney damage as criteria, they showed in rats and rabbits,

that uranium dioxide dust with a mass-median particle diameter of 0.5 micron was considerably more toxic than the same inhaled concentration having a mass-median particle diameter of 2.3 microns. Similarly, the ability of beryllium oxide (23) to produce an acute pneumonitis and of silicon dioxide to induce silicosis in animals (24) is found to increase as average particle size decreases. This may be related to the larger surface area of the smaller particles.

2. Radioactive Materials

During the war years, experimental studies were made of the retention and fate of inhaled fission product aerosols and of various individual radioactive materials, including alpha emitters. These were primarily acute exposures and provided useful preliminary figures regarding retention and subsequent distribution to tissues. Abrams, et al., (25) showed that Strontium 89 left the lungs quite rapidly but that Zirconium 95, Yttrium 91, and Cerium 144 were eliminated much more slowly. Translocation to the skeleton occurred in each case. These same authors investigated the fate of inhaled plutonium aerosols (26) and showed that valence state and the presence of complexing agents are important in pulmonary retention. The deposition and fate of plutonium, uranium, and their fission products were studied in detail by Hamilton and his associates (27). The distribution of Polonium 210 inhaled by rats was found by Fink, et al. (28) to be similar to that which occurs after intravenous injection.

Another aspect of the problem is illustrated by work with radon. Radon itself is a noble gas and behaves in the body in accordance with its solubility in body fluids. The gas itself remains in the lungs for relatively short periods and constant exposure would be necessary to produce significant lung damage. The same would apply to the radioactive gases occurring in nuclear fission. However, as was first pointed out by Bale (29) and subsequently shown experimentally by Cohn, et al. (30) and by Shapiro and Bale (31), the decay products of radon may deposit on atmospheric dust and be of primary importance. The dust particles with their contained radon decay products may remain in the respiratory tree, being distributed more or less as a function of particle size, and contribute much larger radiation doses than radon itself. Although this is of more importance to mining and ore processing operations than to fission product "fallout," the importance of considering carrier dust and decay products is illustrated by this work.

All of these acute studies indicate that evaluation of the hazard to the lung depends upon the compound inhaled and its physical-chemical

state. This has been borne out by more recent work, in which animals have been exposed to "fallout" or simulated fallout and fission products as reviewed in the succeeding paragraphs.

Studies involving the exposure of animals to airborne radioactive particles have been made both in the field and in the laboratory. The results of tests conducted at the Nevada Proving Grounds during the past few years indicate that the retention of particulate matter in the respiratory system of exposed animals was insignificant, even in the presence of an appreciable external radiation flux (20).

In the Pacific test of March 1, 1954, a large number of human beings and animals were accidentally exposed to fallout from nuclear detonation (32, 33). In this situation considerably larger amounts of radionuclides were taken up and retained than in the continental tests. In the Pacific exposure, the type of detonation and the carrier material of the fallout differed from those encountered in the Nevada tests.

Studies of the animals exposed to the fallout from the above-mentioned Pacific nuclear detonation provided data on the uptake, distribution, and retention of the various fission products (33). Routes of entry for the material were both inhalation and ingestion, with the latter the more important.

Although a large number of fission products were present in the environment, relatively few gained entry into the body. These included Strontium 89, Barium 140, Iodine 131, and some of the rare earth elements. The elements which enter the body are characterized chiefly by their solubility. Biological removal and radioactive decay reduced levels of radioactivity in the lungs of pigs rapidly, so that at three months only 0.02% of the beta-ray activity of the entire body was present in the lungs. At six months after the detonation, the radioactivity levels in the lungs of pigs were barely detectable.

The amount of fission products deposited in the body from inhalation and ingestion of this fallout material was insufficient to contribute to the acute radiation effects observed. The possibility of delayed effects occurring from internally deposited radioactive material is very small.

Studies in the laboratory designed to provide data on the results of exposing small animals to fallout material have been of two types: those which utilize pulverized radioactive material from the field, and those which attempt to reproduce fallout material.

In the former studies, rabbits were exposed to aerosols (0-3 microns in diameter) developed from materials collected from the Nevada Proving Grounds (21). The materials were used several months after the contaminating event, so that only the long-lived fission products were present. The materials were further characterized by the fact that they were siliceous and therefore highly insoluble (one percent in water).

Following single 4-hour exposures to a dust concentration of $1 \mu\text{c}/\text{m}^3$ with particles having a mean diameter of 0-3 microns, the amount initially retained in the lungs (369 d/s) was about one-ninth that found in the stomach (2326 d/s). Clearance from the lung and the gastrointestinal tract was practically complete by 96 days (0.8 d/s and 5.2 d/s respectively). Values for the clearance from both systems were parallel, and followed an exponential function, with about 85% lung clearance in 7 days and about 95% clearance from the gastrointestinal tract in the same time.

Products from two-day-old neutron bombarded uranium were employed in the various simulants used in the laboratory experiments, designed to re-create various types of fallout (34, 35). In this inhalation experiment the animals received many of the short-lived fission products in addition to the longer-lived radiisotopes. The distribution and retention of the fission products in these animals confirmed that fact mentioned previously that the uptake and metabolism of the inhaled radioactive particles depends largely on the physical and chemical characteristics of the carrier material. It was found that the retention and metabolism by the lungs and other tissues could be altered by the injection of the chemical, zirconium citrate, immediately preceding or soon after exposure (35).

The quantity of fission products retained by the mice as a result of inhalation exposure was proportional both to the length of exposure and to the concentration of airborne radioactivity. The internally deposited radioactivity in the lungs, as well as in the skeleton and soft tissues, decayed rapidly. This resulted from the fact that the activity of the aerosol was contributed chiefly by radioisotopes of short half-lives, and that the biological turnover in the lungs and soft tissues was rapid.

The accumulated evidence from these controlled experiments in the laboratory and field studies all point to the conclusion that the internal radiation hazard following an acute exposure to fallout is very small in comparison with the overwhelming external dose. This conclusion, of course, applies to the inhalation hazard immediately

following exposure to a nuclear detonation, and would not necessarily apply to the effects produced by acute exposure to long-lived radioisotopes such as Strontium 90 and Plutonium 239, or to chronic exposure to small amounts of long-lived fission products.

In repeated exposure studies (21), in which rabbits and rats were given as many as 60 6-hour exposures five days each week to the siliceous radioactive material (from Nevada) using dust concentrations of $0.01 \mu\text{c}/\text{m}^3$, pulmonary retention increased in proportion to the number of exposures. Lung clearance values were much lower than for animals subjected to a single exposure, being only about 30% in 30 days, and 70-75% in 60 days.

V Radiation Effects on the Respiratory Tract

Insofar as is known, the amount of damage suffered by any tissue depends upon the amount of energy absorbed. The determinants are:

1. The nature and intensity of the source
2. Time
 - a. Duration of exposure
 - b. Rate
 - C. Whether exposure is continuous or intermittent.

As regards such late effects as neoplasia, when the radioactive particle has an indefinite biological half-life, and is fixed by some mechanism within the tissue, the total volume of tissue affected may be small, but nevertheless of great significance; it is theoretically possible that a single cell exposed to a single radioactive particle may be the source of a neoplastic cell lineage that can ultimately destroy the host. Of course, with larger numbers of cells exposed, the statistical chance of such an event becomes greater.

Within the above parameters the effects to be expected may be classified as acute or chronic.

A. Acute Effects

Acute effects may be arbitrarily defined as effects occurring within the first six weeks.

Information that has accrued on the pathology of acute effects is largely based on changes produced by externally applied x-rays in

the treatment of cancer of the breast. With adequate exposure, two or three thousand to fifteen thousand roentgens, some cases showed lesions that consisted of alterations in the cells of distal air passages. There was enlargement of the passages, and sometimes an increased basophilia of the cytoplasm. The nucleoli likewise became very prominent.

Distinctive acidophilic hyaline membranes were often formed early in the tissue response to irradiation of the lung. These underwent absorption finally but not organization.

A characteristic and early change was edema of the alveoli together with congestion. The cellularity of the walls of the alveoli was increased, in part by swelling of the lining cells and endothelial elements, and sometimes by infiltration of small numbers of lymphocytes, plasma cells, and large mononuclear elements.

Pulmonary scarring occurred only with the larger doses of x-rays.

The lymphatics and small blood vessels became congested early. With large doses, the large vessels showed a striking edema of their walls, and occasionally cellular infiltration. The elastica may become reduplicated and focally coarsened. The lymphoid tissue within the lungs may atrophy, as elsewhere, but when the doses are appropriately spaced regenerative activity may keep pace with the destructive action of the ionizing radiations.

From available data, it would seem that single doses applied locally in excess of 2000-3000 roentgens at 150 to 200 kv are necessary to produce these acute tissue responses in the lung. It has been found that when rats are injected with 30 to 159 microcuries of Phosphorus 32, changes resembling those of the acute tissue response in the lung to x-rays appear within seven days.

B. Long-Term Effects

Experiments of Lorenz, et al. with strain A mice chronically exposed to gamma rays for a total of 2000 rad have shown an incidence of lung tumors 50% higher in experimental than in the control mice at nine and one-half months (37). It has long been known that extremely small doses of radioisotopes can produce neoplasia. A classical example is sarcoma of bone after the retention of as little as 1 microcurie of radium. Even lesser amounts, of the order of 0.4 microcurie, have recently been shown to produce bone necrosis in man (38). These studies, together with unreported work by other groups, suggest that

occupational exposure to appreciable amount of ionizing radiation has been common among miners and has existed for a long time (39). Earlier reports indicated that radon inhalation by the Jachymov miners resulted in lung carcinoma (40). Unquestionable evidence that carcinoma resulted from exposure to radon in these miners does not exist.

C. Effects of Radioactive Particles (Internal Emitters) on the Respiratory Tract

Available experimental data include the production of epidermoid carcinoma (10) of the lung within one year in mice of the BAF₁ strain (a strain known to have a low prevalence of naturally occurring lung tumors) by as little as 0.06 microcuries of colloidal plutonium oxide administered intratracheally. An early response to this material that occurred within three months was fibrosis and atypical epithelial proliferation in the terminal respiratory passages. Within three months, mice exposed similarly to Ruthenium oxide (Ru¹⁰⁶O₂) in doses of 1.5 to 2.5 microcuries, showed focal scarring of the pulmonary parenchyma. At one year there was apparently no progression in the scarring (10). In the lungs of rats exposed by Cember and his group (41) to Barium sulfate (BaS³⁵O₄) particles for a period of a year there were doubtful minute foci of fibrosis. No neoplastic changes were observed. A number of 1-2 year experiments in which animals were exposed daily to varying doses of x-rays and neutrons have produced no demonstrably pulmonary effects (42). Another pertinent, although negative, experiment may be cited: 5-1/2-mm particles of siliceous atomic debris from a Nevada test site each particle containing 10⁻⁵ microcuries of alpha emitters and 10⁻² microcuries of beta emitters per particle, were implanted in the lungs of rats. Only a foreign body response comparable to that of non-radioactive siliceous material occurred after one year (21).

Information obtained with other tissues may give an indication of the mechanism for the damage to the respiratory tract produced by radioactive particles. For instance, Passonneau (43) has performed some experiments to determine the incidence of skin tumors in rats exposed to beta radiation from point sources of Strontium 90-Yttrium 90. The efficiency of tumor production in these rats decreased as the amount of radioactive material in the individual point sources was increased (44). This decrease in efficiency is presumably dependent on the wasting of radiation energy on those tissues which are killed by the high radiation levels present at short distances from the point sources. Calculations (45) indicate that if the tumor production is a linear function of the radiation intensity, the efficiency of tumor production will increase as the amount of radioactive material in the individual point sources is decreased. If the tumor production depends upon the square

or higher power of the radiation intensity, the efficiency of tumor production will exhibit a maximum for some definite amount of radioactive material in the point sources.

VI Conclusions

1. With reference to fallout from nuclear detonations, consideration of physical factors (such as strength and type of detonation, particle size distribution, decay rates, meteorological factors, airborne radioactivity levels, and percentages of radioactivity in the respirable size range), and actual experience, indicate that the acute external beta-gamma radiation hazard is many times greater than that from inhalation.

An additional safety factor for the lung (of perhaps 10) is represented by the respiratory clearance mechanisms.

2. In industrial or research work with nuclear reactors and radioisotopes, situations may occur wherein relatively small numbers of people may receive significant radiation exposure to parts of the respiratory system from inhaling radioactive particles containing long-lived isotopes of high specific activity, without simultaneously exceeding tolerance levels for whole body exposure.

3. Little information is available on the potential hazard to the respiratory system and other organs following chronic exposure to small amounts of long-lived radioisotopes such as Strontium 90 and Plutonium 239. The occurrence of epidermoid carcinoma in the lungs of mice after exposure to plutonium particles suggests that accumulations of such materials may present a similar hazard to man.

VII Recommendations

1. More information should be obtained on storage and clearance mechanisms, immediate and long-term, in respect to various radioisotopes in various chemical forms and particle sizes, in both the upper and lower respiratory tracts.

2. A concerted effort should be made to compare the behavior and effects of inhaled radioactive and non-radioactive particles with the objective of utilizing the large amount of data already available on non-radioactive materials.

3. Possible cumulative storage within the respiratory tract, following repeated exposure to long-lived isotopes, should be given special attention.

4. Analyses of human lungs for radioactive particles should be made; the study of lungs containing tumors may be especially fruitful.

5. Spatial-dose relationships should be further worked out and carefully considered in studying the chronic effects of particles containing long-lived radioisotopes on tissues in general and on the respiratory tract in particular.

6. Species differences must be considered in evaluating the effects of ionizing radiations on the lungs; special attention should be paid to species with a long lifespan in consideration of time-intensity factors.

7. Further studies should be made of the combined effects of external and internal radiations on the lungs.

8. Further work should be done on the development of instruments for the preparation and collection of radioactive aerosols with particular attention to the physical parameters needed for interpreting biological experiments.

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APPENDIX IV

REPORT OF THE SUBCOMMITTEE ON
PERMANENT AND DELAYED BIOLOGICAL EFFECTS OF
IONIZING RADIATIONS FROM EXTERNAL SOURCES

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PERMANENT AND DELAYED EFFECTS OF IONIZING RADIATIONS FROM EXTERNAL SOURCES

I. Introduction

While it was recognized soon after their discovery that x-rays and the radiations from radioactive materials could cause acute injury to living tissue it did not become apparent until later that they could also give rise to more subtle permanent and delayed effects which are of prime significance in considering the problem of permissible human exposure.

Laboratory studies of long term effects have been relatively few, partly because their importance was not early appreciated and partly because they are very expensive and time consuming owing to the necessity for maintaining considerable numbers of animals for all, or most, of their normal life spans. In consequence the data on late effects in animals are meager in certain areas. Such data as there are in man are sufficiently in agreement with those on other mammals to lead to the expectation that extrapolation from lower mammals to man will be possible with fair accuracy.

It is the present purpose to review the long term biologic effects (other than genetic) of radiations from external sources, with emphasis on man, although results of animal experimentation will be drawn upon to illustrate fundamental principles and mechanisms in radiation biology.

II. Permanent and Delayed Effects of Ionizing Radiation In General

If animals, which have been irradiated, escape death initially they appear to recover but tend to die prematurely. It is becoming established that in mammals, shortening of life span is a general effect of whole body exposure to ionizing radiation.

There has been a tendency to seek the cause of premature death as a consequence of irradiation in increased incidence of specific disease, especially cancer. While this may be justified in the case of partial body irradiation from external sources or from locally deposited radioactive materials, it probably is not for whole body irradiation. There is evidence that at the median death time populations of irradiated animals have approximately the same incidence of the same diseases as do the controls at their median death time. This is more reasonably interpreted as indicating that irradiation produces primarily the syndrome of premature aging, with concomitant disease, rather than that it, in itself, induces all the diseases of advanced age.

The major permanent and delayed effects of total-body irradiation may be listed categorically in terms of pathologic entities as follows:

A. Increased incidence and/or severity, at given ages, of disease entities to which particular animal species or populations are susceptible. This may occur, and probably usually does, largely as a result of accelerating the time of onset of these diseases and may therefore be considered a part of the acceleration of aging produced by irradiation. It appears that the clinical history of the animals is compressed or telescoped in time in these respects. Included with these disease entities are cancers of various types to which the animals are susceptible, and possibly also cataracts which develop late in a species in a manner similar to the development of cataracts with age in that species.

B. Temporally accelerated involutinal, hypoplastic or atrophic, and fibrotic changes in tissues and organs, which changes do not constitute individual disease entities but which are identical in appearance with those occurring during the "normal" course of aging. There is a high degree of correlation between the degree of temporal acceleration of this pathologic picture of accelerated aging and the size of total-body dose or daily dose rate. It should be emphasized, however, that an accurate evaluation of the degree of acceleration of involutinal changes produced by certain doses can only be observed in experimental animals at times, after single doses, long after maximum regeneration and repair of the single insult has occurred, or with chronic irradiation, after irradiation has been stopped and recent acute effects on cells have repaired as much as they will.

Although differences exist among species, some of the radiation-accelerated senescent changes in tissues and organs which have been observed are:

(1) Hypoplasia or atrophy of many tissues and organs, especially the thymus, lymph nodes, splenic lymphatic tissue, bone marrow, germinal epithelium, skin, and bone growth centers. Hypoplastic changes in hemopoietic organs are reflected in lowered blood cell counts.

(2) Fibrotic changes which are fairly generalized, but which are commonly noticed in blood vessels generally, in skin where there appears to be increased collagenous tissue and decreased or degenerate elastic tissue, in and/or around lymphatic organs and endocrine organs, and in the myocardium, where focalized fibrosis occurs with age. If the small arteries of the kidney are affected sufficiently, there may develop nephrosclerosis and hypertensive disease.

(3) Pigmentary changes, including greying of hair and increases of pigments in cells of the epidermis, connective tissues, endocrine glands, myocardium and other tissues.

General physiologic changes which are usually associated with aging and which may be accelerated by irradiation include, among others: decreased muscular strength and endurance, lowered recuperative powers and tissue repair capacity and speed, lowered fertility and potency, generalized reduction of elasticity, and increased blood pressure.

Factors included in these first two categories are among those which constitute the general change which may be called "radiation-accelerated aging". The fundamental mechanisms of this change are as incompletely understood as are those of "normal" aging, except that radiations and their known effects are recognized as accelerating agents. The subsequent development of the histologic changes in both radiation-accelerated and "normal" aging appear qualitatively identical. However, it is at present sometimes difficult to distinguish between accelerated aging effects and induced pathologic effects except by arbitrary definition.

C. Induced disease entities or definitive effects, not necessarily specific for irradiation, which rarely occur spontaneously in animals of any age in the species in question, or certain effects and diseases whose known pathogeneses may differ from those occurring in the aging process but which may produce similar final results. In the latter case such effects occur earlier than the specifically comparable effects associated with accelerated aging.

Included in this category are, among other effects:

1. Nephrosclerosis and related hypertension produced essentially by the relatively direct damaging effects of radiation on cells in the kidneys, e. g. components of vessel walls, so that this disease occurs well in advance of any considerable degree of acceleration of other senescent changes. According to some data, renal hypertension, once established and progressive, may increase the vascular sclerotic processes in many regions throughout the body and these changes are sometimes associated also with progressive hypoplasia or atrophy of organs in which the vessels become fibrotic.

2. Cataract formation which occurs well in advance of the generalized aging processes if the radiation dose to the lens has been sufficiently high to damage or destroy cells of the anterior epithelium and/or depolymerize the cement substance between fibers. There are

two general histologic types of radiation cataract, the purely vacuolar type, which is reversible, and the granular type which is irreversible. The senile cataract, although similar in the ultimate effect to radiation cataracts, is generally more progressive, occurs usually when other aging changes are considerable, and may have a different pathogenesis.

3. Decreased fertility resulting from direct damaging actions of radiation on gametogenic cells and gametes. The mechanisms by which direct actions of radiations decrease fertility are quite different and more numerous, as far as we know, compared with those involved in decrease of fertility due to aging or accelerated aging.

In senescence of the testis, as in testicular damage resulting from infectious and cachectic diseases and physical and chemical damaging agents, the spermatozoa and more mature spermatogenic elements are affected first and most markedly in the seminiferous epithelium, and decreased fertility, if potency is retained, is due to lack of production of sufficient numbers of spermatozoa. In the case of the senescent ovary, there is depletion and/or failure of development of follicles, which is associated with a complicated endocrine disturbance.

Irradiation effects on the gametogenic cells and gametes themselves may decrease fertility in more than one way, prior to and in addition to, the effects involved in acceleration of aging, and these mechanisms, other than those genetic and relating to the fertility of future populations, are as follows:

(a) by reducing the number of gametes produced through effects on primitive radiosensitive precursors of the gametes. This reduction may be partial or complete, or temporary with partial or complete recovery, or permanently complete, depending upon dose. The number of gametes produced may be reduced also indirectly by other diseases which irradiation causes or accelerates.

(b) by damaging in various ways the gametes produced so that they are incapable of fertilization.

(c) by damaging chromosomes of gametes in such ways that they are capable of fertilization but produce zygotes which are incapable of complete and normal development to full-term viable foetuses and die in utero. The results of such effects constitute the condition known as "semisterility," which is genetically transmissible to viable offspring.

4. Increase in incidence of other non-neoplastic diseases not common to the species even during the senescent period. There are not sufficient conclusive data in this area of the problem to warrant discussion, but it would appear worthwhile to indicate that research is needed in this aspect of the study of long-term effects of irradiation.

5. Induction of neoplasms rarely, if ever, occurring spontaneously in a species, but caused by the destructive actions of radiation on specific tissues with the initial establishment of precancerous states. It is possible that the later influences which cause the development of neoplasia from these precancerous states may be brought about by the same mechanisms which cause the development or accelerated development of the neoplasms which are of common occurrence in the species with advancing age.

III. Permanent And Delayed Effects Of Ionizing Radiation In Particular

A. The Shortening of Life Span by Ionizing Radiation

Since there is some evidence that radiation effects depend upon the age of the animal at the time of exposure, some consideration will be given first to the lethal dose as a function of age.

1. Lethal Dose as a Function of Age

The average of median acute lethal dose, LD₅₀-30 days, for young adult mammals is similar for those species which have been studied and lies within or near the range 600 ± 300 roentgens. While it is customary to refer to LD₅₀ of a given strain as if it were a specific property, independent of age, this is not justifiable.

In the mouse the susceptibility is maximal at 30 days then decreases rapidly to that seen in young adults. In the rat, which has been studied more extensively, the LD₅₀ at three months of age is about double that at three weeks. Beyond three months it diminishes with age and there is some indication that, for the adult animal, the LD₅₀ decreases about as the life expectancy. More study of this relation is required to make it wholly quantitative, but it is evident, now, that the susceptibility of a whole population is not describable by a single LD₅₀. The published values are usually obtained from the young adult and are therefore maximal or nearly maximal for the strain. In attempts to estimate LD₅₀ in man this age dependance should be taken into consideration.

2. Life Shortening by Single Doses

Existing data on rodents subjected to single whole-body doses of radiation are compatible with the view that life is shortened in proportion to the dose for doses less than about two-thirds of LD₅₀. In this range life shortening is about 25% of the adult span per LD₅₀. With greater doses this effect increases more rapidly, attaining about 50% for survivors of LD₅₀. No similar data are available for longer-lived mammals, or for man, but it may be possible eventually to obtain some estimate of the effects of single doses in man from the Japanese survivors.

There are a few data from the rat indicating that shortening of life for a given single dose is about the same, independently of the age at which it is administered to the adult animal, providing the animal is destined to live long enough to make the shortening wholly manifest.

Owing to the difficulty of detecting small changes with limited numbers of animals it cannot be assumed with confidence that life-shortening is proportional to dose down to small doses at the rate given above. Actually there is reason to suppose that the effect of small doses is less than that indicated by the present data. This point will be discussed in considering the effects of chronic irradiation.

3. Life Shortening by Multiple Doses or Chronic Irradiation

Small laboratory animals subjected to irradiation either at high daily rates for short periods or low daily rates for long periods suffer about 7% life shortening per LD₅₀ and the effect is proportional to dose, or nearly so, for doses up to about three times LD₅₀. The data for low daily rates and small total doses in the 100 r range are not definitive, there being almost as many showing prolongation, as shortening, of life. While this again is probably due to failure to use sufficient numbers of animals to measure small effects, it leaves to be resolved the possibility that low daily doses actually prolong life, unlikely as this may seem.

No satisfactory explanation has been offered for the greater shortening of life from single doses than from divided doses of the same total magnitude. Nevertheless the difference appears to be well established for large single doses. However, because divided doses, at rates at least as high as 120 r per day, cause the same effect per accumulated roentgen as divided doses at quite low daily rates, it is difficult to understand why a single dose of 120 r would not act the same. Possibly it

does and the apparent disagreement is owing to inaccuracy of single dose data for doses in the 100 r range and below.

4. The Concept of Irreversible Injury

To account for shortening of life as an after effect of irradiation it may be supposed that radiation injury is in part reversible and in part irreversible and that the irreversible component is equivalent to premature aging in the sense that it ultimately deprives the animal of part of its expected life span. This view of irreversible injury does not prescribe whether it is equivalent to abrupt aging at the time of injury or consists in the initiation of aging processes which gradually develop. It is interesting that limited observations in the rat indicate that irreversible injury is measurable, after an interval of presumed complete repair, as a reduction in acute lethal dose. This suggests that aging or its counterpart is laid down at least partially at the time of injury and is potentially observable as some form of persisting lesion, but as yet this phenomenon has not been related to histopathologic changes to be discussed below.

5. The Effect of Chronic Irradiation in Man

The deaths of 82,441 physicians reported in the Journal of the American Medical Association from January 1, 1930 until December 31, 1954, were reviewed by Shields Warren.* In physicians grouped according to possible radiation exposure the average age of death was as follows:

No known contact with radiation	65.7 years
Some exposure (dermatologists, gastroenterologists, tuberculosis specialists, urologists)	63.3 years
Radiologists	60.5 years
U. S. population over 20 years of age	67.1 years

In comparison with non-exposed physicians the shortening of life of radiologists is 5.2 years or 11% of the adult life span (after 20 years). If extrapolation from the animal data, reviewed above, is permissible, this would be expected to result from chronic whole body exposure to about 1.5 LD₅₀ dose or possibly 1000 roentgens. Although this exposure was partial body and possibly less effective, it seems unlikely that the equivalent whole body exposure differed from the above value by a factor greater than 2 or 3. Consequently it appears that,

*Before the Radiation Research Society, May 19, 1956, Chicago, Illinois.

within these limits at least, extrapolation from short-lived animals to man may be made with some confidence on the basis of percent life-shortening per unit dose.

B. Acceleration of Aging by Irradiation

There are no definitive data on the effects of total body irradiation on the aging processes per se of man. Perhaps some information on this effect in man will be forthcoming in time as a result of observations which may be made on survivors of the atomic bombing in Hiroshima and Nagasaki. The delayed effects which have been observed in these Japanese are reported subsequently under other headings.

In view of the relation between the degree of acceleration of aging observed histologically in experimental animals and the size of the total body dose which the animals received, and in view of the probability that populations of irradiated animals dying prematurely die essentially as the result of premature aging and associated diseases, it seems reasonable to expect that a direct relation may exist in irradiated populations between the amount of life shortening caused by irradiation and the degree to which irradiation has accelerated aging, and that any total-body dose of external radiation which has caused shortening of life in a population of animals has caused a proportional acceleration of aging.

Some of the localized tissue effects produced by partial body irradiation in humans are histologically similar to changes occurring in the syndrome of premature aging. However, many of these changes, some of which are mentioned below, are effects induced directly rather than phenomena of accelerated aging.

In the human skin single doses of 500 r to 700 r of x-rays may produce permanent epilation. Somewhat smaller doses causing temporary epilation may cause decreased pigmentation or greying of hair which returns in the irradiated areas. These 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 of skin, vascular sclerosis, and dermatitis may also be late sequelae of irradiation of skin. Surface doses of about 1600 r more or less may produce considerable permanent dilatation of capillaries (telangiectasia) in the area irradiated.

Changes in skin are also late effects of chronic irradiation and are seen commonly in the skin of the hands of persons working with

radiations. Roentgen dermatitis and the roentgen ulcers which often develop from this condition are considered precancerous conditions because of the frequent development of malignancy in such regions.

Renal hypertension may be produced in man within periods from several months to several years by single localized doses of x-rays of about 3000 to 5000 r or by chronic irradiation, e. g. by a total dose of 2300 r in 35 daily doses to the abdomen, but there are no definitive dose-effect data on the late incidence of kidney disease and arteriosclerosis related to generalized radiation acceleration of aging in man. In rats, nephrosclerosis, with renal hypertension, and generalized arteriosclerosis are characteristic delayed effects associated with accelerated aging changes late in their lives following single total-body doses of 500 and 600 r or greater. Much larger doses localized to the kidney are required to cause these renal changes and associated effects to appear early in the life of irradiated animals.

Irradiation of parts of the brain of man with total doses of about 5000 r or more given as a single dose or within 2 or 3 weeks in fairly large fractions may cause progressive sclerosis of blood vessels with subsequent secondary degeneration of brain tissue and sometimes rupture of blood vessels and hemorrhage from one to several years after exposure.

Hypoplastic and atrophic changes, often associated with arterial sclerosis, have been observed in human hemopoietic organs long after localized irradiation. Permanent effects have also been observed in bone heavily irradiated, and in the length of bones irradiated heavily over their epiphyseal ends during the growth period.

The fragmentary data on delayed effects of localized irradiation in human tissues which are similar qualitatively to changes which are associated with aging, are difficult to interpret in terms of accelerated aging, especially since many of the human cases from which the data are obtained suffered from malignancy or other serious disease processes.

C. Late Hematologic Effects of Irradiation

Data collected during the period after World War II may be summarized very briefly as follows:

With respect to occupational or daily exposures over periods of months or years, doses in the range of 0.05 r/day have been reported effective in producing slight depression of the number of circulating

lymphocytes and total leukocytes in the peripheral blood of man. A 77 week period of exposure to doses averaging 0.2 r/week effected a decrease in the number of leukocytes in another group of workers. One authority has found some statistical evidence indicating that doses as low as 0.5 r/year may depress the lymphocyte count very slightly. These and similar findings (which are considered in more detail and tabulated in the review cited at the end of this paper) are not unequivocal, of course, and do not indicate with certainty that injury has occurred to the personnel in question, but they indicate in a general way, the presently accepted estimates of the "lowest effective dose".

Slightly larger exposures, for example a total x-ray dose of 40 r given in increments of 15-20 r, or a total dose of 200-300 r received as a series of daily 5-10 r exposures, caused depression of the peripheral blood lymphocyte level in man, the larger cumulative dose being associated with decreased numbers of all types of white blood cells.

Survivors (924) of the Hiroshima atomic bombing, receiving doses estimated at 400 r total-body, and all showing epilation, revealed relative lymphopenia 2 years after exposure. There was greater than normal variability in the blood picture of this group. Four of 5,075 survivors exposed at less than 1500 meters in the Nagasaki bombing revealed, after latent periods of 4 to 7 years, refractory (fatal) anemia, with associated leukopenia and thrombocytopenia.

A statistical analysis in 1954 of the hematologic data obtained by the Atomic Bomb Casualty Commission on Hiroshima survivors 5 to 8 years after the bombing indicated that there was no increase in leukopenia, leukocytosis, or anemia in the exposed as compared to the control population. Up to 1953 no cases of aplastic anemia had been found in the survivors in Hiroshima.

Observable changes in the structure of leukocytes (in contrast to the changes in numbers described above) appear to offer considerable promise as sensitive biological indicators of radiation exposure.

Two of the most sensitive morphologic indicators of radiation effect on blood are increased numbers of refractile neutral red bodies in lymphocytes, (observed in humans receiving .05 r per day) and an increased incidence of lymphocytes with bilobed nuclei in peripheral blood, which has been observed in a considerable number of cyclotron workers after they had worked about 3-1/2 months during which they received exposures which did not exceed the M. P. E. The incidence of the abnormal lymphocytes returned to normal after extra shielding was installed.

Although there is much conflicting information and opinion relative to late hematologic effects of exposure to ionizing radiation, a review of the available data leads to the formation of certain fairly clear impressions if not definite conclusions.

Early radiologists and radiation workers developed blood pictures characterized by moderate lymphocytosis and leukopenia. These changes were often sufficiently definite to be recognized on an individual basis, as well as by statistical analysis of grouped data. They have been interpreted in various ways, of which the most likely seems to be as follows: initial injury causes a depression of lymphopoiesis, which is followed by a recovery phase characterized by a compensatory increase in activity. During chronic exposure lymphopoiesis presumably "escapes" from the depressing effect and enters the compensatory hypertrophy state. Most of the early workers had exposures which would undoubtedly greatly exceed present maximum permissible doses.

Studies made during the more recent period reveal that the most characteristic changes following chronic exposures in or below the maximum permissible dose range are slight lymphopenia and morphologic alteration of the leukocytes, particularly lymphocytes. The absence of lymphocytosis might be explained by the fact that even chronic exposures are much more intermittent now than earlier. Furthermore, since both injury and the compensatory hypertrophy are, within limits, proportional to the magnitude of exposure, it is possible that present chronic exposures are too slight, as well as too intermittent, to produce adequate stimulus for "escape" into the compensatory hypertrophic phase.

In any event, morphologic changes are probably the most sensitive indication of radiation injury. This is not surprising, for one might expect to find larger numbers of young cells being released into the blood stream following transient bursts of increased leukocytopoiesis. Furthermore, when parent cells have been injured by radiation, abnormalities of mitosis (with the production of abnormal daughter cells) would be expected to occur more frequently than normally. Hence abnormal as well as early cells should appear in the peripheral blood in increased numbers.

The relationship of this type of change to the incidence of leukemia and other latent effects of exposure is very poorly understood, and it is highly desirable that more information be obtained. The compilation of data representing sensitive hematologic indices of radiation exposure in large groups of radiation workers should be vigorously pursued so that eventually there may be enough long-term studies of

the health of the workers to permit adequate evaluation of the significance of the more sensitive radiation-induced biologic changes. Should such changes prove to be truly premonitory of an increased incidence of latent effects, it would be important to adapt biologic monitoring procedures accordingly.

One of the greatest hindrances to the present interpretation of highly sensitive hematologic and presumably other biologic changes is the absence of adequate physical monitoring data for exposures below the maximum permissible dose range, so that evaluation of exposures of individual radiation workers is grossly inadequate for the interpretation of hematologic data of the type under discussion. It is important that in selected situations, individual physical monitoring be instituted which is in the same range of sensitivity, with regard to quantitative interpretation, as the biologic monitoring.

D. Carcinogenesis by Radiation from External Sources

This section deals primarily with malignant disease in human populations exposed to ionizing radiation.

It has been clearly established that malignant disease may arise in tissues heavily irradiated by ionizing radiation. Animal experimentation and experience with irradiated human subjects show that almost any tissue can become neoplastic under the proper conditions of exposure. This report does not treat of the type of radiation-induced malignancy which is usually the result of intense, repeated exposure of a small portion of the body, but will consider only malignant disease in populations in which the entire body or at least a large portion of the body of human subjects has been exposed to acute or chronic doses of ionizing radiation from external sources.

Leukemia is commonly associated with exposure of the body to radiation. The close association between exposure and the disease has been described under three different conditions of exposure. The first is that noted in the radiologists who have been chronically exposed. It should be pointed out that the actual number of cases of leukemia is not great even though the incidence is much higher than that noted in the general male population and in other physicians. March, in a review, was able to find only 37 published cases. Furth and Lorenz state that one reason for such a low incidence of leukemia in these persons who were probably heavily exposed in the early days of x-ray technology is that their exposure was partial body rather than total-body. The average age of the 14 radiologists dying of leukemia from 1928-1949 was 58.8 years.

The increased incidence of leukemia in the Japanese exposed to the nuclear explosion in Hiroshima and Nagasaki is the only example of this disease occurring after a single acute exposure of the entire body to ionizing radiation. In this case there is a good correlation between the disease and the dose. Even in the highest exposure group, however, the incidence is still small (1.25%). Most of the cases are of the myeloid type. However, lymphoid leukemia is known to be comparatively rare in Japan.

There are two examples which illustrate the increased incidence of leukemia under the third condition, i. e., that observed in persons given therapeutic treatment with x-rays to a large portion of their body. One is found in persons with ankylosing spondylitis who have received intensive treatment with x-rays to the entire length of their spine. A total dose of 2,000 r was not unusual in a treatment series and such series were often repeated. There is a good correlation between the incidence of leukemia and the number of treatment courses. The second example is found in children given one or more treatments to their chests in infancy for enlargement of their thymus glands. In one study of children receiving 100 to 1500 r in 1 to 3 treatments to the chest, 7 of 1,722 treated children developed leukemia. This incidence was ten times that expected for children in the state in which the study was done. There were no cases of leukemia in 1,795 untreated siblings at the time of the study. There were 3 cases of leukemia among 604 children receiving less than 200 r, and 4 cases among 804 children receiving more than 200 r. The children in this study showed leukemia incidence of about 0.4%, but they may represent a special situation since the treatment was given when they were very young and since there is no apparent correlation with the x-ray dose.

Aside from leukemia, the only studies on malignant disease in persons exposed to radiation from external sources are found in statistical surveys by Dublin and Spiegelman and by Warren of the cause of death in radiologists and other physicians. Dublin and Spiegelman find that the incidence of malignant disease is lower in physicians than in the general male population of comparable age. It is slightly higher in radiologists but, apparently, not significantly different from that in other specialists or non-specialists who presumably have not received the same exposure to radiation. Interesting is the observation that the highest cancer incidence, twice that in the total group, is found in psychiatrists and neurologists. The data of Shields Warren on a much larger series of physicians show a somewhat higher percentage of cancer deaths in radiologists than in other physicians.

In consideration of animal experiments, uncertainty exists as to whether or not there is a true dose threshold for the production of malignant tumors by irradiation. The answering of this question would require an extremely expensive, massive experimental program employing very large numbers of animals and much time. Experimentation of this kind with low doses is further complicated by the occurrence of spontaneous malignancies to which various species of animals are susceptible, and also by the variability in response of equally exposed animals. If the fundamental cause, or one of the indispensable factors, in radiation carcinogenesis is the induction of somatic mutations, it would appear possible that radiation carcinogenesis, or perhaps the induction of precancerous states by irradiation, has no dose threshold. However, this reasoning may be applied to other disease states and accelerated aging as well.

In any event the incidence of cancer in exposed populations is not sufficiently great to be regarded as an important contribution to the degree of premature death occurring in a group such as that of the American physicians discussed above.

E. Radiation Cataracts

In this section emphasis is placed upon the effects of the radiations from nuclear disintegrations and high energy particle accelerators on the development of ocular, especially lenticular, lesions in humans. This in no sense deprecates the excellent work done with other animals in which the pathologic development, biochemical changes, and dose-time relationships of lenticular abnormalities have been elucidated. The present reservoir of several thousand persons who have been exposed to the radiations from atomic weapons, and the few hundred humans exposed to the beams of particle generators during the last ten to fifteen years makes it apparent that a reasonably accurate evaluation of the magnitude of the problem of radiation-induction of cataracts in humans can be made from the information currently available.

There are no quantitative or definitive dose-effect data from humans or animals in regard to increased incidence of cataracts late in life as a result of radiation acceleration of aging processes. It is hoped that long-term observation of persons exposed to radiation and of animals in life-span experiments will provide such information.

It is not surprising that a great variety of possible causes of cataracts have been discovered. Histologically the lens is such a simple structure that its possible ultimate response to injury is limited almost

exclusively to cataract formation. Considering only idiopathic forms of the disease and excluding those cataracts resulting from injury, including radiation injury, metabolic disease, congenital defects, etc., one is left with a phenomenon definitely related to increasing age.

Despite much effort it is still not yet clear just how the senescent process causes this local change. However, there are differences histologically in the development of this change as compared with the development of radiation-induced cataract. In the aging process the lens grows continuously throughout life but the growth rate becomes slower with advancing age, never reaching zero until the tissue dies in cataract formation. Radiation-induced cataract is the result of direct destructive actions of radiation on the anterior epithelium and possibly on the cement substance between fibers.

It is interesting to note that before it was recognized that radiation cataracts were appearing in cyclotron workers, Evans reported in 1948 that cataract production in mice by fast neutrons relative to x-rays increased significantly with chronic exposure. Young animals exposed during the pre-natal or early post-natal period show markedly greater lenticular radiosensitivity than do older animals.

By December 1948 it was known that at least five nuclear physicists of mean age 31 had incipient cataracts. In January 1949, eleven physicists were examined and ten were found to have cataracts, in three cases severe with definitely impaired vision, in four cases moderate, and in three cases minimal. They were estimated to have received, over periods of 10 to 250 weeks, a median dose of fast neutrons of 50 n , while the range of doses was 10 n to 135 n . At the time the cataractogenic exposures were being received, most of the men were given periodic blood counts, which revealed no change in blood picture warning of overexposure to radiation.

In adult humans exposure to x-rays in excess of about 2000 r has been thought necessary to produce cataracts.

Fillmore, in a survey of the Hiroshima Japanese survivors, based in part upon studies by Kimura in 1949, about 5 years after the detonations, reported 98 cases of cataracts, eighty-five of which were among the 922 survivors 1000 meters or less from the hypocenter. In 1955 Sinskey reported the results of an intensive investigation of 3700 exposed and nonexposed individuals made between May 1951 and December 1953, six to eight years after exposure. There were 154 survivors with posterior subcapsular polychromatic plaques large enough to be visible with the ophthalmoscope. These radiation-induced

pathologic changes in the lens did not in general impair vision significantly when examined, and in most cases were correctable with proper lenses to provide normal vision. Of this group only 25 individuals had vision less than 20/25.

According to Sinskey's study, the human lens is quite sensitive to nuclear radiation in doses which produce epilation and other acute effects but are insignificant with respect to impairment of vision.

Of the approximately 8000 exposed survivors of Hiroshima and Nagasaki who have been examined during the last decade there have been found 10 cases of severe cataract, approximately 25 cases of slightly impaired vision due to posterior polychromatic plaques and perhaps two hundred cases with minimal pathologic lenticular lesions detectable by competent slit lamp examination.

It may be concluded that the atomic bomb explosions over Japan have resulted in negligible loss of vision to date.

F. Effects of Ionizing Radiation on Gametogenesis and Fertility

1. The Male

Spermatogonia are the most radiosensitive cells of the seminiferous epithelium and one of the most sensitive of the body with respect to inhibition of division and with respect to the destructive actions of radiation. Apparently both inhibition of mitosis and destruction of spermatogonia, and differentiation of these cells following irradiation contribute to their disappearance from the seminiferous tubules, the relative contribution of each mechanism varying quantitatively according to size and mode of administration of dose.

The delay in the beginning of regeneration of these cells after irradiation is dependent to a considerable extent upon the dose. Following reduction or depletion of spermatogonia the later germ cell generations undergo maturation-depletion and disappear in the order in which they are formed until a point of maximum hypoplasia is reached. The destruction of some of the cells of more mature generations by relatively high doses may hasten this process. Spermatocytes, spermatids, and spermatozoa are of increasing radioresistance in the order given. The time for the development of maximum hypoplasia of the seminiferous epithelium is about 3 to 4 weeks, sometimes longer, depending upon dose and species, and this time is close to that required for the development of a spermatozoon from a spermatogonium.

Histological sterility, by definition a lack of spermatogenic elements and sperm, may be temporary or permanent and the two often appear very similar upon casual histologic examination. The time factor is of great importance in the prognosis as regards sterility.

For relatively low doses and for certain laboratory animals whose germinal recovery capacity is relatively large, regeneration, if it is to occur, begins before the height of depopulation of germinal epithelium is reached or soon thereafter. With certain higher doses given to such animals, a delay of beginning of regeneration for about 10 months is considered by some to be indicative of permanent sterilization. Actually, in much of the work employing large single doses of radiation the animals were not studied for the maximum time possible or desirable.

It is probable that the critical interval of time for beginning of regeneration varies among species and that for some of the larger animals, including man, whose powers of germinal regeneration are comparatively low, active regeneration may be delayed following severe radiation effects much longer than 10 months. Whether permanency of sterilization or length of the temporary sterile period is due to effects on cells involved directly in spermatogenesis or rather indirectly to effects on supporting tissues is not clear.

The testicular effects of irradiation are qualitatively similar in all mammals studied, including man, but vary quantitatively according to differences in testicular radiosensitivity and recovery capacities among species. Whether a dose of radiation sterilizes permanently or temporarily depends at least as much on the natural capacity for regeneration of primitive spermatogenic cells as on the radiosensitivity of the spermatogenic cells existing at the time of irradiation.

Sertoli cells and interstitial (endocrine) cells are relatively radioresistant. Male mammals may be sterilized permanently without prominent histologic changes in the interstitial cells and without decrease in sexual potency or libido.

Following single doses of irradiation and preceding the sterile or subfertile period produced there is a period of fertility, the length of which is much less dependent on low doses than on doses high enough to affect the fertilizing capacity of mature sperm. Lower doses are required to destroy the fertilizing capacity of sperm than are necessary to affect the viability or motility of sperm present at the time of irradiation and therefore during the initial fertile period.

This first period of continued fertility is due largely to sperm mature at the time of irradiation and possibly to some sperm in the spermatid stage or even a few in the spermatocyte stage, depending upon the dose and the length of the fertile period. The subsequent period of infertility or sterility is due to decreased numbers of sperm produced, and the fertile period following the period of sterility, if recovery occurs, is due to sperm that were developed from cells which were in the spermatogonial stage or were primordial undifferentiated cells at the time of irradiation.

In the initial fertile period litter size is subject to reduction with sufficient dose and the amount of reduction is dependent upon the dose. Litter size in the fertile period after the sterile period is usually normal or perhaps slightly less than normal. Reduction in litter size is explained on the basis of induction in sperm, and perhaps to some extent in precursors of sperm, of chromosomal aberrations which do not interfere with fertilization but which cause death of the zygote or embryo in utero. In terms of human considerations the equivalent result would be manifest in the form of increased incidence of spontaneous abortion following death of embryos or foetuses in utero.

This reduction in litter size caused by irradiation is called "semisterility", and the condition is transmissible genetically to viable offspring. Chronic irradiation at low daily dose rates appears to be much less effective in the production of semisterility, according to existing data. This may be explained on the basis that low doses are delivered to sperm populations which are continually renewed in the genitalia, and that relatively fewer sperm are subject to doses large enough to induce the chromosomal defects involved in semisterility. The lesser reduction in litter size during the second fertile period after irradiation with large single doses suggests that similar chromosomal defects in primitive spermatogenic cells or primordial undifferentiated cells are either not as significant in terms of the production of semisterility or are largely eliminated in some manner. More long-term investigations of this problem in chronic radiation experiments seems desirable to verify the degree to which regenerated sperm populations are defective in terms of semisterility.

The so-called sterile period may be a period of complete sterility or a period of subfertility or of fertility with reduced spermatogenesis, as manifest by partial atrophy of seminiferous epithelium and partially reduced sperm counts. Since critical or minimal numbers of normal potentially effective sperm per ejaculate are necessary for consistent successful reproduction, practical sterility or infertility may be associated with considerable but subnormal degrees of

spermatogenesis. When spermatogenesis is partially arrested the number of sperm produced decreases and the percentages of sperm motile, alive, and normal tend to decrease also. With chronic irradiation spermatogenesis may stabilize at reduced levels for long periods of time if complete arrest does not occur, and further depressions may be slow in occurrence. Reduced sperm count and decreased quality of sperm persist accordingly.

The effects of irradiation on seminiferous epithelium are direct in that irradiation of the body with testes shielded does not produce them.

The effects of x-rays, gamma rays, and neutrons on spermatogenesis and reproduction are qualitatively similar, but neutrons are more potent in their effects on spermatogenesis and five or six times as potent in reducing litter size in matings done during the initial fertile period.

In regard to the efficiency of fractionated versus undivided doses of the same total size in producing testicular effects, there are experimental reports indicating no difference, others indicating less effect with fractionation, and others showing greater effects with fractionation.

Protraction of the dose fraction has little influence apparently on testicular effects unless the protraction is extreme, in which case the effect of a given total dose may be decreased, probably by virtue of permitting biologic recovery processes to operate at a more favourable rate with respect to the rate of production of injury by radiation.

The effects of fractionation of dose 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 total doses. Fractionation of large doses appears to increase damage in the mechanisms responsible for regeneration of germinal epithelium.

The dose-effect relationships in different species often appear contradictory, but are probably in reality complementary. For each species there is probably a different dose-time relationship, in irradiation with divided doses, which is optimum for the efficient production of radiation injury. The empirical work which has been done on the testis has already made this apparent. Theoretically, in a tissue in which stem cells are radiosensitive and have the capacity both for

active division and for differentiation, the most efficient mode of administration of radiation (per roentgen) to produce sterility in animals of a given species would be that designed, with respect to dose-time relationships, to take advantage of the biologic actions and reactions of the cells themselves. One of the most efficient dose-time relationships in spaced irradiation of the germinal epithelium would be one in which the dose fraction was small enough to permit attempts at division in 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 inter-dose time interval in either direction would decrease the efficiency of the irradiation with respect to utilization of mitotic-linked death of spermatogonia.

In the case of cells having the capacity both for division and differentiation, irradiation tends to diminish the number of resting cells and dividing cells and by inhibition of division to increase the number of differentiating cells. It may be possible to increase to a maximum this effect in spermatogonia by suitable arrangement of the dose-time relationships in chronic irradiation. If the dose-time relationship optimum for maximum differentiation effects was quite different from that optimum for maximum mitotic-linked death, an optimum compromise might be found, or these biologic effects could be handled separately with greater efficiency than is now the case.

There has been little investigation of the effects of irradiation on gametogenesis and reproduction in mammals, except for the work on rodents and some recent work on dogs. The single doses to the testes required to cause complete or nearly complete atrophy of the seminiferous epithelium are similar in size in these small animals and in the dog and man as well, all of the doses being within the LD₅₀ range. However, the regenerative capacity of the seminiferous epithelium of the small laboratory animals is so great that very large single or divided doses, well above total-body LD₁₀₀ doses, are required to sterilize permanently most or all of the animals of a group.

It would appear from data at hand that the dog, of all of the animals investigated in these respects, is the animal most similar to the human in terms of radiosensitivity and regenerative capacity of seminiferous epithelium. In general both dog and man reveal similar sensitivity which is greater than that in other experimental animals. In both cases, however, there is only little and fragmentary information on the effects of irradiation on spermatogenesis and reproduction, the minimal single or chronic permanent sterilization dose has not been studied definitively, and there is only little known of the regenerative capacity following irradiation.

The following table summarizes careful observations on male beagle dogs subjected to chronic exposure to x-rays from a 1000 kvp x-ray machine and, in some cases, to neutrons from a cyclotron, five or six days per week.

Dose/ Week	Approx. total dose	Duration of Exposure	Observations
0.3 r	62 r	4 yr.	No significant change in sperm count
0.6 r	124 r	4 yr.	No significant change in sperm count
0.6 r	62 r	2 yr.	Little change in germinal epithelium
0.6 <u>n</u>	31 <u>n</u>	1 yr.	Little change in germinal epithelium
3.0 r	156 r	1 yr.	80% sterile; 20% reduced sperm counts
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
10.2 <u>n</u>	398-561 <u>n</u>	39-55 wks.	Extreme atrophy of germinal epithelium
15.4 r	477 r	31 wks.	Aspermic after 375 r; sterile 1.25 years post-irradiation so far
15.4 r	634 r	41 wks.	Aspermic after 375 r; sterile 1 year post-irradiation so far

Although cases of testicular atrophy in humans following irradiation have been observed since 1904, and were commonly observed soon after the Hiroshima and Nagasaki bombings, little is known at present of the ultimate fate of the lesions produced in survivors and the effects of these lesions on fertility. Regeneration of testes rendered atrophic by various doses and modes of irradiation has not been studied definitively in man. There are, however, isolated cases which have been studied to some extent, and there are reports of a zoospermia or oligonecrospermia or sterility in radiologists. Most of these cases were not studied carefully and extensively and in very few instances are there any reports or accurate estimates of doses involved. However, on the basis of the rather meager data available, certain estimates may be hazarded.

A single x-ray dose of 500 to 600 r is thought to produce permanent sterility for the human male and a dose of 250 r is thought to produce sterility for about one to two years.

If it is permissible at all to compare the meager human data with the results of many animal experiments in which regeneration was studied, the much more delayed and lower rate of testicular regeneration in man is apparent. Marked depletion of germinal epithelium is produced in the small experimental animals by doses in the LD₅₀ range, but regeneration of the seminiferous epithelium is complete or nearly so in a matter of 3 to 5 months.

Man as well as the dog may have fewer of the radioresistant primordial cells, precursors of spermatogonia, or these cells may have less potential than is the case in the smaller or lower mammals. Other possible reasons for the delayed and slow recovery may be intimately associated with differences in metabolic rate and normal differences in rates of spermatogenesis. Factors which determine the relatively late maturation of the normal human testis may also modify the rate of regeneration of the human testis.

2. The Female

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 dependent atrophic changes in accessory genitalia in most mammals.

The ova and follicular cells are the most radiosensitive cells in the mammalian ovary and cells of the corpora lutea and interstitial cells are relatively radioresistant. The radiosensitivity of the ova and follicular cells varies with their functional states at the time of irradiation. There are also marked differences in radiosensitivity between species. In most laboratory mammals the developing and mature follicles and ova appear to be more radiosensitive than the primordial follicles and ovocytes and 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. Histologically, permanent ovarian sterility is indicated by the lack of ovarian follicles.

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

Care should be used in the extrapolation of data from the mouse to human problems in regard to the ovary. The mouse ovary is peculiar in many respects. In it the primary follicles and ovocytes are exceptionally radiosensitive as 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 radiosensitivity and the irreversibility of the effects of relatively low doses of radiation on the mouse ovary, as compared with ovaries of other laboratory mammals and the human female. In the female mouse a single x-ray dose of 150 r results in permanent sterility.

The size of the litter produced in the initial fertile period after irradiation of female animals is reduced and the size of the litter from irradiated females declines more rapidly with rising dose than the size of the litters from irradiated male mice.

Total body irradiation appears to produce greater effects on the ovary and on fertility in female animals than irradiation of ovaries alone with equivalent doses.

Since sterilization of the human ovary is a radiotherapeutic practice under certain circumstances, considerable data have accumulated on the radiosensitivity of this organ.

Single doses to the ovaries of 125 to 150 r may produce amenorrhea in 50% of women. A single dose of 170 r can produce temporary sterility for a period of 12 to 36 months. A dose of 500 r produces permanent sterility in most women, but young women may require a larger dose. Doses between 500 r and 624 r have produced permanent sterility in 94% of a group of women (34 of 36 patients), and a localized dose of 625 r has produced permanent castration in a whole group of 72 patients.

3. Sterility Doses for Men and Women

It seems quite possible that the single doses necessary to cause permanent sterility in 100% of men and women may not be far

apart. However, there is insufficient information on men to permit an intelligent guess as to the exact amount of the difference.

It would appear that both male and female humans are probably among the most radiosensitive of those mammals studied, with respect to gonadal effects of irradiation. It is also probable that the differences between single temporarily sterilizing doses and single permanently sterilizing doses of radiation are relatively small in the case of humans as compared with most of the laboratory mammals studied. On the basis of the data available the single gonadal dose of x- and gamma-radiation which would permanently sterilize most human males and females may be of the order of 500 to 625 r.

In animals with relatively poor gonadal regenerative capacity, such as the human, chronic irradiation may be relatively of more serious consequence, and this tends to be supported by data from experiments on dogs. It is such exposure which may constitute the greatest practical human hazard as far as sterility is concerned.

A few experimental data indicate greater radiosensitivity in prepubertal animals, especially foetuses.

G. Effects of Irradiation on Growth and Development

This section is concerned with post-natal development and growth and does not include a detailed discussion of the effects of irradiation on prenatal development and organogenesis per se.

Regenerative and repair processes of the body appear to be fairly sensitive to the effects of ionizing radiation and inhibition of these processes may be very persistent, especially if vascular integrity and patency are impaired. Much more quantitative investigation of these aspects of the problem 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 exposure to as little as 24 r per week of whole body irradiation. It has been shown that a significant decrease in body weight can be produced by a schedule of repeated whole body exposures which does not cause any decrease in levels of hemoglobin 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. In general, the greatest effect is seen in the youngest

animals. Localized irradiation of the jaws has been followed by decrease in tooth growth.

Studies on children exposed to the atomic bomb in Japan indicate that growth and maturation are slightly retarded. The production of malformation by exposure of embryos or fetuses to irradiation has been investigated extensively in experimental animals. The production of relatively severe malformations in viable human offspring by irradiation in utero, known from some clinical experience, has been confirmed by studies in Japanese atomic bomb survivors. The study of post-natal effects upon growth produced by irradiation of the foetus, however, has been neglected generally.

An extensive series of measurements on 4800 children at 6, 7, and 8 years after exposure to the atomic bomb at Hiroshima revealed in general that growth was retarded and maturation delayed. In another study involving several hundred children surviving the atomic bombings at Hiroshima and Nagasaki in 1945 and studied in the 2nd, 4th, and 5th years after irradiation, it was reported that the physical growth and development of the children were adversely affected, and the resulting retardation of their height, weight, and skeletal development was still evident at the end of 1950. The investigators expressed the belief that factors other than radiation may have contributed to the effects described. This study has been considered by some to be at variance with other studies on the same material.

Studies of children who had been irradiated in utero during the atomic bombings in Japan are noteworthy. In one series of 74 irradiated and 91 control children, roentgenographic survey failed to reveal differences in incidence of skeletal abnormalities between the exposed and control groups. A study of 4400 individuals who had been exposed to the bomb in utero or as children up to age 10 revealed 33 cases of microcephaly, with associated mental retardation in 15 cases, and 19 cases of leukemia. There were also cases of mild visual disability among those now 16 to 19 years old who were exposed within 1800 meters of hypocenter. Observations on 205 children 4 1/2 years old, who had been exposed at Hiroshima within approximately 1200 meters of hypocenter during the first half of uterine life, indicate that central nervous system defects were produced.

The mechanisms of growth inhibition by radiation are not understood. Biochemical and cytologic studies of animals in which growth has been inhibited appears to be indicated. The late effects, including life-span studies of exposure to ionizing radiation in pre-natal and early life merit further study.

IV. Comments and Recommendations

It appears likely that the after-effects of whole body external irradiation are quite general, consisting of irreversible injury to all the organ systems to at least some degree. Specific organ pathology or the incidence of specific disease is not prominent, however, except following large single doses or high intensity chronic irradiation and in even these cases, for the most part, the disease entities are not unusual, but occur earlier in the life of the animal. Although not clearly established at low chronic dosage levels premature aging with shortening of life span appears to be common to all whole body exposure. This effect is sufficiently large that it may provide a better criterion for limitation of exposure than increased incidence of specific disease.

The effects of partial body irradiation on life-span have not been studied except with internally deposited radioactive materials for which the local dosage is not usually well known. Consequently, comparisons with whole body effects are difficult. With partial body irradiation, when highly localized at least, local pathology is probably the best criterion for exposure limitation.

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

Animals prematurely aged by irradiation have not been studied to determine those changes which presumably have occurred in their physiological efficiency.

Except for alterations of pre-natal development very little is known of the after-effects of either whole or partial body irradiation in the young in comparison to mature animals.

Agents which, when administered to animals at the time of irradiation, permit them to survive doses which are ordinarily lethal, do not, according to scanty existing information, reduce the late effects. Consideration should be given to the possibility of increasing the reversibility of radiation injury and of diminishing thereby the late effects.

In anticipation that definitive information on man can be approached only by extrapolation from animals along with comparison to meager human data, studies on animals should be widely extended, not only with respect to experimental numbers to increase the accuracy of observation, but also to a greater variety of species to ascertain the generality of quantitative dose-effect relations.

V. References

This report is based largely on the following detailed reviews, which were prepared in anticipation of the report. These reviews contain bibliographic references to most of the specific experimental works and reviews consulted in the preparation of the report.

Each of the following papers is an University of Rochester Atomic Energy Project Technical Report.

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APPENDIX V

Various Summaries Prepared by

Committee Members

EFFECTS OF RADIATION ON THE EMBRYO AND FETUS

S. P. Hicks

A. Summary

Ionizing radiations have a specifically destructive effect on certain developing cells of all embryos including those of man. This destruction leads to congenital malformations, the nature of which depends on what stage of development is interrupted. It is rather like damaging a building early or late in its construction. If building blocks in the foundation are knocked out, and the building is finished, it will be "malformed", that is not properly constructed. If the injury occurs at later stages the superstructure will show the defects no matter how carefully the workmen try to remake it.

The damage to the embryo from radiation can be severe or relatively mild depending on the dose of radiation. In laboratory rats and mice malformations can result from as little as 25 roentgens but 400 roentgens may kill the embryo outright. These same figures probably apply to other mammals and man. Twenty five roentgens is far above the dose of x-rays given in ordinary diagnostic procedures in the doctor's office, so that ordinary diagnostic x-rays like chest films do not malform embryos. Harmful effects can, however, result from doses of x-rays given to treat cancer. Pregnant women are not usually exposed to these larger doses, but in the past when such women have been so exposed their babies have been malformed. Similarly some of the Japanese women who were exposed to the atomic bombs bore malformed children.

B. Scientific appendix

The initial pathologic effect of ionizing radiations on the mammalian embryo in the range of 200 roentgens of 250 kv x-rays at 50 r per minute is destruction of primitive non-mitotic differentiating cells. Wherever cells are present in this stage of their growth in the embryo they will be damaged. Because this maturing process shifts from tissue to tissue and from one part of an organ to another it is easy to see how the pattern of malformation changes with time.

In rats and mice, the embryo is usually resistant to doses up to 400 roentgens for the first eight days of its life. When its neural folds and head process begin to form about the latter part of the 9th

day, its sensitiveness increases nearly tenfold, and throughout gestation malformations can be induced.

Malformation is not simply the result of knocking out building blocks and causing a defect. The number of cells killed by 200 roentgens is often way out of proportion to the resulting deformity, and the sites most vulnerable to later malformation seem to be where differentiating cells and induction or early growth of a new structure are most active. Repair from the residual cells that are relatively resistant takes place and a good deal of restitution results, more in some places than others. In the four to ten somite stage, for example, nearly half the cells in the embryo are destroyed, but recovery is so great that a nearly normal animal results except that its eyeballs and optic tracts fail to develop. An embryo irradiated a few hours earlier in the pre-somite stage however develops into a monster with a completely malformed head, while a 20 somite embryo develops an encephalocele, eye, spine and tail defects, lung, heart and urogenital anomalies. The most serious visceral, skeletal, eye and brain defects occur in the early stages of embryonic growth, but the brain, whose differentiation continues into neonatal life, runs a whole gamut of malformations depending on the time at which it is irradiated.

Lower doses of radiation produce lesser defects, greater doses magnify the malformation. Many monstrosities cannot live after birth, while still others, especially those with deficient brains survive into adult life.

RADIATION EXPOSURE AND A DISTURBED ENVIRONMENT

H. L. Andrews

Radiation overexposures may occasionally occur outside of a carefully controlled laboratory environment and in some cases personnel may be called on to do physical labor under adverse conditions following a radiation accident. It would be well, therefore, to keep in mind the effects of a disturbed environment superposed on excessive radiation doses. The meagre evidence comes almost entirely from animal experiments and does not take into account the far-from-negligible psychic components to be anticipated from a human population that knows it has been overexposed.

Exercise at a moderate level, even if prolonged, appears to have little effect on the course of radiation injury. Continuous walking at 0.17 miles per hour for 7.5 - 8.0 hours per day has been used as a standard exercise (1). Mice or rats subjected to this regime for various times up to 21 days post-irradiation showed little effect of the exercise, although the mortality was usually slightly greater in the exercised groups. A typical result with rats following nine days walking showed a 30 day mortality of 76 percent to be compared to 60 percent in the irradiated, non-exercised group.

When conditions are made more severe exercise may have a deleterious effect (2). Irradiated rats, weighted and forced to swim to exhaustion, sometimes in cold water, showed a higher mortality than the non-exercised controls.

Symptoms of radiation injury can be temporarily suppressed but not averted, by hibernation (3) or drastic cooling (4). In mice and rats a moderately low environmental temperature (50° F.) results in a significant increase in mortality over that of the controls. Administration of thyroid or dinitrophenol increase both the metabolic rate and the radiation lethality and this may be the mechanism by which low temperature acts to enhance radiation effects.

To simulate post-irradiation evacuation by air, mice have been maintained for four hours at a pressure equivalent to an altitude of 20,000 ft. (5). There was no demonstrable effect on the mortality statistics. In comparable experiments with rats sublethally irradiated animals withstood daily exposures to simulated altitude better than the non-irradiated controls.

Eating patterns of animals after irradiation differ markedly from one species to another, and extension of data to man may be more uncertain than usual. Enforced fasting for moderate periods has no effect on radiation mortality statistics in mice, rats, and guinea pigs (6) and a low statistical effect (7). From present evidence it would appear that moderate dietary deficiencies or short periods of fasting would not significantly alter the usual radiation syndrome.

In summary it appears that moderate deviations from a normally tolerated environment will be without effect on the course of radiation-induced injury. Extremes of external stress will seriously affect some borderline cases, but even here the effect may be less than would be anticipated from the severity of the situation.

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EFFECTS OF IRRADIATION OF THE NERVOUS SYSTEM*

Webb Haymaker

I. EFFECTS OF RADIATION ON THE NERVOUS SYSTEM OF MAN

A. Effects of Atomic Bomb Explosions in Man

In their study of acute changes in the CNS of the casualties in the atom bomb explosions, Liebow and Warren (1947) and Liebow, Warren and Decoursey (1949) noted during the first 6 weeks after the explosion, hyperemia of the cerebral vessels, minor hemorrhages in the pia and cerebral substance, and traumatic contusions. In cases in which survival was longer than 6 weeks, they found meningitis (with polymorphonuclear leucocytes), abscess formation and sinus thrombosis. Nerve cells were described as well preserved, except for those situated in hemorrhagic and necrotic foci.

The Studies by Uchimura and Shiraki (1952). The material consisted of 37 brains, 24 from Hiroshima and 13 from Nagasaki. The cases were gathered at various distances from the center of explosion. The radius of 1,000 meters is usually considered lethal; 20 brains were from individuals in this area at the time of the explosion. From the radius of from 1,000 to 2,000 meters, 4 brains were obtained. In the other cases the exact distance from the hypocenter was not known.

The survival period varied. Death occurred within 3 to 5 weeks in 24 cases, between 6 and 8 weeks in 5 cases, between 3 and 4 months in 2 cases; and in 6 cases the survival period could not be ascertained precisely, but was probably within several weeks. Blast and heat could be excluded as causes of death, because in all cases burns or external

*This report emphasizes the pathological changes which occur in the nervous system following exposure to various forms of radiation, and the dose levels at which they occur. Numerous references to the literature were included for purposes of providing background for the problems with which the Committee is concerned. Time was too short to allow the author to verify all the references personally. Sources heavily quoted included Zeman, in the Henke-Lubarsch Handbuch (1955), and Bakay, in his The Blood-Brain Barrier (1956). Much valuable help was received from Dr. Samuel Hicks, Member of the Panel. The author wishes to express his appreciation to those who provided reports of the current status of studies in which they are engaged.

injuries were only slight. On the other hand, most of the casualties, excepting those with uncertain case histories, showed those injuries to the hematopoietic organs or mucous membranes which are known to follow radiation.

Symptoms pointing to CNS involvement were scanty. Headache, dizziness, nausea and loss of appetite were regarded as being of cerebral origin. Headache and dizziness disappeared either within one day or lasted from one to two weeks. An important feature was clouding of consciousness. Although in cases with a short survival period it has remained uncertain whether the clouding of consciousness was of cerebral origin, the same disturbance was considered to be cerebral in origin when survival was for several weeks. At any rate it is a fact that some patients did show some impairment of consciousness, whereas the majority remained mentally clear to the end. Apart from this symptom the case histories contain hardly any description pointing to involvement of the brain or cranial nerves. Convulsive seizures were absent.

The age distribution was as follows: 2 cases fell into the first decade, 7 into the second, 14 into the third, 4 into the fourth, 3 into the fifth, 2 into the sixth; and in 5 cases the age was unknown. Thus, two-thirds of the patients were under 30 years.

Uchimura and Shiraki were struck by the fact that 2 of the 3 youngest individuals showed the most extensive changes. One of them, a 7-year-old boy, was in a school within the 1,000-meter radius at the time of the explosion, and died 45 days later with the typical picture of radiation damage. The skin showed only very minor changes. In the last 4 or 5 days he was incontinent, probably because of disturbed consciousness.

In this case the pathological changes were confined to the cerebral cortex and immediately adjacent areas. The parietal lobe was characterized by a diffuse disruption of the cytoarchitectonics of the upper cortical laminae with circumscribed patchy necrotic foci. Similar focal necroses were found in the frontal lobes. In the rest of the cortex they were practically absent, with the exception of a few minimal foci. The necrotic areas were of various shapes: rounded, irregular and even 'geographical.' They were sharply defined and only exceptionally extended down into the subcortical white matter. No focus was found inside the white matter proper. The nerve cells showed diffuse changes. They were markedly reduced in number in the necrotized areas. Remaining cells bore the marks of ischemia or other change. The cell loss was most prominent around blood vessels. In the

altered cortical areas the capillaries and precapillaries had an abundance of endothelial nuclei. Mononuclear cell infiltration was scanty. Glial proliferation was entirely absent from the foci and their surroundings. More conspicuous was an area of softening, the size of the tip of the thumb, situated in the orbital part of brain. This lesion was far more advanced than in the aforementioned foci and reached rather deeply into the subcortical white matter. Inside the focus and in its vicinity the perivascular spaces of the small vessels were considerably enlarged and loaded with lymphocytes and, in places, erythrocytes. Here, too, there was a more or less conspicuous increase of endothelial cells and adventitial argyrophilic fibrils.

Similar pictures of focal cortical necrosis with or without vessel changes were found in less degree in 5 other cases. The ages range between 14 and 28 years. Again, the area of predilection was the anterior half of the brain. The changes in the hippocampal formation and cerebellum furnished further proof that circulatory changes had occurred. In a 17-year-old boy who survived for 56 days the hippocampal formation showed selective loss of nerve cells in Sommer's sector. No vascular changes were present here. Almost identical pictures, but still less pronounced, were noted in two further cases. The Purkinje cell layer of the cerebellum was another favored site of pathological change. In 5 cases this layer showed 'glial shrubbery' emanating into the molecular layer. Other parts showed more advanced nuclear pyknosis. The blood vessels are usually unchanged.

Thus, the pathological changes pointed to disturbance of a circulatory mechanism. Other forms of circulatory changes were also seen. Considering hemorrhages first, there were only 2 brains which showed macroscopically demonstrable hemorrhages, one subpial, the other in the white matter of a hemisphere. On the other hand, microscopic examination revealed small extravasations of blood in various parts of the central nervous system in 26 cases. The changes in a 23-year-old man with a 26-day course of illness were, however, somewhat different. In this case, punctate hemorrhages were visible microscopically, their maximum being in the white matter of a hemisphere. This case was characterized by yet another change, best studied with Weigert's fibrin stain and to even greater advantage by Holzer's crystal violet stain for glial fibers. These methods disclosed a delicate dense network the radii of which surrounded longitudinally cut vessels. Such alterations did not coincide with the sites of hemorrhage. The positive fibrin stain was interpreted as signifying fibrinous transudation across the vessel wall.

Over 10 brains prepared with various stains, including azan, failed to show a definite picture of coagulation necrosis or plasma extravasation such as some authors (pp. 6a & 20) have reported in brains injured by roentgen radiation.

Annular hemorrhages of the conventional type were found in occasional organized foci of pons and cerebellum in a 19-year-old individual with a 55-day illness.

It has been mentioned that 2 of the 3 cases in the first decade showed the most marked brain changes. The extensive cortical necrotized foci with vascular changes in one of them have been referred to in the foregoing. The other case, concerning an 11-year-old girl who was exposed to the explosion in the 2,000 meter radius, showed not only the typical clinical picture of radiation injury, but also definite psychological changes during the last 3 weeks of her life. During the day she would be somnolent and during the night delirious. For the last 4 days she failed to react to verbal stimulation and kept murmuring softly to herself. She succumbed to her weakness on the 47th day after exposure. In this case the pathological changes were entirely different. The basal ganglia were affected, whereas the cerebral cortex was relatively spared. The nerve cells of the cerebellar dentate nucleus were either completely destroyed or very severely altered. Not only was this nucleus damaged, but also other, symmetrical, nuclei which will be described next.

The subthalamic nucleus showed different, but equally striking change. The nucleus was riddled with multiple small holes. Close inspection revealed that these corresponded to the areas where nerve cells had dropped out. The basic tissue structure was well preserved, showing hardly any reaction to the injury. On the contrary, the glial cells had suffered regressive changes. The general appearance resembled the picture of status spongiosus. An exact replica of this change was found in the reticular portion of the substantia nigra, especially in its inner third. Here, the large melanin and other nuclear material was seen lying in spaces left by the destroyed nerve cells. The putamen and globus pallidus on both sides showed somewhat different changes. The capillary network was incrustated with pseudocalcareous material giving the iron reaction. The nerve cells escaped damage. In the globus pallidus the material was not confined to the blood vessels, for it was present in the tissue generally, in the glial cells, and even in the large nerve cells. Not infrequently ganglion cells in the external part of the pallidum had been wiped out by these deposits. The amount of pseudocalcareous deposit in this case far exceeded that seen normally, especially if one considers the fact that rather numerous

particles of a similar nature, almost resembling cocci, were found in the perivascular spaces.

The motor nuclei of the cranial and cervical nerves showed an unusual picture, namely, large intracellular vacuoles co-existing with relatively well preserved Nissl substance. In some cases this change was seen only sporadically, while in others it was so frequent as to involve the majority of the nerve cells present in a microscopic field. The question arose whether this was an artefact due to fixation, for the alteration which showed up in the alcohol-treated sections of 11 cases was not found regularly in the formalin-treated sections from the same cases. Evidence was adduced which strengthened the belief that a certain proportion of the motor nerve cells had undergone pathological change although no clinical evidence of cranial nerve involvement was present.

Summary of the Microscopic Changes. Of the 37 cases showing the typical clinical course of radiation injury, significant lesions were found in the CNS in 32. In the other 5 cases, all adults over 22 years, only minor and sporadic extravasations of blood were detected.

If the more or less pronounced, diffuse loss of nerve cells in some cases is disregarded, the changes may be divided into two groups. The more important first group was characterized by its close association with disturbances of circulation. The other group was distinguished by a process of degeneration, i. e., destruction of nerve cells in certain cerebral nuclei.

With reference to the first group, small diapedetic hemorrhages were a major feature but their presence in 26 cases was detected only microscopically, with the exception of 2 in which larger ones were found. More significant was the focal cortical destruction pointing to circulatory origin. This type of lesion was encountered in 6 cases and was particularly marked in a 7-year-old boy. The blood vessels within and around such necrobiotic foci were sometimes thickened and infiltrated with lymphocytes. In another case there were areas around the medium-sized vessels of the white matter which stained well with fibrin and glial fiber stains. These justify the assumption of extravasation of plasma. A thorough search for progressive and regressive alteration of the supporting tissue did not yield anything significant in any of the cases.

Concerning the second group a peculiar loss of cells in the extrapyramidal nuclei was noted bilaterally in an 11-year-old girl.

The pseudocalcareous deposits, also present in the capillary walls of the lenticular nucleus, must be associated with a disturbance of circulation. The large vacuoles seen in several cases in the motor nuclei were considered problematic.

Discussion. There was agreement that the main cause of death occurring weeks after exposure to atomic radiation had to be sought in the effects on both CNS and the viscera in general of the gamma rays and neutrons liberated by the explosion. Comparing the changes with those observed in X-radiation reported in the literature, Uchimura and Shiraki felt that a close relationship existed, namely, the presence of minor hemorrhages, circumscribed focal cortical necroses, cell loss in certain parts of the hippocampal formation, 'glial shrubbery' in the cerebellar cortex, changes in the endothelium of cerebral vessels, and perivascular lymphocyte infiltrates.

On the other hand, they recognized certain dissimilarities. First, the changes in the CNS were severe only in a few atomic bomb explosion cases; in the majority, though subjected presumably to extreme amounts of radioactivity, the alterations were at most only slight. Secondly, some of the atomic bomb explosion cases displayed necrobiotic reactions at a relatively early stage, while vessel-wall changes were sometimes appreciable and sometimes not. Injuries due to atomic energy thus lacked the pathological uniformity which might be expected. This diversity may have been due partly to individual variations of radiosensitivity (including the role played by age) and partly to conditions of exposure, e. g., distances from the center of explosion and the degree of shelter. Further differences lie in the size of the field exposed (i. e., the whole body in the bomb explosion and in the delivery of an enormous momentary dose). Notwithstanding these considerations, Uchimura and Shiraki felt justified in concluding that both the circulatory changes and the early involvement of blood vessels are related to the noxious effect of radioactive penetration. In particular, the rather frequently encountered parenchymal destruction without evidence of vessel-wall changes suggested the possibility of a functional circulatory disorder such as vasoconstriction or dilatation.

The relatively short duration of illness may be held responsible for the absence of the late changes reported by Scholz and others (pp. 6a & 20), such as the infiltration of the vessel walls by blood plasma. In this connection, Uchimura and Shiraki pointed, however, to 2 cases, one with questionable transudation of fibrin, the other with massive pseudocalcareous deposits in the lenticular nucleus. But a convincing picture of plasma extravasation followed by coagulation necrosis was not observed. At least at this stage following Atomic bomb exposure,

the extravasation of plasma did not seem to be an important event.

Uchimura and Shiraki were interested by the pseudocalcareous deposits because certain basal nuclei were selectively, severely, and bilaterally affected, whereas the remaining nuclei and the vascular system were, on the whole, well preserved. The pathogenesis of this ganglion cell destruction puzzled them in view of previous reports in the literature in which the radio-resistance of nervous parenchyma, including nerve cells, is stressed. Considering the lenticular nucleus lesion alone, they felt that a circulatory disturbance might be made partly responsible because the marked pseudocalcareous deposits must have contributed to the cell destruction. According to all investigators, these deposits represent a protein precipitate of blood-plasma origin. However, the cell destruction in the lenticular nucleus seems too severe to be caused entirely by this substance. The changes could have been due partly to compression of branches of the anterior choroidal arteries secondary to presumed brain swelling occurring in early stages following the atomic bomb exposure.

The causal factors were regarded as of a complex nature. The radiation which affected the whole body led to a severe functional disturbance of the hematopoietic system with attendant high-grade anemia and marked platelet loss. Most of these cases came to autopsy in a state of severe anemia. Clinicians and pathologists alike have assumed that the hematological disturbance plays an essential part in the production of hemorrhages and other circulatory disturbances in many systems. One must not fail to consider that the metabolic disorders which gradually arise in various injured organs may affect the CNS secondarily. Anoxemia due to the highgrade anemia might play a certain pathogenic role considering the susceptibility of nervous tissue to oxygen deprivation. But Uchimura and Shiraki argued that the selectivity of the lesions and the relative resistance of motor nuclei against injury in general raise doubts with regard to the effects of anoxemia. All these complexities account, they felt, for the great difficulty in correlating the diverse pathological findings with any single etiological factor. It is, however, striking that changes were found in the motor nuclei of the basal ganglia, with the exception of the red nuclei. Similar pictures including the changes they saw in the nuclei of the motor cranial nerves are exceedingly uncommon under other conditions. They felt that it is also possible that extrapyramidal nuclei may have a special affinity for radioactive substances in view of their particular iron metabolism.

1. Microcephaly in Children of Exposed Mothers

Sutow (1954) and Miller (1956) stated that of the children born to 4,400 pregnant women exposed to the atomic bomb explosion, microcephaly occurred in 33, and that in 15 of the 33 there was associated mental retardation. Mild visual disability was encountered in a larger number. Plummer (1952), in studying 205 4-1/2 year-old children exposed to the atomic bomb explosion during the first half of intra-uterine life, observed that developmental defects can occur in the CNS if the mothers were within approximately 1,200 meters of the hypocenter without effective shielding.

B. Effects of X- and Radium Radiation in Man

No information is available on the precise dosage of radiation necessary to produce alterations in the CNS of man. The tolerance limit of the human adult brain is estimated to be 130 to 150 per cent of the therapeutic dose (Kaplan, 1941; Zeman, 1955). According to Hicks (1953), in the ordinary course of treatment with repeated small doses of X-radiation, no change becomes evident until the accumulated dose is about 3,000 to 4,000 r.

Early CNS Reaction to X-radiation in Man. Observations in this field have been few. Pendergrass, Hodes and Groff (1940) have found severe inflammatory and thrombotic brain changes a few days after exposure of the scalp to radium, but ascribed the changes to a pre-existing brain lesion. In a 3-1/2 year-old boy, who died 3 months after an epilation dose, van Bogaert and Hermanne (1948) found perivascular lymphocyte-plasma cell infiltrates, but they did not believe that the infiltrates were due to the radiation. Brain edema is said to develop 24 to 48 hours after irradiation for intracranial tumor (Beclere, 1928).

Late CNS Reaction to Radiation in Man. In accidental overdose, especially in the application of radium to skin tumors in the region of the head, Hicks (1953) has observed progressive blood vessel changes in the brain. Endothelial cells became swollen, and fibrinoid necrosis sometimes occurred in the walls of small vessels. Thrombi sometimes formed in damaged vessels. Several weeks or months after exposure to excessive doses of X-radiation, the connective tissue of vessels underwent hyaline thickening (hyalinosis). This change was much like that seen in arteriosclerosis. The vessel changes not infrequently led to infarction. A distinguishing feature was that in radiation, bizarre large fibroblasts develop in the adventitia of affected vessels. These fibroblasts, identical with those found elsewhere in the

body following irradiation, may be large and sometimes lobulated or multiple. According to Behrend and Ostertag (1949), the changes in the irradiated brain are so typical that they can be diagnosed by brain biopsy.

One of the earliest observations in this field was made by Fischer and Holfelder (1930). The temporal region of the scalp had been irradiated for carcinoma 7 years earlier, subsequent to which the patient had had attacks of restlessness, aphasia, and numbness and twitching of the left hand and foot. In exploring the underlying brain, they found it blue and full and infiltrated by an amyloid-like substance. This substance, commonly noted by others, has been found not to be amyloid (Kalbfleish, 1946; Markiewicz, 1935; Scholz and Hsü, 1938). It is of interest that Basset and Löwenberg (1948) have reported amyloid degeneration in astrocytes following therapeutic X-radiation.

Markiewicz (1935) described a case, that of a travelling salesman aged 34 who became ill 4-1/2 to 5 years after receiving X-radiation for a scalp condition. Blindness, paraplegia and epileptic attacks developed. A radiation ulcer formed in the occipital region. Death occurred 2 years after the onset of neurological disturbances. Examination of the brain disclosed gross atrophy of the occipital lobes. Microscopically there were multiple hemorrhagic necrotic areas, mostly in the cortex and especially in the occipital-parietal region. The case of Scholz and Hsü (1938) is of interest in that although the entire skull had been irradiated equally, the brain damage was focal and disseminated. The non-homogeneity of the damage was thought to depend on local differences of vascular architecture. In some cases the damage tended to be greatest in the subcortical white matter, and decreased as the pia was approached (Markiewicz, 1935; Pennybacker and Russell, 1948; Zeman, 1949, 1950).

Damage to the brain due to radiation for intracranial tumor at conventional doses has been reported by Chükrü-Aksel (1935), Pennybacker and Russell (1948), and Tarlov (1937). On the other hand, Fenyes and von Kiss (1938) were unable to find any changes in the brain of an 11-year-old girl who had received 2,600 r for cerebellar sarcoma.

The gross picture of the irradiated human brain has varied in a rather wide range. The meninges (including the dura mater) may be thickened and fibrotic (Chükrü-Aksel, 1935; Pennybacker and Russell, 1948; Tarlov, 1937; Zeman, 1955). The brain may resemble fish meat (Markiewicz, 1935), be extensively softened (Scholz and Hsü, 1938), or undergo profound sloughing so that a large cavity forms (Kalbfleisch,

1946). The cortex may be pallid and the subcortical white matter beset with petechiae (Pennybacker and Russell, 1948; Zeman, 1955).

Microscopically the picture is characteristic and almost specific. The van Gieson stain brings out the changes to best advantage. Chiefly the medium-sized vessels undergo collagen swelling (hyalinosis) or fibrotic scarring. Surrounding brain substance is necrotic as the result of inundation by a plasma substance in which fibrin is sometimes demonstrable. Similar regressive changes are seen in the choroid plexus and meninges, including, in one case, the dura (Markiewicz, 1935). Endothelium is decimated or focally proliferated. The elastica is often split and may be the seat of fatty degeneration. Sometimes it has vanished. The muscularis may suffer severely and be replaced by a connective tissue scar. Not infrequently the changes resemble those in arteriosclerosis. Perivascular foci of brain damage of different duration are common.

Spinal Cord of Man. According to Hicks (1953), the spinal cord is rarely damaged at dose levels less than 3,000 r, and in some cases no clinical disturbances have occurred after exposure to allegedly higher doses.

Peripheral Nerves of Man. Peripheral nerves are relatively resistant to the damaging effects of ionizing radiation. Hicks (1953) has noted that when the skin is irradiated, the subcutaneous connective tissue becomes hyalinized and afibrillar, elastic fibers undergo marked degeneration, and bizarre large fibroblasts form. Blood vessels in the field undergo degenerative and proliferative changes and may become thrombosed. In such a field the nerves often escape noticeable injury. When exposed to several thousand r, the cutaneous nerves may be damaged secondarily by vascular occlusion etc., or be entirely spared. John (1946) has found myelin and axis cylinder degeneration in the cutaneous nerves of the axillary region some 17 years after irradiation of the axilla.

Brain damage following therapeutic irradiation for intracranial tumor has been described in a few cases. Little of a positive nature was found by Alpers and Pancoast (1933) in the brain tissue adjacent to irradiated gliomas, which led them to suggest that the conventionally used dose could be raised: they observed merely a reduction of cortical nerve cells with an accumulation of fat in other nerve cells as well as in capillary endothelium and astrocytes. Four cases were presented by O'Connell and Brunschwig (1937). In 2 cerebral gliomas, in adults aged 45 and 23 years respectively, 13,275 and 15,500 r had been given over 5 to 12 months, respectively, after operation, with death occurring

12 to 20 months after initiation of the treatment. The other two cases were medulloblastomas in children.

In considering in some detail the glial and other retrogressive changes in the neighborhood of non-irradiated tumors, O'Connell and Brunschwig reached the conclusion that irradiation produced, both in the cerebral cortex and white matter, 1) retrogressive changes in nerve cells with striking accumulation of lipochrome, damage to neurofibrillae, and so on, 2) clasmatodendrosis, lipochrome deposition, hypertrophy and hyperplasia of astrocytes, 3) swelling of oligodendroglia, 4) hypertrophy and some increase in number of microglia and of lipochrome pigment within them, with development of rod cells and occasionally of gitter cells, and 5) lipochrome deposition in capillaries of the cerebral cortex and the development of macrophages in the walls of larger vessels. No changes were observed in the myelin sheaths. The opinion was expressed that the alterations in the brain elements were direct effects and were not secondary to blood vessel damage. The most striking radiation changes were in the brain which had harbored the tumor for the shortest time, but which had received the heavier dose of radiation. Of the 2 medulloblastomas, the pathological changes were most profound in the case of longest survival after irradiation. Changes of a similar nature have been recounted by Wachowski and Chenault (1945). See also the paper of Frazier and Alpers (1937). In their discussion of radiation therapy of tumors, Arnold, Bailey and Harvey (1954b) pointed to 3 cases in which very marked degenerative changes occurred in fiber tracts and cellular constituents of the brain stem following exposure to 400 kv and 23 mev X-rays at tissue doses of 4,500 to 7,500 r.

Lorey and Schaltenbrand (1932) recorded a case of brain damage in a 5-year-old girl following X-irradiation of a scalp lesion. Complete epilation occurred in 3 weeks. One year later, epileptic attacks and left hemiparesis developed. At 12 the left side of her body was underdeveloped. Minor epileptic seizures were common. Not only were the scalp and cranium damaged, but there was also evidence of dural hematoma. In a second paper, Schaltenbrand (1935) reported that trepanation revealed pachymeningitis hemorrhagica in this case. He then described a second case, that of a 21-year-old woman, who had been given radiation therapy for a scalp lesion when she was 9 years old. At 15 she became nervous and emotional. Later she had an episode of delirium associated with fever. At hospital she was found to have aphasia, right flaccid hemiparesis, deviation of her eyes to the left, and clonic twitchings of the right arm and face. At 21 she was re-admitted to hospital because of increased frequency of epileptic attacks. Little hair remained on the scalp. X-ray examination disclosed patchy

defects in the cranium and in one area some flaky intracranial calcification.

With reference to the effect of irradiation on the amount of cerebrospinal fluid, Skefer (1936) stated that small doses diminished the production, after which production was depressed.

II. THE EFFECTS OF BARIUM¹⁴⁰-LANTHANUM¹⁴⁰ RADIATION ON THE CNS AND PITUITARY GLAND IN MONKEYS

This report, by Haymaker *et al.* (1954, 1956), covers a study of the CNS of 67 young adult male monkeys and the pituitary glands of 77 monkeys receiving head-body barium-lanthanum irradiation at a rate of 1,000 r per minute. The air dose levels were 1,000 to 30,000 r. Most of the animals were severely incapacitated shortly after exposure, as manifested by prostration, ataxia, nystagmus, and retching and vomiting.

The survival period of these animals, shown in Table I, was highly variable. Thus, whereas 5 animals receiving 5,000 r died within 4 hours, 8 animals receiving 30,000 r survived until the 5 to 18 hour period. Further, of the 12 monkeys exposed to 2,500 r, 5 died within 5 hours and the remainder in from 3 to 8 days. At all dose levels from 2,500 to 30,000 r the number of deaths up through the 5th hour was, however, approximately equal. Survival beyond the 2d day occurred only in animals receiving 5,000 r or less. No animal survived more than 10 days.

Pathological changes were found in 54 of the 67 brains. Of the 11 animals which died within 2-1/2 hours after receiving doses of from 2,500 to 30,000 r, pathological changes were noted in 3. In these 3, the earliest change was at 1 hr. and 4 min.; it consisted of swelling of the walls of meningeal and brain vessels and the presence of pools of plasma perivascularly. From 2-1/2 hours onward the pathological changes following irradiation were usually clear-cut, but there were rather wide variations in incidence, site, apparent time of onset, character, and intensity of the lesions.

The most frequent pathological change was that of acute inflammatory cell exudation, presumably in response to altered permeability of vessel walls. Vasculitis was evident in the meninges, choroid plexuses and CNS in 35, 34 and 41 of the 67 animals (51, 50 and 61 per cent) respectively. Data on the meningitis are given in Table II. At all dose levels of 2,500 r and above, focal (nonbacterial) meningitis,

TABLE II

The Incidence, Time of Occurrence and Severity of Meningitis in
67 Monkeys Following Total-Body Radiation

Radiation Dosage (r)	No. of Animals Irradiated	Animals With Meningitis (Optimal Period)		Latest Example	Range of Severity (Average)*	Animals Without Meningitis		
		No. of Animals	Earliest Example			No. before Optimal Period	No. during Optimal Period	No. after Optimal Period
1,000	6	0	-	-	-	-	-	-
2,500	12	4	2 hr., 47 min.	147 hr., 12 min.	0-3+ (1+)	2	4	2
5,000	15	7	1 hr., 04 min.	126 hr., 15 min.	0-3+ (2+)	1	5	2
10,000	11	8	3 hr., 47 min.	32 hr., 36 min.	0-4+ (2+)	3	0	0
15,000	2	2	4 hr., 47 min.	18 hr., 10 min.	2-3+ (2+)	0	0	0
20,000	10	6	2 hr., 30 min.	6 hr., 00 min.	0-3+ (2+)	2	2	0
30,000	11	8	3 hr.,	13 hr.,	0-3+ (2+)	2	1	0
Totals	67	35				10	12	4

*These values take into consideration the animals without meningitis which died during the optimal period.

TABLE III

The Incidence, Location, Severity and Time of Occurrence of Vasculitis in the CNS of 67 Monkeys Following Total-Body Radiation

Radiation Dosage (r)	No. of Animals Irradiated	No. of Animals Affected	Incidence of Involvement (Upper Figure) and Location of Vasculitis and Range of Severity (with Average) (Lower Figure)								Period of Involvement		
			Cerebral Cortex	Cerebral White Matter	Cerebellar Gray Matter	Cerebellar White Matter	Basal Ganglia	Brain Stem	Spinal Cord	Earliest Example Hr.:Min.	Latest Example Hr.:Min.		
1,000	6	1	1 1+(1+)	0	0	0	0	0	0	0	0	123:56	123:56
2,500	12	4	4 1-3+(2+)	2 0-3+(2+)	1 0-2+(1+)	1 0-1+(1+)	2 0-1+(1+)	2 0-1+(1+)	1 0-2+(1+)	1 0	0	2:47	147:12
5,000	15	8	6 1-3+(2+)	7 1-4+(3+)	3 0-2+(1+)	3 0-2+(1+)	7 1-3+(2+)	7 1-3+(2+)	4 1-3+(2+)	1 1+	1	1:04	126:15
10,000	11	9	9 1-4+(2+)	6 1-3+(1+)	4 0-2+(1+)	5 0-3+(1+)	9 1-4+(2+)	9 0-3+(2+)	7 0-3+(2+)	4 2+	4	3:30	32:36
15,000	2	2	2 0-1+(1+)	1 1+(1+)	0 0-0(0)	1 0-3+(2+)	2 1+-2+(2+)	2 1+-2+(2+)	2 2+-3+(3+)	1 2+	1	4:47	18:12
20,000	10	8	8 1-3+(1+)	8 1-2+(1+)	6 0-2+(1+)	6 0-3+(1+)	8 1-3+(1+)	8 0-4+(2+)	7 0-4+(2+)	4 2+	4	2:30	6:00
30,000	11	9	9 1-4+(2+)	5 0-4+(1+)	3 0-4+(2+)	3 0-4+(1+)	4 0-4+(2+)	7 0-4+(2+)	7 0-4+(2+)	4 2+	4	3:17	14:32
Totals	67	41	39	29	17	19	32	28	28				

choroid plexitis and CNS vasculitis were often apparent in the first 2 or 3 or 4 hours after irradiation.

Data of the CNS vasculitis are given in Table III. At early stages the vasculitis are more common in the grey than in the white matter of the brain. Of the grisea, the structures most often affected were the cerebral cortex, basal ganglia and cerebellar nuclei, in that order of frequency. The brain stem suffered about as much as the basal ganglia. The spinal cord was considerably less affected. The vessels of the cerebellar cortex were virtually spared. Vessels of the white matter were affected later than those in the grisea, i. e., beginning at about 12 hours after irradiation. Rather numerous vessels showed focal loss of endothelial cells. Presumably the cells had been damaged sufficiently to drop off into the blood stream. Evidence of damage of intact endothelial cells was very uncommon. Swelling or necrosis of collagen of larger vessels was also decidedly infrequent.

Sponginess or actual disruption of cerebral white matter perivascularly, usually of microscopic proportions, was noted in only 5 of the animals. All these animals had survived for relatively long periods of time (2 or 3 or more days) after radiation doses of 5,000 r or above. In such foci the brain substance was often invaded by leukocytes, mostly neutrophils. In rare instances vessel walls and surrounding brain substance contained a heavy fibrinous exudate and there was advanced destruction of axis cylinders and myelin sheaths and infiltration of many leukocytes in a wide zone (1.0-2.0 mm.) perivascularly. Fat-laden gitter cells were found in an occasional spongy perivascular zone. The perivascular sponginess or disruption was ascribed to a combination of tissue ischemia and the presence of edema fluid secondary to vasculitis.

Axis cylinder and myelin destruction in the white matter unassociated with vasculitis was rare, being observed in only 2 cases. In both instances the affected areas were few and tiny.

Evidence of nerve cell damage in the cerebrum was scanty. There were, however, 3 cases, all of relatively long duration following irradiation doses of 5,000 to 30,000 r, in which severe cortical necrosis of the ischemic type had occurred. The necrosis was of laminar distribution, involving upper or middle or all laminae. Leukocytes had overrun the necrotic areas.

There were clear-cut but rather minor changes in numerous microglia of the white matter diffusely in cases of relatively long duration. Oligodendroglia were pyknotic, but apparently no more frequently

than those in the control animals. Astrocytes in perivascular spongy areas usually showed evidence of activation.

Granule cells of the Cerebellum were pyknotic in 30 of the 67 animals (45 per cent) (Table IV). The pyknosis was observed only in the dose range from 5,000 to 30,000 r, and occurred earlier and was more severe and more widespread at the higher dose levels. Since the pyknosis was not observed in animals surviving the longest, it was regarded as a transitory phenomenon. Purkinje cells showed striking regressive changes, but apparently no more so than in the controls.

Basophil (beta) cells of the anterior pituitary were selectively affected in 31 of 76 cases (41 per cent) (Table V), the alterations consisting of nuclear pyknosis and conversion of the cytoplasmic granules into a dense, homogenous Schiff-positive mass. These changes were observed only at dose levels of 10,000 r and above, but there was no consistent correlation between the number of injured cells and dose level in this range. In incidence and time of occurrence, the pyknosis of basophil cells rather closely paralleled that of the cerebellar granule cells.

Neurosecretory substance (Table VI) seemed to have disappeared from the hypothalamohypophysial system more rapidly than can be explained by dehydration alone. Local irradiation and emotional stress may have been contributing factors.

III. EFFECTS ON THE CNS AND PITUITARY GLAND OF HEAD, BODY AND HEAD-BODY COBALT⁶⁰ (GAMMA) RADIATION IN MONKEYS

This study, carried out by Vogel, Hoak and Haymaker (1956), was performed on 48 macaque monkeys with a view to shedding light on the pathogenesis of acute morphological changes in the CNS following head-body irradiation. The general plan consisted of radiating the animal at a tissue dose level of 10,000 r, at the rate of about 1,000 r per minute, and sacrificing them by decapitation after periods of 2, 4, 8, 12, 24, 48, 72 and 96 hours. There were 3 groups of animals, 16 in each group. One group received radiation to the head with the body shielded, another to the body with the head shielded, and the third to the entire animal. Five monkeys served for control purposes. The viscera of all these animals were studied in detail. The changes in the brains of the animals irradiated to the head or to the head-body were much the same as the monkeys receiving Ba¹⁴⁰ - La¹⁴⁰ radiation recounted on the foregoing pages. On the other hand, the animals exposed solely to body radiation and the control animals showed no visible CNS changes.

TABLE IV

The Incidence, Time of Occurrence and Severity of Pyknosis of the Granule Cells of the Cerebellum in 67 Monkeys Following Total-Body Radiation

Radiation Dosage (r)	No. of Animals Irradiated	Animals With Pyknosis of Granule Cells			Animals Without Pyknosis of Granule Cell			
		No. of Animals	Earliest Example	Latest Example	Range of Severity (Average)*	No. before Optimal Period	No. during Optimal Period	No. after Optimal Period
1,000	6	0	-	-	-	-	-	-
2,500	12	0	-	-	-	-	-	-
5,000	15	4	9 hr., 04 min.	153 hr., 30 min.	0-4+(1+)	5	6	0
10,000	11	6	5 hr., 10 min.	13 hr., 40 min.	1+-2 (1+)	4	0	-
15,000	2	2	4 hr., 47 min.	18 hr., 10 min.	-	-	-	-
20,000	10	8	2 hr., 30 min.	6 hr., 00 min.	1+-4+(3+)	2	0	0
30,000	11	10	1 hr.,	14 hr.,	1+-4+(2+)	1	0	0
Totals	67	30				12	6	0

*These figures take into consideration the animals without meningitis which died during the optimal period.

TABLE V

The Incidence, Time of Occurrence and Severity of Pyknosis of the Basophil Cells of the Anterior Lobe of 76 Pituitary Glands. 1 indicates scattered basophil cell pyknosis, 4 a nearly uniform pyknosis of these cells.

Radiation Dosage (r)	No. of Animals Irradiated	Animals With Pyknosis of Basophil Cells			Animals Without Pyknosis of Basophil Cells		
		No. of Animals	Earliest Example	Latest Example	Range of Severity (Average)*	No. before Optimal Period	No. during Optimal Period
1,000	6	0	-	-	-	-	-
2,500	10	0	-	-	-	-	-
5,000	16	1	17 hr., 40 min.	17 hr., 40 min.	-	-	-
10,000	23	15	2 hr., 10 min.	26 hr., 50 min.	0-4+(2+)	3	2
15,000	2	2	4 hr., 47 min.	18 hr., 10 min.	-	-	-
20,000	10	7	2 hr., 30 min.	6 hr., 00 min.	0-4+(3+)	3	0
30,000	10	7	3 hr., 28 min.	14 hr., 32 min.	0-4+(3+)	2	1
Totals	76	31			8	3	3

*These values take into consideration the animals without basophil cell pyknosis which died during the optimal period.

TABLE VI

Data on the Serially Sectioned Hypothalamus and Neurohypophysis Stained for Neurosecretion. There are 34 experimental monkeys and 3 controls. 0 indicates presence of granules in nerve cells of the supraoptic and paraventricular nuclei and fiber tracts; 1 to 3 indicates degree of depletion of granules from these sites.

AFIP No.	Dose (r)	Time Hr. Min.	Hypo- thalamus	Neurohypoph.	AFIP No.	Dose (r)	Time Hr. Min.	Hypo- thalamus	Neurohypoph.
602563	2,500	3 16	1+	-	602604	20,000	4 40	2+	0
248402	2,500	54 40	3+	3+	602605	20,000	4 58	2+	-
248398	5,000	3 27	0	1+	602600	20,000	5 22	1+	-
602555	5,000	13 7	0	0	602603	20,000	6 00	2+	3+
248404	5,000	98 43	3+	4+	602587	30,000	1 53	0	0
248405	5,000	126 15	2+	3+	602588	30,000	3 17	2+	-
602543	10,000	3 47	2+	0	602581	30,000	3 17	0	0
602545	10,000	5 10	0	1+	602590	30,000	3 28	2+	1+
602550	10,000	6 10	1+	2+	602580	30,000	4 10	0	-
602541	10,000	10 20	0	0	602586	30,000	4 30	2+	-
602539	10,000	12 15	2+	2+	602577	30,000	5 42	1+	0
602544	10,000	13 40	2+	0	602585	30,000	6 52	2+	0
248400	15,000	4 47	-	1+	602584	30,000	10 24	2+	0
248401	15,000	18 10	2+	2+	602583	30,000	13 45	2+	-
602606	20,000	1 15	0	0	248399	30,000	14 32	2+	3+
602608	20,000	2 30	2+	1+	248406	Control		0	0
602601	20,000	2 40	0	-	248407	Control		0	0
602607	20,000	4 15	0	-	602579	Control		0	0
602591	20,000	4 39	1+	-					

Since much tissue destruction occurs after head-body exposure to massive doses of radiation, it has seemed possible to some workers that certain of the decomposition products may induce cytological alterations in the brain. The observations derived from the present study provide strong evidence, however, that the acute pathological changes which occur in the CNS of monkeys after head-body exposure to high intensity gamma radiation are direct effects of the ionizing rays and are neither initiated by nor perceptibly enhanced by any supposed toxic products liberated in the body. The same has been found to apply to the eye, for acute cytological alterations in the retina as well as cataract formation have been observed only when irradiation is administered directly to the region of the orbit. On the other hand, when bone marrow is locally irradiated, widespread bone marrow alterations develop.

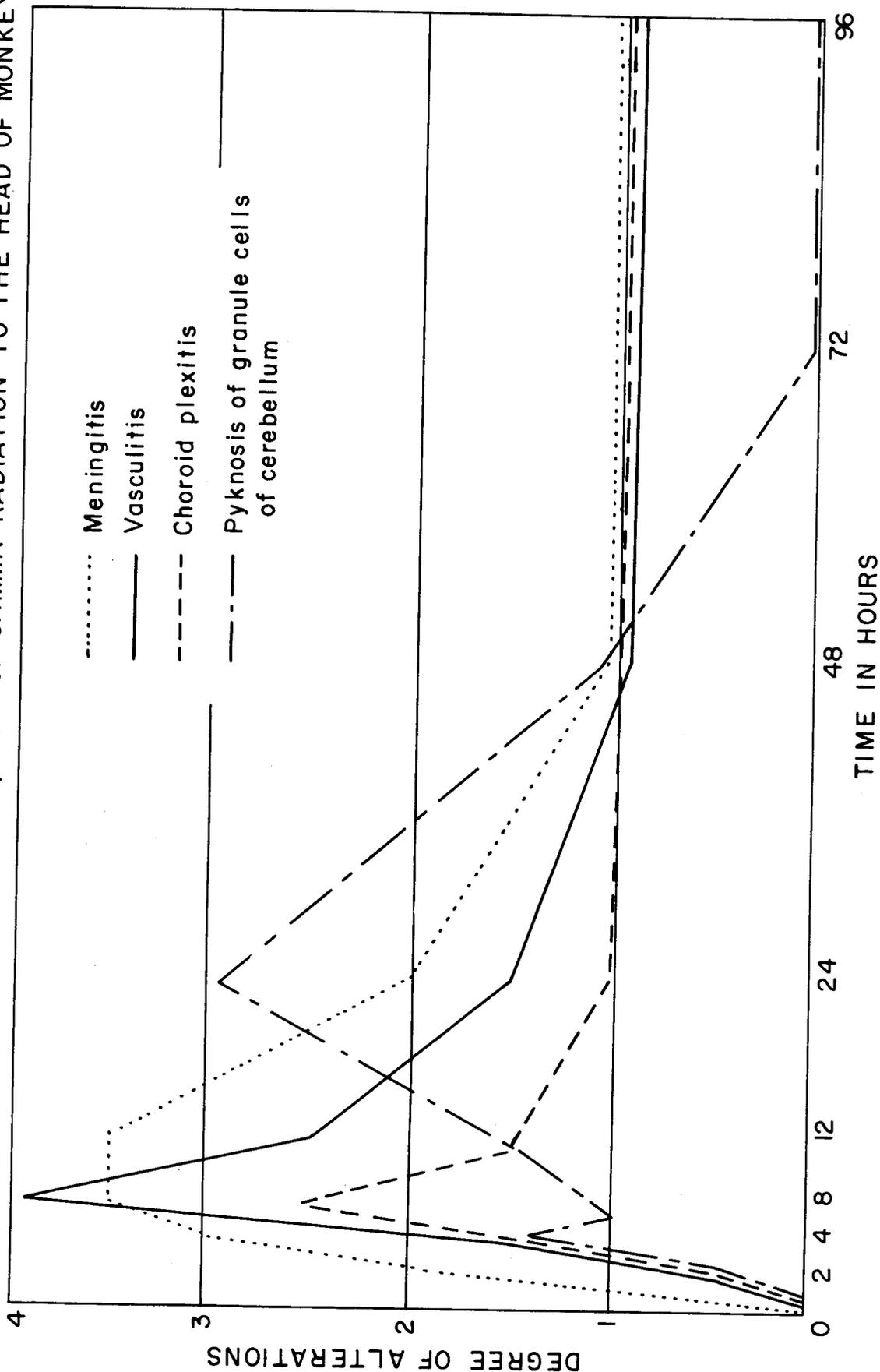
The sameness of the cytological changes in the gastrointestinal tract and hematopoietic organs after body and after head-body irradiation in this series of monkeys suggests that the structural and functional derangement that occurs in the brain after massive doses of head irradiation plays no appreciable role in the pathogenesis of the cytological responses in the body.

It was evident that the meningitis, vasculitis and choroid plexitis were transitory (Fig. 1). The absence of consistent structural alterations in the collagen or elastica or lining cells in meninges, choroid plexus or vessels leaves obscure any possible relationship that might exist between the acute and transient inflammatory response and the progressive chronic proliferative changes that are induced with time in these tissues by lesser doses of radiation. It is of interest that basophil cells of the pituitary gland underwent destruction. As to the pyknosis of the granule cells of the cerebellum, the evidence at hand, namely, the absence of karyorrhexis, neuronophagia, clasmotodendrosis, lysis or numerical decrease in the cells by the 96th hour, suggests that cobalt⁶⁰ at the 10,000 r dose level exerts merely a transitory, non-lethal effect upon these cells.

In summary, exposure of the entire head and body of monkeys to 10,000 r of high intensity gamma radiation consistently induced meningitis, choroid plexitis, vasculitis, and pyknosis of granule cells of the cerebellum. These lesions were well established within 2 hours after irradiation; they attained a maximum intensity within 8 to 24 hours and then regressed or disappeared. By contrast, rather numerous basophil cells of the pituitary gland suffered irreversible damage. The lesions were of the same character and intensity whether the head-body or simply the head was irradiated. They did not occur when the radiation was applied to the body with the head shielded.

FIGURE I.

FIGURE I. TEMPORAL RELATIONSHIP OF THE ALTERATIONS INDUCED IN THE CENTRAL NERVOUS SYSTEM BY 10,000 r OF GAMMA RADIATION TO THE HEAD OF MONKEYS



The cytological alterations in the visceral lymph nodes, spleen, bone marrow and gastrointestinal tract were the same in monkeys irradiated over the body with the head shielded as in those which received total head-body radiation. No cellular alterations were observed in the viscera of animals irradiated over the head with the body shielded.

The observations as a whole provide strong evidence that the acute pathological alterations which occur in the CNS after total head-body irradiation in monkeys are induced by ionizing rays acting directly on the CNS and are not enhanced by any supposed toxic substance liberated from the irradiated body. The changes were found to be transitory except for basophil cells of the pituitary gland, which were moderately to severely injured. These observations further suggest that damage of the CNS plays no role in the pathogenesis of the cytological alterations that occur in the gastrointestinal and hematopoietic organs after head- or head-body gamma irradiation.

IV. EFFECTS OF ROENTGEN, CATHODE AND OTHER RADIATION ON THE NERVOUS SYSTEM OF YOUNG AND ADULT EXPERIMENTAL ANIMALS

In general, the CNS is relatively resistant to the commonly used forms of therapeutic radiation, but shows evidence of damage - either acute or delayed and in varied patterns - when exposed to large doses of high voltage X-rays or to the newer forms of high-intensity radiation. Type and degree of pathological change vary depending on the animal and its age, and on numerous extrinsic factors, such as number of exposures and time-intensity. From the biological standpoint, high-energy X-rays have been found less effective quantitatively than low-energy X-rays, but the exact coefficient of biological effectiveness is debatable. Arnold, Bailey and Harvey (1954b) have used a factor of 0.60. Fractional radiation has been found less damaging to the brain than equivalent one-dose radiation (Arnold et al., 1954; Bagg, 1921). The radiosensitivity of brain substance in adult animals is about 1/5th that of epidermis and about 1/7th that of vascular endothelium, while the radiosensitivity of cerebral vessels is approximately equal to that of vessels elsewhere (Duggar, 1936; Flaskamp, 1930; Zimmern and Chavany, 1931).

The work by Hicks (1953, 1956), on mice, in which several forms of radiation were employed, has shown that ordinary X-rays at high doses damage rather few cells in the CNS. If the rate of radiation -- say of 20,000 to 30,000 r -- is increased, more oligodendroglia, neurons, cerebellar granule cells, retinal and internal ear cells are

damaged than at lower rates. If radiation is given in the form of megavolt electrons (2.5 mev cathode rays) at 30,000 rep in one second, the damaging effect is even greater. Two events occurred after large doses of high-intensity cathode rays which did not take place after 150, 250, 400 kv and 4 mev X-rays were given at rapid rates: namely, acute demyelinating lesions in some animals and instantaneous death in others.

By proper shielding, Hicks found that the lower half of the medulla oblongata was the critical zone for instant death. If this part of the brain stem were shielded, the animal lived for some hours. Under such conditions the exposed part of the brain was almost wholly destroyed and the animal simply wriggled and breathed before it became moribund some 6 or 8 hours later. Through selective shielding, Hicks also found that damage to the internal ear, which begins to appear morphologically at about 20,000 rep, is not the cause of the instant death.

Sensitivity of the brain stem to radiation is referred to elsewhere in this report (pp. 26 & 27). In this connection it is of interest that in goldfish receiving total body radiation the most profound changes occurred in the medulla oblongata (Davison and Ellinger, 1942; Ellinger, 1940).

A. Effects of Roentgen Radiation in Macaque Monkeys

Davidoff et al. (1938) reported a study of the brains of 16 *Macacus rhesus* monkeys which were irradiated after removal of the overlying skull. Of the 2 monkeys which died in the acute stage of illness, one (No. 2) received 4,800 r in doses of 2,400 r (to one hemisphere) one week apart and died 7 days after the second exposure. The other (No. 3) received 7,200 r in similarly divided doses and died 3 days after the second exposure.

Vessel changes were inconspicuous. In both animals there was merely swelling of endothelial cells, slight thickening of vessel walls, and "some degeneration of vessel walls with small hemorrhages." Astrocytes were diffusely hypertrophied and some exhibited clasmatodendrosis; a few oligodendroglia were acutely swollen; microglia were beginning to be transformed into rod cells; and there were rather numerous gitter cells. In monkey No. 2 slight demyelination had occurred. Considerable emphasis was placed on chromatolysis etc. of the nerve cells, but there was no mention of control studies. Satellitosis and neuronophagia were said to be absent.

As to the animals which died or were sacrificed in the chronic stage (120th to 249th day), the dosage, delivered to one hemisphere,

ranged from 1,856 to 5,000 r. The meninges were usually thickened and adherent to the brain. Breakdown of tissue (probably the white matter) with astrocytic response was described as a characteristic feature. In some monkeys the astrocytes were monstrous, and a few astrocytes, binucleate. Breakdown of white matter into cavities was noted, and around such cavities gliosis was either sparse or abundant. Fat-laden gitter cells were commonly noted, often around blood vessels. The blood vessels showed slight connective tissue thickening and in a few instances hyalinization; and in some cases perivascular hemorrhages were noted. In two of the animals (No. 1, 5,400 r, 148 days' survival; and No. 16, 5,000 r, about 120 days' survival) both hemispheres were characterized by widespread, patchy demyelination throughout the centrum semiovale and internal capsule and in less measure in the basal ganglia and pons. These changes were most pronounced on the side of the brain irradiated. In another animal (No. 15, 4,000 r, 156 days' survival) there was patchy demyelination of the centrum semiovale, chiefly on the irradiated side.

In two monkeys the exposed cerebellum and medulla oblongata were irradiated. Progressive ataxia occurred. One (No. 9, 4,000 r) survived 8 months, and the other (No. 10, 5,000 r) 4 months. Patchy degeneration of nerve fibers in the white matter of the cerebellum was observed. Many Purkinje cells were described as chromatolytic. The brain stem and spinal cord were riddled with cavities surrounded by slightly hypertrophied astrocytes. In one animal (No. 9) there was slight thickening of connective tissue and hyalinization of blood vessels and occasional proliferative changes in the endothelial and adventitial cells, leading to narrowing of the vascular lumen. In the other (No. 10), marked connective tissue thickening of blood vessels was noted. In both animals many cells of the choroid plexus were said to be vacuolated or degenerated.

In summary, the authors remarked that a dose of 4,000 r or more to one cerebral hemisphere was followed almost immediately by a more or less well-marked paralysis of the contralateral limbs, and that after exposure to 2,000 to 3,000 r, hemiparesis developed after several months. Irradiation of the exposed cerebellum produced no acute manifestations, but ataxia, etc. did appear 3 to 5 months afterward. "Surprising as it may seem," they stated, "the changes in the blood vessels were slight in degree." Also . . . "the axis cylinders sometimes appeared to be less severely involved than the myelin sheaths." They had nothing to say about the granular layer of the cerebellum.

B. Effects on Experimental Animals Other Than Monkeys

Effects of Exposure to Radium and Related Radioactive Substances. Exposure of the brains of rats to radium has resulted in early breakdown of cerebral tissue (including nerve cells) attended by severe inflammatory reaction but with little reparative activity on the part of the glia (Colwell and Gladstone, 1937; Horsley and Finzi, 1910-11). In the brains of rabbits in which radon or radium needles had been implanted, nerve-cell damage and tissue necrosis occurred, but vessels were spared (Paterson, Ross, 1931). Cats and rats given radioactive water to drink have developed, after a few weeks, changes not unlike those in lead chronic lead poisoning, which is understandable from the decay of the water into stable lead (van der Horst, 1940).

Effects of Exposure of Young and Adult Animals. Irradiation of the cerebrum of very young dogs and rabbits has resulted in profound cerebral atrophy with disappearance of rather numerous nerve cells and proliferative changes in blood vessels (Demel, 1926; Turner and George, 1910-11).

A comparison has been made by Hicks and Wright (1954) of the effects on the mouse and rat of 20,000 r of X-rays given 1) at 250 kv at 70 r per minute, 2) at 250 kv at 1000 r per minute, and 3) at 2.5 mev at 1 second. At 250 kv given at 70 r per minute at the 20,000 r dose level, little change occurred in the CNS, but when the same dose was given at the rate of 1000 r per minute, severe alterations occurred in the cerebellum. The animals were crippled within a few hours. Cathode rays, 20,000 rep, 2.5 mev, in 1 second, and 20,000 r of 2.5 mev X-rays at 1,000 r per minute induced alterations not only in the cerebellum but also in neurons of the cerebral cortex, diencephalon, and brain stem. Sometimes the white matter was affected. Cathode rays above 30,000 rep in 1 second may kill a mouse almost instantly, the vulnerable area being the brain stem as shown by shielding experiments (p. 17).

In dogs and cats a few days old, the granule cells of the cerebellum have been found highly radiosensitive, as little as 4 HED (Holzknecht units) causing destruction in several days (Brunner, 1920).

In a dog receiving 4-1/2 HED over the spinal column in the kidney region, hemorrhages and vascular engorgement were seen 5 months later in the meninges and in the anterior horns of the spinal cord over the epilated area (Gabriel, 1926). In adult dogs exposed to 1 to 2 HED radiation, Mogilnitzky and Podljaschuk (1929, 1930) have found, 60 to 85 days later, thickening of the meninges and of the walls of medium-sized vessels, but no brain or choroid plexus damage. In rabbits which

died within a few days after receiving 3-1/2 to 10-1/2 HED (as a single dose), they found vascular changes (including swelling of endothelial cells), hemorrhages, and perivascular edema. Similar observations have been made in rabbits (Koidumi, 1937), in dogs (in both brain and spinal cord) (Sicard and Bauer, 1907), and in various animals (Krause and Ziegler, 1906; Nemenow, 1934). Russell, Wilson and Tansley (1949) exposed the heads of adult rabbits to 4 different doses of X-radiation; 2850, 2440, 2030, and 1625 r. The 2030 and 1625 r groups showed microscopically normal brains at 25 months after radiation. After this time the two higher dosage groups showed 1) vascular damage and 2) fibrinoid necrosis, progressive degeneration and sclerosis of the brain substance. At the lower doses the latent period before development of symptoms was 240 days.

Studies carried out on young dogs by Lyman, Kupalov and Scholz (1933) and Scholz (1934, 1935) have disclosed brain lesions within a few days after exposure of the head to 1 to 2 HED X-radiation (therapeutic dose for adult dogs). These consisted of foci of brain pallor or brain necrosis attributable to disturbances in vascular function. Nerve cells and nerve fibers outside the irradiated field did not show any change. The blood vessels were free from changes.

In adult dogs, X-radiation produced cerebral changes a few weeks after exposure to 4 or more HED, at a time when no clinical disturbances were evident. Scattered vessels, particularly in the white matter, showed perivascular lymphocyte-plasma cell infiltrates with discrete focal microglial proliferation. This reaction was usually evident in 4 to 6 weeks and disappeared completely after about 3 months. Approximately 5 to 6 months after irradiation - however only with doses of 8 or more HED - progressive changes in the CNS set in, resulting in paralyses, blindness, and loss of consciousness. At this time, focal changes were evident in small and medium-sized vessels. The collagen fibers of the adventitia had undergone profound swelling. Cells of the vessel wall, often including the endothelium, were focally destroyed and had become hyperplastic. Dense protein-rich material having the features of plasma inundated and destroyed the perivascular brain substance as would "a stream of lava." The outpouring of the plasma was regarded as due to an alteration of vascular permeability. Diapedesis and rhexis hemorrhages occurred in terminal stages. Only the inundated nerve cells were damaged, not any others. No part of the brain was particularly predisposed to damage, though multiple areas of white matter of the centrum semiovale suffered the most. The regressive changes in granule cells of the cerebellum that occurred were attributed to edema fluid.

Certain earlier workers have contended that CNS nerve cells are primarily damaged by radiation (Balli, 1915; Brunner, 1920, 1921; Heinecke, 1903-04).

The sequelae of exposure of the head of rabbits to high intensity X-radiation has been carried out by Gerstner, Pickering and Dugi (1954). A summary of their studies follows:

The heads of 28 rabbits were exposed to high-intensity X-radiation; the total dose delivered to the brain was approximately 12,500 r (12.5 kr). In the sequelae, developing rapidly after exposure, several distinct phases could be recognized: latent or prodromal period (mean duration, 29 minutes); convulsive phase (approximate duration, 2 hours); somnolent phase (approximate duration, 3 hours); ataxic phase (duration, until death); and death (mean survival time, 2-1/2 days).

In mice, rats and monkeys exposed to massive doses of gamma radiation from multi-kilocurie sources of Ba^{140} - La^{140} , with dose rates varying from 1,000 to 6,500 r per minute and the total dose ranging as high as 150,000 r, Langham (1954) observed what was referred to as the hyperacute radiation syndrome. This consisted of 1) a transient ataxic phase beginning immediately and lasting about 5 minutes, 2) a lethargic phase the time of onset and the duration of which were dependent on radiation dose, 3) an excited, hyperactive convulsive phase, and 4) a terminal phase. In general, the onset of each phase was more rapid and the signs became more pronounced as total dose was increased.

C. Changes in the Peripheral and Autonomic Nervous Systems

Studies thus far indicate that the cranio-spinal peripheral nervous system is comparatively radioresistant. Exposure of rats and frogs to 10,000 r X-radiation failed to induce any physiological or morphological change in peripheral nerve fibers (Janzen and Warren, 1942; Schaefer and Schmitz, 1933). Nerve growth has continued through regions which have received 2,000 r radium or X-radiation (Meissel, 1930). In newborn rats a dose of 1,000 r has been found to retard peripheral nerve myelination, while after 4,000 r myelin and axis cylinder damage is the rule (Leboucq, 1934). In pigeons exposed to large doses of radium in the anal region, regressive changes (mostly a loss of argentophilia of axis cylinders) have been observed in myelinated and non-myelinated nerve fibers (Masumoto, 1934).

Functional radiosensitivity of the autonomic nervous system has been recognized (Langer, 1935; Nemenow, 1935; Vieten, 1949), but little work has been done from the morphological standpoint. In rats,

no alterations have been observed in the lumbar sympathetic ganglionated chain following radiation (Griffith and Pendergrass, 1934). In young rats, degenerative and destructive changes have been noted in ganglion cells of Meissner's plexus a few days following irradiation with 246 mgh. radium (Colwell and Gladstone, 1936). In rabbits, the inferior mesenteric ganglion has shown degenerative nerve cell changes 4 to 7 weeks after high-dose radiation (Suzuki, 1931).

V. CNS CHANGES FOLLOWING EXPOSURE OF EMBRYOS AND FETUSES TO RADIATION

A. Experimental Animals

Among the earlier workers to show that irradiated embryos develop cerebral agenesis or malformation was Ostertag (1938). Studies carried on by Hicks (1950, 1953, 1954, 1956) have indicated that exposure of embryos or fetuses to ordinary therapeutic X-rays (250 kv and 2 mev) induces necrotizing changes in primitive differentiating non-mitotic cells of the nervous system at a dose level as low as 30 or 40 r. Malformations developed readily after exposure to 100 to 200 r. The nature of the malformation at a given dose is determined by the stage of development of the embryo and the capacity of the embryo to recover at that stage. In the first somite stage, radiation has induced severe head and brain defects (anencephaly). Irradiation at subsequent stages has been characterized by a variety of reproducible brain, eye, skeletal and visceral abnormalities.

B. Man

A variety of defects from microcephaly to eye and skeletal deformities have been observed in newborns following pelvic irradiation during early gestation (Murphy, 1929). Microcephaly occurring under such conditions has been mentioned by Hicks (1953), who remarked that "in view of the fact that 30 to 40 r damages neuroblasts and since alteration of cartilage may occur in a similar or lower range, this order of magnitude might serve as a point of departure for estimating clinical risks."

VI. EFFECTS OF TOTAL HEAD-BODY X-RADIATION IN GUINEA PIGS WHILE UNDER VARIOUS SIMULATED FLYING CONDITIONS

Work in this field has been carried out by Konecni and Taylor (1954). Flying conditions were simulated by means of a plastic low-pressure chamber. A total of 250 male guinea pigs were utilized in 17 different procedures. Total head-body exposures were given with a

dose rate of 145 r per minute of 260 KVP and 18 ma. of X-radiation.

Severe hypoxia greatly increased survival time over ground-level controls in all dose levels tested (i. e., 500, 1,600, 4,000 and 8,000 r). No increase in radiosensitivity resulted from breathing 100 per cent oxygen. Cold alone slightly increased survival time, but cold at altitude with 100 per cent oxygen showed no such protection. Cold plus severe hypoxia markedly increased survival time. Nondigestible diet (asbestos fiber) and long flight both significantly increased survival times. The results indicated that the general conditions met while flying were not detrimental to the guinea pig in combination with exposure to ionizing radiation.

VII. INCREASE IN SURVIVAL TIME OF IRRADIATED GUINEA PIGS GIVEN PENTOBARBITAL SODIUM

Studies carried out by Andrews and associates (1956), of the National Institutes of Health, Bethesda, have indicated that pentobarbital sodium has a protective action in irradiated guinea pigs. The animals lived about twice as long as untreated irradiated controls. The data are as follows:

<u>Dose, r</u>	<u>Treatment Schedule</u>	<u>Survival Time, Hours and Std. Error</u>	
5,000	None	146.0	± 16.6
7,500	"	17.7	± 1.0
10,000	"	16.4	± 2.3
15,000	"	16.9	± 2.1
7,500	Pentobarbital sodium, 35 mg before r	89.5	± 9.5
10,000	" " " "	73.5	± 18.2
15,000	" " " "	39.1	± 4.1
7,500	" " " after r	19.7	± 2.1
7,500	Diphenyl Hydantoinate, 25 mg before r	18.6	± 1.3
7,500	" " " before and after r	29.1	± 3.7
7,500	Morphine sulphate, 50 mg before r	29.5	± 7.5
7,500	Chlorpromazine, 2 mg before r	17.6	± 3.6
7,500	Cysteine, 800 mg before r	31.6	± 8.5

These data were obtained with guinea pigs weighing very nearly 1 kilogram, so the doses represent very nearly mg-kg.

It is of interest that the convulsions seen after 7,500 r were controlled by both Diphenyl Hydantoinate and Chlorpromazine even though

there was only a slight effect on survival. It was thought that the slight increase in survival time seen with Diphenyl Hydantoinate was due to the reduction of muscular activity, but this cannot be the case with Chlorpromazine. It is of interest that the Pentobarbital animals all lived well beyond the duration of drug action (16 hours) so that the animals are not depressed until death. Pyknosis of granule cells of the cerebellum occurred in the irradiated controls but not in the irradiated animals treated with pentobarbital sodium.

VIII. BRAIN CHANGES IN MACAQUE MONKEY AND MAN EXPOSED TO BETATRON X-RAYS

General Survey of CNS Effects in 60 Monkeys (Arnold et al., 1954a). Most of the brains in this series were exposed to 23 mev. X-rays produced by the betatron, and a few to 200 and 400 kev. X-rays. The range of doses of 1,500 to 14,000 r of 23 mev. X-rays was equivalent to 900 to 8,400 r of 250 kev. X-rays. The radiation was in the form of a beam, the dose-rate with the 1.0 cm. beam being 150 r/min. and that with the 2.5 cm. beam, 75 r/min. The tissue-dose-distribution was fairly uniform, 95 per cent of the entrance dose being detected in the region of exit of the beam from the skull.

Single tissue doses of 7,000 r or more produced acute necrosis of all tissues traversed by the beam. Thus, at this dosage there was no evidence of radioselectivity of the different brain elements. In the dose range of 5,000 to 7,000 r the acute changes consisted of inflammatory reaction, edema, hemorrhages and sparse areas of acute necrosis. The "areas of necrosis" were not further remarked on by the authors except for the statement that as time went on these areas persisted. Most of the monkeys exposed to this dose range recovered from their acute symptoms and remained well for 4 months or longer. Then, rather abruptly, they fell ill and in 10 days to 2 weeks became comatose and quadriplegic, and finally expired. Microscopic examination disclosed extensive nonselective radionecrosis throughout the entire path of the beam, and only in that path.

Examination of the brains of the monkeys sacrificed during the acute stage of the 3,000 to 5,000 r dose range revealed throughout the irradiated part of the brain a very intense inflammatory reaction, hemorrhages, and edema, with some of the acute inflammatory cellular reactions spreading beyond the specifically irradiated area and producing a moderately diffuse meningoencephalitis. During the intermediate stage (in which symptoms and signs of cerebral involvement virtually disappeared), only minor neural and glial changes were

observed in the tissue in the path of the beam. Some 6 to 8 months later the animals became sick and quickly died. The delayed radionecrosis was found to be strikingly selective for the white matter. Changes in nerve cells were slight. The authors emphasized that the radiosensitivity for the white matter began as a demyelinating process and that it proceeded with time and increasing dose to necrosis of myelin, axons, and glia. Reparative processes were found to be neither active nor extensive, as the gliosis and fibrosis occurring in the tissues surrounding the areas of necrosis were only of moderate degree. Their contention that myelin was primarily affected and that the breakdown of the white matter was a direct effect of the irradiation was based on the lack of vascular changes at this time or of vascular occlusion.

With doses of 1,500 to 3,000 r, the changes were reported as the same as those in monkeys receiving 3,000 to 5,000 r, but were less intense. Rats exposed to as low a dose as 300 r were also found to exhibit CNS changes.

The authors stated that "the pathological changes produced by these irradiations are due to a direct effect upon the neural elements."

B. Selectivity of CNS Changes in 40 Monkeys and in Man (Arnold, Bailey and Laughlin, 1954c). In this article the following conclusions are reached:

1. The CNS is more radiosensitive than is generally supposed.
2. The effects of high energy X-rays on the brain of monkey and man appear to be direct effects and are not secondary to vascular occlusion.
3. The brain stem appears to be most responsive to X-radiation.
4. The white matter of the deep portions of the centrum semiovale, internal capsule and brain stem are peculiarly responsive to X-radiation.
5. The cells of the paraventricular and supraoptic nuclei of the hypothalamus are radiosensitive.

The histological changes are indicated in Table VII.

TABLE VII

Spectrum of Histologic Changes Postradiation (Arnold, Bailey, Laughlin 1954c)

	Acute stage	Intermediate stage	Late stages
1. Betatron (r) (23 mev.)	(1 day-6 wks.)	stage	(5 mos. -8 mos.) (8 mos. -12 mos.) (12 mos. -24 mos.)
2. Dose in x-ray r (400 kev.)*	(6 wks. -5 mos.)		
1. 7,000-14,000 r	Acute necrosis of all neural components and small vessels. Large vessels patent.	Acute stage persists. No recovery. No gliosis.	Little or no gliosis in adjacent tissues.
2. 4,200-8,400 r			
1. 5,000-7,000 r	Acute inflammation, hemorrhages, perivascular exudates, partial necrosis, myelin changes, edema. Abnormal EEG.	Partial recovery histologically. Abnormal EEG.	Delayed, non-selective diffuse radionecrosis. Abnormal EEG.
2. 3,000-4,200 r			Very slight gliosis of radio-active areas. Vascular hyalinization. Abnormal EEG.
1. 3,000-5,000 r	Acute inflammation, hemorrhages, perivascular exudates, edema. Abnormal EEG.	Complete recovery histologically. Abnormal EEG.	Moderate to intense gliosis of radionecrotic areas. Obliterated vascular channels. Abnormal EEG.
2. 1,800-3,000 r			
1. 1,500-3,000 r	Acute inflammation, exudates, edema. Abnormal EEG.	Complete recovery histologically. Abnormal EEG.	Mild gliosis of radionecrotic white matter. Vascular changes. Abnormal EEG.
2. 900-1,800 r			
1. 375-1,500 r	Studies incomplete. Abnormal EEG.	Studies incomplete. Abnormal EEG.	Delayed radionecrosis (selective for white matter). Deficient gliosis. Abnormal EEG.
2. 225-900 r			

*Equivalent dose of 400 kev. x-rays based on biologic effectiveness.

Arnold and associates emphasized that the white matter was particularly vulnerable, and that the white matter change was primary. They pointed to the observation of Reynolds (1946) that the polarizing microscope is helpful in detecting changes in the white matter following irradiation. EEG abnormalities occurred following exposure to a dose as low as 375 r of 23 mev. X-rays, which would indicate a reaction of the neurons to radiation. This was the lowest dose they used. They also emphasized that this figure (375r) does not in any way imply that damage will occur in the human brain following a tumor dose of 1500 r, given in a fractionated course in a patient with brain tumor. The types of histological response detected in their experimental animals have, however, been noted in patients receiving X-ray therapy. "We have now observed a number of patients in whom delayed radionecrosis has occurred a year or more after radiation, following a tumor dose of 4,000 r of 200-400 kev X-rays given in one or more well fractionated courses, and following a tumor dose of 6,000-7,000 r of 23 mev. X-rays given in one fractionated course." The brain tissue rendered necrotic by radiation has a tendency to behave as a swollen tumor mass in some cases. Other discussion of effects of radiation on the CNS in connection with X-ray therapy of tumors is to be found on page 12.

VIII. VULNERABILITY OF THE HYPOTHALAMUS AND BRAIN STEM TO RADIATION

A. Studies in Man

Very Low Radiation Exposures (Birkner and Trautmann, 1953).

The technical data were as follows: The diencephalic region was exposed to 180 kv, 0.35 mm. Cu-filter, 0.74 mm. Cu HWS, FHA 30 cm., 2 temporal fields 6x8 cm., single dose 30-50 r, total dose per field, 150 to 250 r. Estimated total dose to diencephalon, 150 r.

Two human volunteers were subjected to 100 r in the diencephalic region. About 1-1/2 hours later they complained of tinnitus, generalized numbness, and apathy. Shortly thereafter they felt psychically stimulated. Sleep that night was very deep. The next morning they were exceedingly active and euphoric. They then became unusually quiet. The disturbances lasted about 7 to 10 days.

Two individuals suffering from severe psychic depression showed striking improvement after exposure to small radiation doses. The improvement lasted about 6 months.

Altogether 120 patients were subjected to this procedure. Psychic changes were noted in 49 per cent, alterations in sleep-wakefulness in 51 per cent, and changes in gonadal function in 37.5 per cent. Since there were no consistent changes in vegetative function (in blood pressure, BMR, or blood-sugar level) the authors were disinclined to believe that the effects were attributable solely to alterations of hypothalamic function.

Therapeutic Radiation in the Pituitary-Hypothalamic Region.

Arnold (1954) and Arnold, Bailey and Harvey (1954b) have drawn attention to the radiosensitivity of the hypothalamus and brain stem, and have suggested that the amelioration of symptoms and signs following irradiation of the pituitary region may be accounted for on the basis of hypothalamic damage. Reference was to irradiation for such conditions as malignant exophthalmos (Beierwaltes, 1953), arterial hypertension (Pendergrass et al., 1947), and assorted gynecological disorders (Kaplan 1946; Kotz and Parker, 1940; Randall, 1947).

Therapeutic Radiation in Region of Brain Stem. Boden (1950) reviewed 7 cases in which 4,500 to 6,050 r had been given to the region of the brain stem for cancer of the middle ear, nasopharynx, and parotid area. The patients died rather soon thereafter, and from 1 to 6 months after onset of cancer growth. The radiation was administered over 19 days. Characteristic clinical features were nystagmus, spastic quadriplegia, and hypesthesia. Pathologically there was advanced radiation 'myelitis'. The authors left open the question whether the blood vessels were primarily involved.

B. Studies in Experimental Animals

Effects of Irradiation of the Hypothalamus and Brain Stem

(Arnold, 1954; Arnold, Bailey and Harvey, 1954b). These papers deal with monkeys which were sacrificed over a period of 3 years after receiving small (1.0 or 2.5 cm.) circular beams of high-energy (23 mev) X-rays (from the betatron) transfrontally or transtemporally across the head, in single doses of 375 to 14,000 r. In one set of experiments the brain stem (particularly the pars basilaris pontis) was found much more radioresponsive than the cerebral hemispheres. In irradiation of the hypothalamus the supraoptic and paraventricular nuclei were alone damaged, many cells being wiped out. Little glial reaction occurred.

X. TISSUE CULTURE STUDIES OF BRAINS SUBJECTED TO RADIATION

Work has just been completed by Pomerat and Hild (1956) on the cultivation of tissues (cerebellum, cerebrum, meninges, retina,

pituitary) from the brains of monkeys which received 10,000 r cobalt⁶⁰ (gamma) radiation to the head. These investigators were unable to maintain neurons (particularly granule cells of the cerebellum) and neuroglia of these brains in tissue culture. Positive results pointing to evidence of primary destruction of brain tissue by ionizing radiation were the following: 1) amount of phagocytosis, 2) injury and early death of macrophages which emigrated from irradiated tissues, 3) undue denseness and rigidity of tonofibrillae of cells, which might indicate radiation injury to the long-chain proteins which compose such structures, and 4) the development of giant cells, multinucleation and marked variation in nuclear size in epithelia forming the outgrowth from the pituitary of irradiated animals.

XI. RADIOACTIVE ISOTOPES AND THE BLOOD-BRAIN BARRIER

Penetration of Radioactive Isotopes into the Normal Brain. In general, most radioactive ions pass through the blood-brain barrier at a very slow rate, and the amount which gets through is small when comparison is made with other tissues.

P³². Penetration of P³² into the brain is slow and incomplete after 12 hours, and only about 0.02 per cent of the amount injected i. v. is deposited in the brain (Bakay and Lindberg, 1949; Hevesy, 1948; Samuels et al., 1951). A faster transfer of P³², chiefly in the form of adenosinetriphosphate and phosphocreatine, has been noted by Lindberg and Ernster (1950) and Sacks and Culbreth (1951). Following i. v. injection of 20 microcuries of P³² per kilogram of body weight (in rabbits), Bakay (1951) noted that the largest amount of the P³² had penetrated in the pituitary gland, that a fairly high concentration was present in the choroid plexus, but that little had reached the brain substance. When P³² was injected intracisternally it quickly sought out the CNS. Bakay (1956) expressed the belief that in the initial phase of absorption, P³² enters the brain via the CSF after it has passed the blood-CSF barrier, and that in the later phase, in which P³² concentration in the brain is slow and gradual, the absorption is presumably due to direct passage of the tracer through the blood-brain barrier by transcapillary exchange.

I¹³¹. In the rabbit, the highest CNS concentration is reached at about 24 hours after s. c. injection, whereas maximal penetration in the other organs is reached within the first 5 hours (Perlman, Chaikoff and Norton, 1941). Very little I¹³¹ accumulates in the brain (Hubbard and Anderson, 1942).

D₂O (Deuterium). Exchange of D₂O with the brain is very rapid and in large amounts (Bering, 1952).

Br⁸². Following injection intraperitoneally in rabbits, the exchange of the Br⁸² between the blood stream and brain has been found relatively slow, with the cerebral activity being 30 to 35 per cent of that in the blood in 70 hours (Gruner et al., 1951). In these experiments the cerebral white matter took up most of the Br⁸². In studies carried out on rabbits by Brattgard and Lindquist (1954), the cerebellum was the best seeker. The greatest retention of Br⁸² has been in those parts of the brain where penetration is the slowest (Tubiana et al., 1951).

C¹⁴. Uptake of C¹⁴ by the brain is slight and slow (Nardi, 1953).

K⁴². Equilibrium of the isotope in the blood stream and brain is almost completed in 6 hours; it is finally achieved in from 18 to 42 hours or longer depending on the experimental animal used (Ginsburg and Wilde, 1954; Locksley et al., 1954; Noonan, Fenn and Haeghe, 1941).

N²⁴. Some 3 to 12 hours are required for N²⁴ to enter the brain. (Locksley et al., 1954; Manery and Bale, 1941). On administration of labeled NaCl, 31 per cent has been recovered in the brain in 62 hours (Hahn and Hevesy, 1940).

Chloride. Radioactive chloride has been found in the brain tissue in a relatively small amount 1 hour after injection (Manery, 1940).

Other Isotopes. Other radioactive isotopes have also been found to penetrate the brain slowly and in small amount. These include As⁷⁴ (Hunter, Kip and Irvine, 1942), Cu⁶⁴ (Hevesy, 1948), Au¹⁹⁸ (Hevesy, 1948), S³⁵ (Dziewiatkowski, 1945), Zn⁶⁵ (Sheline et al., 1943), and borax compounds (Locksley and Sweet, 1954; Locksley et al., 1954).

Alterations in the Blood-Brain Barrier Following X-radiation. Alterations in the barrier have usually been detected by means of trypan blue (Rachmanow, 1926). The barrier is more prone to be damaged by multiple than by single X-ray exposures (Mogilnitzsky and Podljaschuk, 1930). Barrier changes have been noted in monkeys receiving 1,500 to 6,000 r X-radiation to the head with body shielded (Clemente and Holst, 1954). Peripherally administered P³² into the brain has been found unaltered in amount following irradiation of the brain with 20,000 r hard X-rays (Florsheim and Morton, 1954).

Brain Tumors and the Blood-Brain Barrier. -- This aspect of the subject has been thoroughly reviewed by Bakey (1956) and Moore (1953). References to the treatment of glioblastoma multiforme by means of neutron capture, using boron¹⁰, are also to be found in the following: Farr, Robertson and Stickley (1954), Farr et al. (1954a and b), and Godwin et al. (1955).

XII. BRAIN CHANGES IN MONKEYS EXPOSED TO NEUTRONS

This is a preliminary report of studies carried on by Vogel et al. (1956). The primary purpose was to determine the effect of neutrons upon the eyes. The source contained 5 to 10 per cent of gamma rays. Three groups of monkeys were exposed over the ocular region to 14 mev neutrons. Two animals that received 75 rep died 6 to 9 months later. No change was found in the CNS. The same was true of two other animals exposed to 250 rep. One died after 2 months.

Seven monkeys received 850 rep. One died after 2 months without changes in the CNS. Thus, a latent period was established: The brains of 6 that were sacrificed between the period of 1 year 3 months and 1 year 10 months showed gross atrophy of the frontal lobes. Study of these brains disclosed loss of axis cylinders of the white matter, with gliosis. Lower laminae of the cortex were affected by contiguity.

Three other groups of monkeys were exposed to neutrons with energies below 1 mev. One animal received 825 rep and died 10 months later. Two were exposed to 2,500 rep and survived for 1 year and 11 months, and 2 years and 6 months; a last animal received 8,500 rep and survived for 5 months. No changes were noted in the brains.

XIII. RADIATION EFFECTS ON THE GLIA

A. In Monkeys

Reference has been made on page 12 to the rather minor changes which glia undergo in the few hours or days following exposure to high doses of Ba¹⁴⁰-La¹⁴⁰ radiation. Arnold and Bailey (1954) have paid particular attention to the glia in irradiated monkeys which were serially sacrificed over relatively long periods of time. The monkeys were exposed to low-energy X-rays from conventional X-ray machines at 200 to 400 kv and high-energy X-rays from the betatron (which produces X-rays at a peak intensity of 23 mev). The type and manner of the response

of the glia (astrocytes, microglia and oligodendroglia), they found, could be readily correlated with 1) the total dose of radiation, 2) the intensity of dose administration, 3) the uniformity of dose distribution within the tissue, and 4) the duration of time of observation after irradiation.

1) Glial Response as Related to the Total Dose of Radiation.

With a comparatively large dose (7,000 r or more) of high-energy X-rays (23 mev) given in a single exposure, all cellular elements and nearly all the vessels were destroyed. In the necrotized area and beyond, very few, if any, gitter cells or microglia appeared. Astrocytes seemed to swell and to proliferate somewhat, then disintegrate. Oligodendroglia underwent early cytoplasmic swelling and nuclear pyknosis, then disappeared. At 6 weeks no vascular proliferation was visible in the junctional area. In short, reactive propensities of the glia were drastically affected by radiation. After some months the astrocytes in the junctional area slowly underwent proliferation, and after a year, gliosis was intense.

As the X-ray dose was reduced below the necrotizing level (e. g., 3,000-5,000 r of 23 mev X-rays) the reactive capacities of the glia were still impaired. Of the glia, the astrocytes were the most hardy; they soon increased in the junctional area, but only some months later did they proliferate somewhat in the necrotized area. Intense gliosis and fibrosis became evident a year or more after the irradiation, and striking hypertrophy of individual glial cells occurred.

With still lower doses (1,500 to 3,000 r of 23 mev X-rays), neurons, myelin and endothelial cells became swollen, but the glia did not undergo significant acute reactions. Some of the oligodendroglia showed cytoplasmic swelling and nuclear pyknosis. The process subsided, and not until some months later did necrosis of the white matter set in. With the passage of time an intense reaction gliosis and fibrosis appeared in and about the areas of necrosis.

"In general, it would appear that the functions of the glial cells are depressed or inhibited by X-irradiation. With the passage of time a recovery of the glial elements occurs, and they perform their function with a somewhat increased and perhaps 'uninhibited' vigor, thereby producing a very intense gliosis of previously radio-necrotized and radio-injured areas."

2) Glial Responses as Related to Intensity of Dose. Comparison of the effects of the administration of neutrons at variable dose rates from 75 to 1,000 r per minute indicated that a very rapid rate of

administration of a single dose gives a greater intensity of effect than the same dose given at a much slower dose-rate. Fractionated doses were less damaging than a single equivalent dose.

3) Glial Responses as Related to Uniformity of Dose-Distribution Within the Tissue. These vary depending upon penetration of the ionizing rays.

4) Glial Responses as Related to Duration of Time of Observation After Irradiation. At first there was inhibition of glia, then recovery with eventual intense gliosis. In time, giant or monstrous glia appeared.

B. In Other Animals

Hicks and Montgomery's (1952) studies were done on rats and mice receiving 50 to 20,000 r X-radiation to the head or head-body. The animals were from 3 to 12 months old at the time of irradiation. They were sacrificed in 6 to 48 hours after irradiation except for those exposed to the head -- these were allowed to survive for several days or until they died, usually on the 9th or 11th day. In general, several cell types were necrotized - oligodendroglia, occasional neurons in the "olfactory brain," subependymal cells, and rod cells of the retina.

Oligodendroglia were reported as necrotic within 6 to 24 hours after 1,200 r radiation to the head. They were scattered in both white and grey matter. They were also found in the spinal cord. Necrotized retinal rod cells were seen in 5 rats sacrificed between 6 and 11 days, but the changes were not evident until the 6th day. In younger animals the small subependymal cells of the lateral ventricle were found necrotic in 6 to 12 hours. Necrosis was always considerable at 200 r, but was rare or absent both in rats and mice at 50 and 100 r. Sympathetic ganglia and peripheral nerve trunks were negative.

Globus, Wang and Mailbach (1952) implanted radon seeds in the medulla oblongata of dogs and noted very little glial response in the necrotized zone. Very few, if any, microglia or gitter cells appeared. Neuronophagia of affected neurons was slight. After 106 days considerable astrocytosis had occurred, but no giant glia had yet formed.

XIV. OCULAR CHANGES PRODUCED BY RADIATION

Time for the preparation of this report allowed only passing reference to retinal changes following irradiation. As to cataract formation, pertinent references are the following: Brown (1954), Brown

and Pickering (1955), Cogan and Dreisler (1953), and Upton, Christenberry and Furth (1953).

XV. THE EFFECT OF RADIATION OF ALKALINE PHOSPHATASES OF THE BRAIN

The histological distribution of alkaline phosphatase in the monkey brain following cobalt⁶⁰ irradiation is under study by Cammermeyer and Haymaker (1956). The distribution of alkaline phosphatase was determined photometrically in Gomori-treated sections from the cerebrum, cerebellum, and pons. Five animals were used as controls. Forty-five were exposed to radiation of 10,000 r.; 15 animals received whole body irradiation, 15 irradiation of the head only, and 15 of the body only. They were allowed to live 2, 4, 8, 12, 24, 48, 72, and 96 hours after irradiation. In general, two animals were used for each time group.

The walls of all vessels except veins were intensely stained. The cerebral cortex displayed an additional diffuse staining of the ground substance. The intensity of the staining was greatest in the subpial part of the first cortical layer and slightly less in the 3d and 4th cortical layers. In general, the distribution of stainable material resembled that observed by other authors with microhistochemical techniques. In the controls this pattern was retained fairly uniformly with minimal individual variation. In the treated animals considerable individual variation indicated that irradiation had exerted some influence.

In the cerebellar cortex the molecular layer was diffusely but faintly stained. Sections of the cerebellum from the irradiated animals showed individual variation; the greatest changes were noted at time intervals other than those at which changes in the cerebrum were seen.

The sections of the pons showed uniform staining capacity.

XVI. EFFECT OF IRRADIATION ON SUSCEPTIBILITY OF MICE TO POLIOMYELITIS AND INFLUENZA INFECTION

Studies in this field are currently being conducted by Eddy and Smith (1956) of the National Institutes of Health, Bethesda, Maryland. A single strain of male and female albino mice were received at 4 weeks of age, half of each sex were given identifying marks, and 5 each marked and unmarked were caged together. The following day the

marked mice were irradiated, 20 at a time in a partitioned plastic container 29 cm. in diameter, 2.5 cm. deep, on a rotating table. A Van de Graaff generator was used operating at 2.5 mev., 0.6 ma, on a gold transmission target. The H. V. L. was 1 cm. lead, target distance 1 meter and dose rate 250-300 r per min. Filtration consisted of 3 mm. stainless steel, a brass field flattener of 12 mm. maximum thickness, and 13 mm. of water. The dose used was 400 r, estimated to kill 2.5% of the mice in 30 days. In the course of the experiments reported below two of 100 irradiated control and none of 100 nonirradiated control mice died.

On the third day after irradiation the mice were challenged intracerebrally with 0.03 ml. of varying ten-fold dilutions of the M. E. F. ₁ strain of Type 2 poliomyelitis virus. Ten irradiated and ten nonirradiated mice were used for each dilution of virus. The mice were observed for paralysis and death for a period of 21 days. Three tests were carried out. The percentages of deaths among the irradiated mice were not significantly different from control values. Under the conditions of these experiments it is concluded that irradiation did not increase the susceptibility of the mouse to infection with the M. E. F. ₁ strain of Type 2 poliomyelitis.

Mice similarly irradiated and control mice were challenged by intranasal inoculations with 0.05 ml. doses of different tenfold dilutions of two egg adapted and partially mouse adapted influenza viruses, one a Type A prime and one a Type B. In two experiments with one strain and in one experiment with the other strain, the virulence titers were significantly higher in the irradiated mice.

The experiments on influenza and poliomyelitis differ in that the M. E. F. ₁ poliomyelitis strain is virulent for mice whether they are irradiated or not. Both influenza virus strains tested had been passed in mice only a limited number of times and were not fully adapted to mice. To complete these experiments it is planned to test a fully mouse adapted strain of influenza virus such as PR⁸ or Lee and a non-mouse adapted strain of poliomyelitis virus such as Mahoney or Saukett in irradiated and nonirradiated mice.

XVII. SUGGESTED AREAS OF RESEARCH ON EFFECTS OF RADIATION ON THE NERVOUS SYSTEM

1. With reference to fallout, it is of importance to determine whether any of the radioactive elements concerned collect in the CNS. Since some of these elements have been shown to be picked up by human beings as far east as Washington, D. C. following the Nevada tests, it

is pertinent to determine which of them, if any, can damage the brain when present only in low concentration. It is possible that human fetuses will be particularly vulnerable to fallout. When I^{131} reached the fetal thyroid of experimental animals it collects there. Radioactive elements might also accumulate in the fetal CNS. The problem could be tackled by introducing isotopes into pregnant animals and doing scintillator-counter determinations of the fetal brains. Histological and other studies could be continued on isotopes which prove to be "brain seekers." In areas of fallout (e. g., Chicago) especial effort should be made to obtain human fetal material for scintillator-counter study. Elements that should be studied include I^{131} , I^{133} , Sr^{90} , Ba^{140} - La^{140} , Cs^{144} , Mo, Zr-Y, Pr^{141} , Nd, and Ru.

2. The radiation dosage necessary to damage the human nervous system during intrauterine life is not known. Hicks has estimated that as low a dose as 30 or 40 r may be damaging at early stages of gestation. To obtain more information on this point, CNS material in all cases in which the pelvis of pregnant women has been irradiated should be collected and studied.

3. Thus far no brain changes have been found which will account for the shortening of life span following low-dose head-body irradiation. More studies along this line should be carried out. This involves long-term studies, preferably on monkeys, which have been irradiated at sublethal levels at varying intervals after birth.

4. Another approach to the study of the pathological effects of sublethal irradiation of the human brain is that of tissue culture studies of irradiated monkey brains. A good beginning has been made in this direction (p. 39). Some simple biological indicator of radiation damage to the CNS should be continued to be sought for.

5. Studies carried out on human beings have indicated that clinical changes occur after irradiation in the region of the diencephalon with as low a dose as 100 r (p. 38). There is good evidence that the hypothalamus and brain stem are more radiosensitive than ordinarily thought (p. 39). It would be worth while to spot-check the records and restudy the CNS of individuals who have received radiation for pituitary adenoma and the like in the past, and in the future to examine, on a larger scale, the CNS in therapeutic radiation in general.

6. Rather little effort has been made thus far to determine the sequence of changes in the irradiated CNS. Such studies should be done on monkeys, at various dose levels, with serial sacrifice at fairly frequent intervals for 2 or 3 years or longer.

7. More studies should be directed to determining the degree of radiosensitivity of the autonomic and the craniospinal peripheral nervous systems.

8. Studies of the brain subjected to gamma radiation have disclosed that in primates either the vessels or the nerve fibers are primarily damaged. In rodents the vessels are usually spared and the nerve fibers damaged. Monkeys exposed to predominant neutron radiation show white matter damage which is presumed to be primary. Reasons for such selectivity should be sought. For instance does the degree of brain swelling and edema in early stages play a role in the myelin loss? Approaches to these problems include 1) isotope studies of the blood-brain barrier, 2) studies of brain metabolism, and 3) cytological and histological studies by sensitive methods (e.g., fluorescent microscopy, polarization microscopy, esterase and phosphatase techniques, and the gallocyanine method) on brains which have been fixed in situ by perfusion. It would be helpful to those not entirely familiar with the field of neuropathology to have available an outline on methods of brain fixation.

9. Sudden or rapid death following high-dose, high-intensity radiation can be prevented by shielding the lower part of the medulla oblongata (p. 28). Further work along this line is in order. Could the incapacitation due to lesser doses be delayed if the entire brain stem were shielded?

10. Further work on the effects of radiation on viruses and other infectious agents is in order.

11. The same goes for studies on the eye and optic nerve.

12. Relatively few studies have been carried out on the internal ear following irradiation. It would be of interest to know to what degree the vertigo, nystagmus and retching following high-level irradiation are attributable to damage of the internal ear.

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RADIATION EFFECTS ON ENDOCRINE ORGANS

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All endocrine organs with the exception of the ovary are regarded as being radioresistant but this is true only if one considers early and direct effects. Radiation impairs the regenerative capacity of endocrine as well as of other organs. It induces in many endocrine organs subtle changes which become intensified in time, interfere with the normal hormonal feed-back regulation, and lead to imbalances which ultimately result in tumor formation in endocrine and endocrine-dependent organs.

The keyboard of the endocrine system is the pituitary gland. By virtue of the six hormones it is known to secrete, it influences directly the function of many endocrine organs, and directly or indirectly, several non-endocrine organs.

There are no reports on the effects of radiation on the posterior lobe of the pituitary which, among others, is concerned with water metabolism. Numerous studies indicate that all cells of the anterior lobe are radioresistant. Perhaps the most sensitive are the "basophiles" which may undergo necrosis at about 10,000 r (?). (After Haymaker) In mice, late after irradiation of the head (including the pituitary) with doses above 1000 r, there is atrophy of the pituitary and its target organs. In man, doses of $\pm 10,000_r$ are required to cause functional depression of this organ. Useful information will be forthcoming from the Donner Laboratory from radio-hypophysectomies in patients with advanced cancers. Late functional changes in the pituitary have not been carefully investigated. Endocrine organs are composed of cells capable of self-perpetuation and if only a few remain intact, they will regenerate and function is restored.

The pituitary, itself, is under the influence of the hypothalamus and this, in turn, is influenced by higher centers. The relative resistance of the central nervous system to irradiation has been reviewed by Dr. Haymaker. Contradicting current belief, Arnold et al state that dose levels above 1500 r cause late injury in the CNS. The extraordinary sensitivity of the cells of the NS during development is indicated by the work of Hicks. Certain cells seem sensitive to doses as small as 200 r. There is no information on the effect of radiation on hypothalamic-pituitary relationship.

In the genesis of endocrine organs, the specific (direct) irradiation effect is minor, while interference with the pituitary-target organ relationship frequently leads to tumor development in different organs in experimental animals of several species. Therefore, changes in the endocrine organs are best surveyed by considering the different pituitary hormone-target organ systems.

Female gonad. In women, ionizing irradiation as used in the clinic to produce or to treat sterility ($\pm 170-350$ r), does not usually induce ovarian tumors, although there are a few clinical observations suggesting, but not proving, that it may do so. In mice, however, irradiation of the ovaries almost invariably induces tumors. Radiation at first causes depression of hormonal production, as indicated by irregularities of estrus, but, when regeneration occurs, hormone production is increased. Regeneration proceeds to tumor formation in most mice of all strains studied. This ovarian tumor induction is not dose-dependent. 30 r by single exposure or a total of 90 r after long continued exposures (in even such small fractions as 0.1 r daily) will increase the ovarian tumor incidence. Development of ovarian tumors can be prevented by administration of ovarian hormones. Ovarian depression caused hypersecretion of gonadal-stimulating hormones of the pituitary. This hormone acts on a target organ (the ovary) which does not respond normally. The essential change is a disturbance in feedback mechanism. Irradiated ovaries are more likely to undergo tumor development by hyperstimulation with GSH than non-irradiated ovaries.

Uterus. The development of uterine carcinoma is influenced by gonadal hormones. Increase in development of uterine carcinoma in the rabbit by ionizing irradiation has been suggested by a small scale experiment of Lorenz. This field has not been adequately studied but no conspicuous influence of irradiation on uterine tumor development is suggested by any other observation.

Mammary gland. Increase in estrogen secretion by the ovaries late after irradiation is the probable cause of the increase of mammary tumor development noted in mice, rats and guinea pigs following total body exposure. In C3H mice with high spontaneous mammary gland tumor incidence, a decrease was reported. In mice, mammary tumors are most common in animals which also have a functional ovarian tumor. A hormonal imbalance has, however, not been demonstrated in rats and guinea pigs, in which total body irradiation did not lead to ovarian tumor development. Increased incidence of mammary gland carcinomas and sarcomas in mice and rats as a late consequence of total surface β - irradiation (after doses of 4-5,000 rep) is on record. Confirmation and explanation of the pathogenesis of these tumors are

desirable. There is no report indicating that in man, irradiation enhances mammary gland tumor development.

Testis. The hormone-secreting cells of the testis are known to be highly radioresistant. Dosages which result in complete cessation of spermatogenesis affect neither the androgen-secreting Leydig cells nor the estrogen-secreting Sertoli cells. Neoplasms of these cells have not been induced by irradiation. "Castration cells" do, however, appear in the pituitary after sterilizing irradiation.

Thyroid. Depression or destruction of the thyroid gland by I^{131} , an accepted clinical procedure, did not produce thyroid carcinomas in man, but five cases of leukemia have been reported. The latter is believed to result from incidental general irradiation.

The high sensitivity of the children's thyroid to ionizing irradiation is indicated by the development of thyroid tumors in children who have been treated with x-rays for enlargement of thymus or lymphadenopathy with doses somewhat above 200 r (Simpson et al). This possibility deserves experimental study. Since low iodine diet and goiterogens alone are tumorigenic to the thyroid, the development of thyroid tumors after irradiation is most likely in people subject to such combined influences. All of these procedures (thyroid destruction, low iodine diet, and goiterogens) reduce TH output and consequently, stimulate TSH secretion and therefore, act synergistically.

In euthyroid patients, no histological changes were noted 7 days after administration of 17-20 mc of I^{131} (14-31,000 rep); marked destructive changes occurred after 26-59 mc of I^{131} .

In rats, the induction of malignant thyroid tumors by 400 μ c of I^{131} was reported by one investigator only. The possibility of enhancing tumorigenesis of the thyroid by radio-iodine and simultaneous administration of an anti-thyroidal compound is indicated by another investigator. In hundreds of mice given various doses of I^{131} , thyroid tumors other than non-invasive adenomas were not noted. In rats, doses above 5 μ c of I^{131} (5800 rep) lower the proliferative capacity of the thyroid.

The parathyroid is certainly radioresistant. No tumor has ever been described in this organ after total body or local irradiation. This organ is not under the pituitary influence.

Pituitary tumors composed entirely of thyrotropes (TSH-producing cells) can be induced in almost every mouse by destruction of thyroid with radio-iodine. This is, undoubtedly, due to a derangement

of the feed-back mechanism, since similar tumors can be induced by surgical thyroidectomy or by blocking thyroid hormonal synthesis with a goiterogen. Administration of TH will prevent the development of these tumors. Since the latter is common practice in man, it is unlikely that pituitary tumors will develop in people treated with massive doses of I^{131} .

Adrenals and adrenotropes of the pituitary. One of the earliest effects of whole body x-irradiation is that of discharge of 17-hydroxycorticosteroids -- a non-specific stress effect. This rise disappears within a few days. From the morphologic standpoint, the adrenal is highly radioresistant. Late changes in the adrenals after irradiation have not been described. On the other hand, many mice exposed to total body irradiation develop, at an advanced age, adrenotropic pituitary tumors. It is highly probable that this is a consequence of an interference in adrenal-pituitary feed-back mechanism triggered by irradiation.

Mammotropic pituitary tumors are the commonest type among the pituitary neoplasms induced in mice by ionizing irradiation. They are very slow growing, appearing at senescence in animals exposed when young adults. Recent experimental studies indicate that estrogens are the stimulants of the mammotropes of the pituitary and that these tumors, as those of the mammary gland, are induced by hyperestrogenization. The latter is caused by the ovarian change (granulosa cell proliferation) initiated by ionizing irradiation.

General comments. Mention should be made that the development of leukemias in mice is strongly influenced by hormones. Correspondingly, the induction of leukemia by ionizing irradiation has been shown to be greatly influenced by the status of estrogenic, androgenic, and adrenal hormones. All of these are under pituitary influence.

Thus, while on morphologic grounds all endocrine organs with exception of the ovaries have been classified among those most radioresistant, it appears that from the standpoint of functional modification, they are fairly radiosensitive. Changes induced by small or moderate doses of ionizing irradiation not only do not terminate in recovery, but may be aggravated in time with such late severe consequences as development of neoplasia in diverse organs. Some pituitary hormones (such as somatotropins and adrenotropins) influence regeneration and growth of almost all cells in the body; it is possible that subtle changes in these cells of the pituitary or in higher centers, may account for the late degenerative changes and premature aging.

Detection of changes caused by irradiation in diverse organs and knowledge of their pathophysiology may lead to preventive procedures.

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