9

Acute Whole Body Radiation Injury: Pathogenesis. Pre- and Postradiation Protection

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"False facts are highly injurious to the progress of science for they often endure long; but false views, if supported by some evidence, do little harm for everyone takes a salutory pleasure in proving their falseness."

CHARLES DARWIN

9.1 General Notes

Exposure of the body to penetrating radiations produces ionization in the tissues. There is a disagreement as to the initial biological effect therefrom and the sequence of subsequent effects is not adequately known. At the present time it is not possible to bridge satisfactorily the gaps between the effects of radiation on pure chemical systems, the single cell, and the integrated mammal. Accordingly, it can be stated that little is known about the precise mechanisms of the action of ionizing radiation at the mammalian level. On the other hand, effects at the various levels have been studied extensively and certainly the end results in the mammal are well characterized today.

Radiation illness in its broad sense can be produced by all types of ionizing radiation. However, the dose required varies with the kind, the rate of administration and the penetrability of the rays. Furthermore, there may be situations in which the injuries are produced by a combination of different radiations, some of which are highly penetrating and some of which may be absorbed completely by the surface layers of the body.

Much confusion has arisen because of the inadequate means of measuring the response to radiation and the standardization of a physical unit that is adaptable for all sizes of animals and all types of radiation. The roentgen, or "r," a measure of the ionization in air, does not necessarily measure the

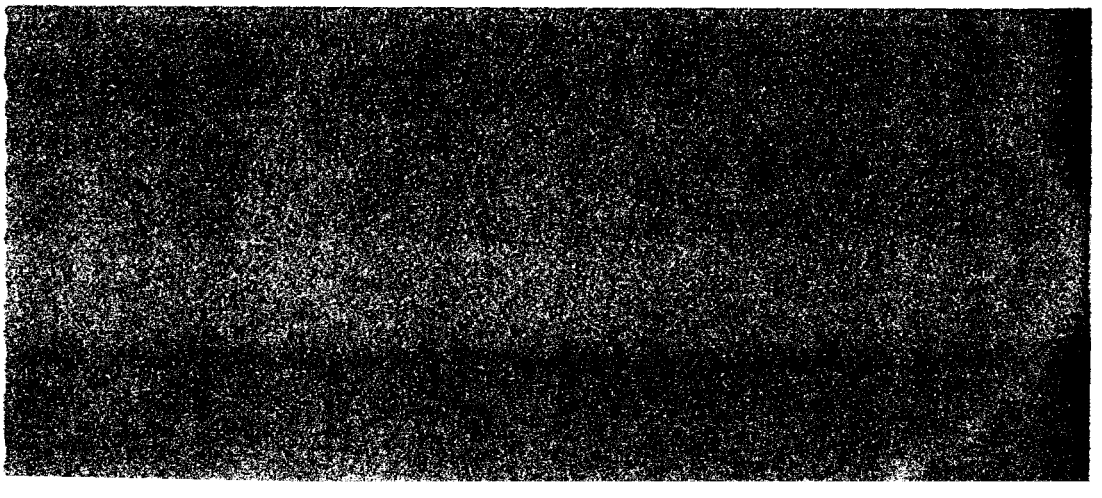
dose absorbed by the tissue. At relatively recent meetings (1956–1962) of the International Commission on Radiological Units (ICRU), while it was stated that the roentgen (symbol r) be retained as the unit of measurement of gamma and x-radiation, it was recommended that when ever feasible "the dose be expressed in terms of the quantity of energy absorbed per unit mass (ergs per gram) of irradiated material at the place of interest." The unit is the "rad," 100 ergs per gram, which replaced the older "rep" which could be assigned values ranging from approximately 80 to 100 ergs per gram. The rad is not readily determined for gamma or x-radiation; however, tables for its estimation from exposure dose in tissue are provided in reports of the Commission. The conditions under which the exposure dose is measured should be designated as free in air, at skin surface, or at x-centimeters depth, and the data such as scatter, half-value layer, target-to-skin distance, and KVP should be included. In commenting on the Commission's recommendations, Failla stated that "no physical unit can fulfill the ideal requirements of making all biological effects of ionizing radiation appear independent of wave length or more generally, independent of specific ionization," and that "in the present state of our knowledge no chemical or biological unit can fulfill the ideal requirement either." For the purposes of correlating dose with effects on the whole body, depth dose and distribution of the absorbed energy becomes of great importance, as shown by Tullis *et al.* and Bond *et al.* Further, no single physical unit can satisfactorily characterize the total dose because of differences in relative absorption by different tissues.

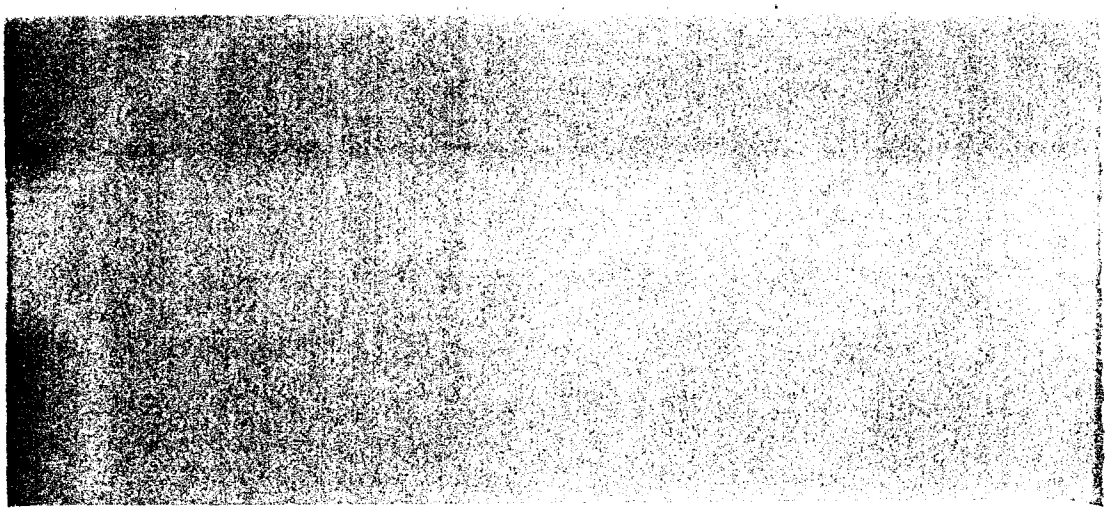
It is essential to attempt quantification of the biological response, as well as the physically measured dose, when trying to correlate effect with dose. The biological measure may include the LD_{50} and the slope of the dose mortality curve, as in all toxicological studies. Other biological measurements of dose are splenic-thymic weight decrease (Carter *et al.*), body weight (Chapman and Jerome), gut weight (Conard), the hematological response, survival time, iron uptake by erythrocytes (Hennessey *et al.*) and histological changes. Quantitative measures of biological effect useful in mammalian radiology have been reviewed by Storer *et al.*

9.2 Classification of Radiation Injuries

Radiation injuries can be divided into two general categories, early and late injuries. The early type results from brief intense exposure; the late type either from exposure to large single doses, or from prolonged exposures of lower intensity. The following is an outline of the two categories, only the first of which is dealt with extensively in this chapter:

9.2.1. *The Early Injuries Produced by Brief Exposure to Large Doses of Radiation.*





9.2.1.1 *Injuries from penetrating radiation.*

1. Total body exposure: The acute illness produced by total body radiation may occur in man from exposure to gamma and/or neutron radiations from a detonating atomic bomb, gamma exposure from close-in fallout from atomic bombs, from accidents with radioactive materials as nuclear power sources, or in radiotherapy either for malignancy or as a means of depressing antibody response preparatory to tissue transplantation. Exposure of animals to such whole body radiation under experimental conditions results in this type of illness.

2. Partial body exposure: Acute illness may result from partial body exposure to penetrating radiations as is commonly seen in therapeutic radiation as for cancer.

9.2.1.2 *Injuries from poorly penetrating radiations.* Acute injury of the skin or other body integuments may result from beta ray exposures of the skin as is seen with fallout radiation or from accidents involving handling of radioactive materials. This type of injury is discussed in the chapter on skin.

9.2.1.3 *Injuries from absorption of radioactive materials.* Absorption of radioactive materials may occur from inhalation, ingestion or entrance into the body from open wounds of fallout from atomic bombs or of radioactive materials in laboratory accidents. Such a hazard is much more likely to result in chronic long-term effects than in early effects. This type of hazard is discussed in the chapter on internal effects.

9.2.2 *Chronic Radiation Injury*

9.2.2.1 *Injuries from penetrating radiation.* Total body or partial body exposure may result in late effects, some of which are listed below.

1. Blood dyscrasias such as anemia, purpura, leukemia.
2. Increase in degenerative diseases.
3. Shortening of life-span; perhaps accelerated aging.
4. Increase in incidence of cancer.
5. Retardation of growth and development in children.
6. Increased incidence of cataracts.
7. Impaired fertility.
8. Genetic effects.

All such late effects are not discussed in detail in this book but are covered elsewhere (National Academy of Sciences report on Pathological and Genetic Effects of Radiation; Report of the United Nations Scientific Committee on the effects of atomic radiation). However, basic considerations are presented in Chapter 15, genetics in Chapter 14, and results of damage *in utero* in Chapter 13.

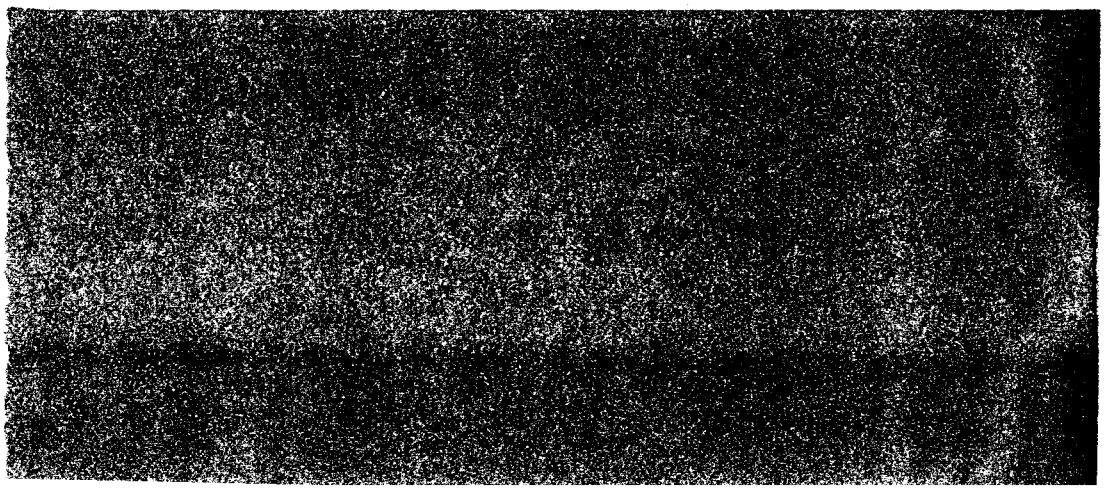
9.2.2.2 *Injuries from poorly penetrating radiation.* Beta radiation injury may result in continuing effects on the skin in the form of chronic radiation

dermatitis and cancer of the skin. Such effects on the skin are discussed in Chapter 12.

9.2.2.3 *Injuries from absorption of radioactive materials.* Absorption of radioactive materials include long-term effects such as leukemia and cancer of the bone. Such effects are discussed in Chapter 11.

9.3 Acute Illness from Total Body Exposure to Penetrating Radiations.

This illness may be produced by exposure to a single type or a combination of different types of radiation (x-ray, gamma rays, or fast neutrons). It will be a rare occurrence in civil life and for practical purposes will not be seen short of industrial accidents and atomic warfare. The syndrome in fulminating form was observed in the Japanese (appropriately termed "atombombendisease" by them) following the atomic bombings of Hiroshima and Nagasaki in August 1945, and was seen also, in mild form, in the Marshallese exposed to fallout radiations in 1954. In Japan, accurate clinical observations and laboratory studies were scanty during the first 3 weeks after the bombings. In the fallout accident involving the Marshallese, extensive clinical and laboratory observations were made, providing extensive data in the sublethal range. A number of industrial and laboratory accidents have occurred in which human beings have received relatively large doses of x-ray, gamma, or neutron irradiation, and these incidents have been reviewed and summarized (Hayes, 1956, and 1957). Some of the more serious accidents have provided extensive data on human beings exposed to both whole body and partial body radiation in the near-lethal to lethal dose ranges [Andrews *et al.;* Mathé *et al.;* Hemplemann; Howland, *et al.*, 1961). In addition, patients have been exposed extensively to whole body radiation, either for radiotherapy of malignancies or to depress the immune response in connection with bone marrow- or other tissue transplantation (Miller, Fletcher and Gerstner; Gerstner; Thomas, Lochte, and Ferrebee, Haurani, Repplinger, and Tocantius; Merrill, Murray, Harrison, Friedman, Dealy and Damin). Although considerable data on human beings has thus been provided, the information is far from complete. One or more of the following difficulties has obtained in each instance: incomplete dosimetric information; range of doses inadequate; number of patients small; exposed individuals have serious underlying disease; observations, for varying reasons, were not made in sufficient detail or with sufficient frequency; course of the disease was altered by necessary treatment. Thus many inferences for man with respect to dose-response relationships, survival time, mortality rate and symptomatology still are based on animal experimentation. Initially, therefore, the response of different species of animals to whole body irradiation will be considered.



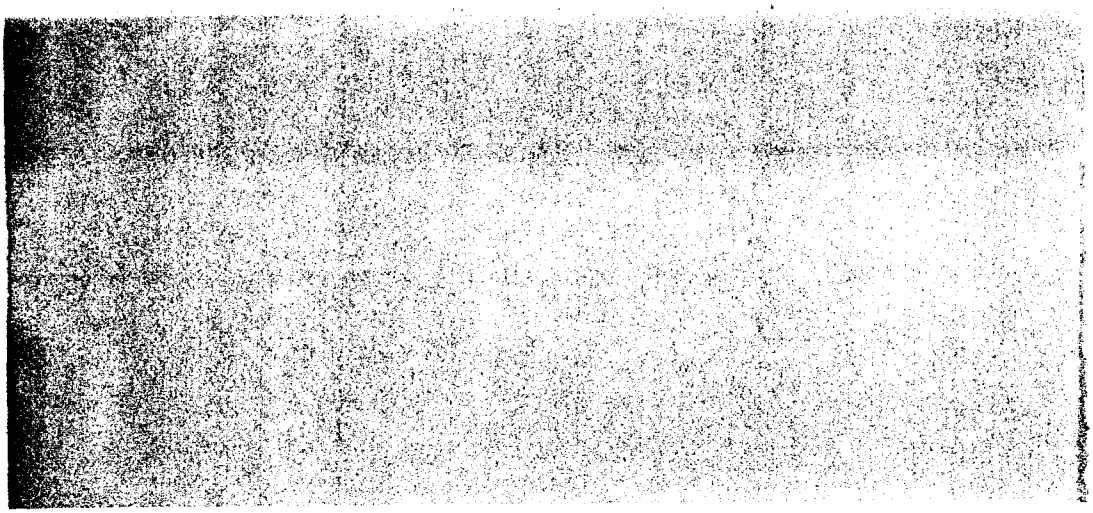


TABLE I

SPECIES	TYPE OF RADIATION	LD_{50} 30 DAY	
		Air exposure dose in r	Absorbed dose in rads at midcenter
Mouse	250 KVP x-ray	443	638
Rat	200 KVP x-ray	640	796
Guinea pig	200 KVP x-ray	337	400
Rabbit	250 KVP x-ray	805	751
Monkey	250 KVP x-ray	760	546
Dog	250 KVP x-ray	281	244
Swine	1000 KVP x-ray	510	247
Sheep	Gamma approx. 0.7 mev.	524	205
Goat	200 KVP x-ray	350	237
Burro	Gamma approx. 1.1 mev.	651	256

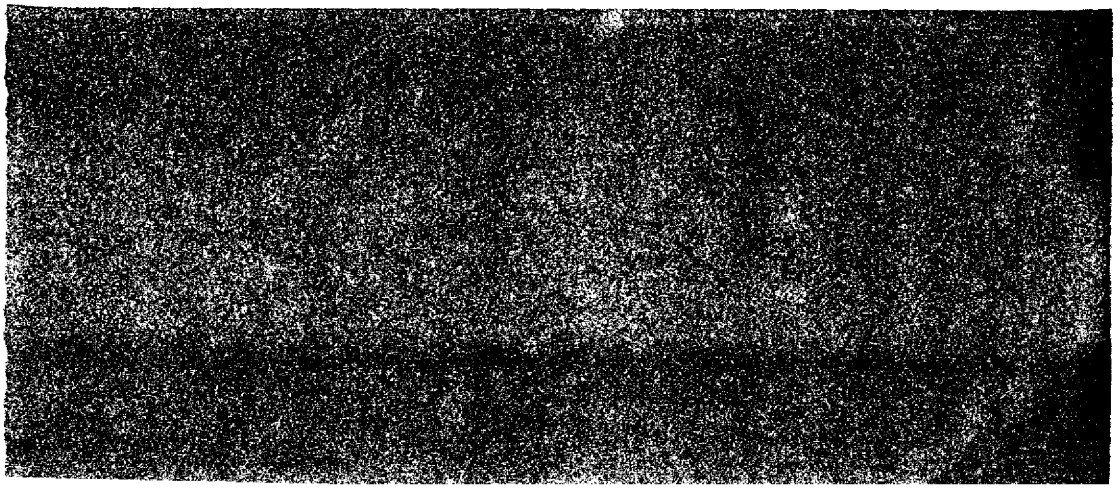
Representative LD_{50} per 30 day values for a number of species are given in Table I (Bond and Robertson). The absorbed dose in rads is the significant parameter that determines the degree of biological response. All mortality data in the table refer to conditions of exposure such that dose distribution throughout the body is essentially uniform. The dose at midcenter has no particular significance except that it is convenient and represents the approximate dose that all tissues received (no single parameter is adequate to characterize an exposure under conditions of nonuniform dose distribution through the tissues). It can be seen at once from the table that the LD_{50} values show no consistent pattern as air dose. Expressed as absorbed dose, however, the LD_{50} values for large animals are considerably smaller than for small species, and the degree of variation among species is less with large animals. The LD_{50} of man is not known with any degree of accuracy; however, it is expected that for uniform whole body exposure the value is approximately 300 to 400 r, expressed as midcenter tissue dose.

The distribution of deaths as a function of time after irradiation varies with the dose of radiation and with species. For example, with the dog in the lethal range, the mean survival time is approximately 12 days, with deaths occurring 6 to 26 days after exposure. With doses of 1000 to 1500 r, some deaths occur earlier (3rd and 4th days) and the toxic symptoms of vomiting, anorexia, and diarrhea become more prominent. With doses of 1500 to 6000 r, all dogs die on the 3rd and 4th day. Severe diarrhea is present. With the mouse, the distribution of deaths after irradiation with doses less than an LD_{50} is essentially unimodal with peak of deaths occurring 11 days after exposure (Cronkite, Bond, Chapman and Lee). In the LD_{50} range the deaths become bimodal with a peak at 4 to 6 days and another at 11 days

As the dose is increased above the LD_{100} the first peak of deaths becomes progressively more prominent and the second peak fades out so that with doses of 1500 to 10,000 r the mean survival time is approximately 4 days. A similar phenomenon is seen with rats; however, the first peak is more prominent at lesser doses of radiation. The first peak of deaths has been correlated with severe gastrointestinal injury and dysfunction (Bond *et al.;* Quastler *et al.;* Brecher and Cronkite; Cronkite and others). The relative sensitivities of the species differ, the rat GI tract being relatively more sensitive. The second peak of deaths is correlated with the sequelae of pancytopenia (infection, hemorrhage, and anemia). If the LD_{50} of the species is low so that amounts of radiation are less than that needed to produce the severe GI injury and dysfunction, the species has essentially a unimodal distribution of deaths in the lethal range, with a mean survival time of approximately 10 to 15 days, e.g., the dog. If LD_{50} is high, a modal distribution of deaths may appear, e.g., mouse, rat and rabbit. Where man fits into the above relative sensitivities of tissue is not yet known; however the evidence indicates that man responds in a manner similar to the dog.

The early diarrhea (first 4 days) is correlated with direct radiation injury of the gastrointestinal tract; however, late diarrhea (7 to 24 days) occurs as a result of ulcerations and hemorrhage due to the pancytopenia. Studies strongly indicate that complete histological recovery of the bowel occurs by 4 to 5 days, hence if the animals survive to the stage of late diarrhea, the bowel has been reconstituted. Histological studies show typical hemorrhagic and agranulocytic lesions in a bowel that is otherwise approximately normal in appearance (Conard *et al.* and Brecher *et al.*).

With the preceding in mind, the following is formulated with regard to the probable response of man to penetrating radiation exposure at different dose levels. With small amounts of total-body radiation (under 100 to 150 r), there may be no symptoms or at most a transient nausea. Leukopenia, particularly the lymphocytopenia, will be mild and of short duration. With larger amounts of radiation, 150 to 1000 r, the characteristic clinical picture may develop. Within a few hours, pronounced nausea, vomiting, malaise, weakness, headache, dizziness, anorexia, tachycardia, irritability and insomnia will generally appear. Leukopenia, anemia and thrombocytopenia will develop at different rates (Cronkite; Lawrence, Dowdy and Valentine; Jacobson *et al.;* LeRoy). The symptoms will usually subside within 24 to 48 hours to appear again after a few days. The interval between the initial and the subsequent symptoms has been termed "the latent period." This latent period will become shorter with larger doses and may be absent if the dosage is sufficiently high. With termination of the la-



tent period, infections and hemorrhages will become more prominent. In the Japanese, infections were particularly apparent 3 to 5 weeks after exposure and hemorrhagic phenomena four to 6 weeks after exposure (LeRoy). Details of the serial blood changes have been covered in a previous chapter. With large amounts of radiation (2000 to 30,000 r), the signs and symptoms appear in an intensified form with mean survival time of about 3 to 4 days. With doses in excess of 30,000 r sudden deaths occur in mice preceded by convulsions, central nervous system symptoms, or respiratory difficulty (Langham *et al.*).

9.4 Acute Illness from Partial Exposure to Penetrating Radiations

The acute illness that is produced by exposure of part of the body to penetrating radiations is seen characteristically in patients undergoing high voltage x-ray therapy for cancer. With respect to the initial so-called "toxic symptoms," they are similar to the syndrome produced by a single intense exposure of the whole body to penetrating radiation. Radiation of certain areas of the body will produce the illness with greater frequency, or with less radiation than for exposure of other parts of the body. Exposure of a relatively small area of the body does not produce the severe pancytopenia that results from exposure of the whole body to the same amount and type of radiation. Irradiation of the thorax and abdomen, particularly the upper abdomen, produces a high incidence of nausea, vomiting, and anorexia. In contrast to this, irradiation of the head and extremities rarely produces these symptoms. Since the clinical course and handling of this type of reaction to penetrating irradiation have been amply covered in recent text books and reviews of clinical radiology, further discussion is not necessary.

These initial "toxic symptoms" should be distinguished sharply from the serious syndromes that can develop in days or weeks if sizeable regions of the body are exposed to high doses of radiation. For instance in the Lockport accident (Howland *et al.*) a variety of signs and symptoms including severe pancytopenia developed after exposure of the head, thorax, and abdomen to large doses of x-radiation. In general, following partial or surface exposure, the organism is able to react locally and generally to injury, in accordance with the concept of adaptation (Selye). Bond *et al.* have demonstrated that local irradiation of the abdomen and elsewhere in the body produces the alarm reaction as described by Selye. In contrast to this, exposure of the whole body to large amounts of penetrating radiation produces diffuse injury of varying degrees to all tissues and the organism may be less able or unable to react with the usual protective and adaptive mechanisms.

9.5 Pathogenesis of Radiation Injury

Numerous theories have been advanced to explain the biological effects of ionizing radiations. Only those theories which may help to understand the pathogenesis of total body radiation and which may indicate a possible therapeutic approach will be considered in this chapter.

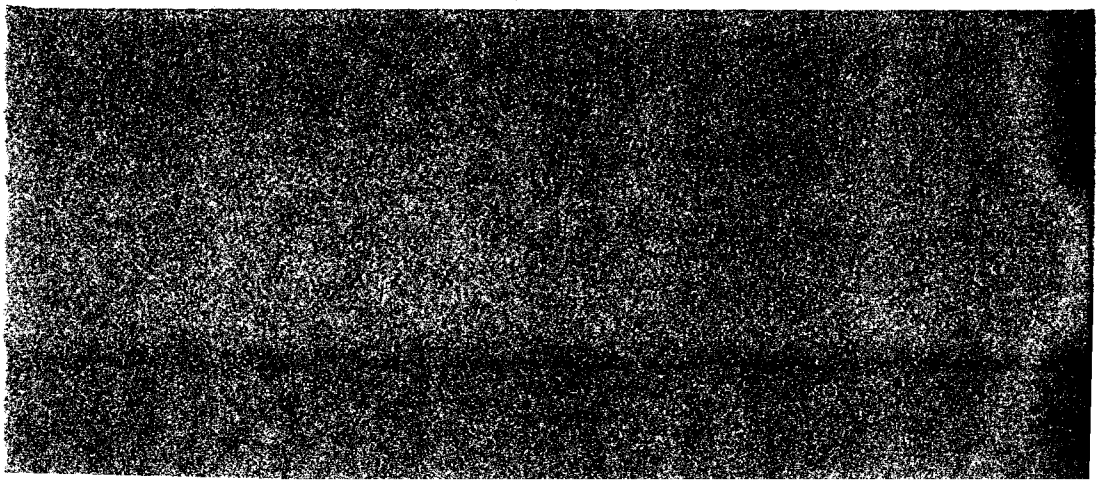
It is probable that the primary interaction between radiation and tissue may involve either direct "hits" on biochemical molecules, or "indirect effects" on such molecules mediated through radicals produced by interaction of the radiation with water and other chemical substances in the tissue. These primary phenomena will not be considered in detail here. For purposes of discussion, only those mechanisms at the biochemical or higher level that have been considered to play a role in initiating and continuing the acute radiation syndrome will be considered. Several possible mechanisms that have been considered to be contributory are listed and discussed below, even though some of these are currently believed to play a minor, if any, role in the development of the signs and symptoms observed.

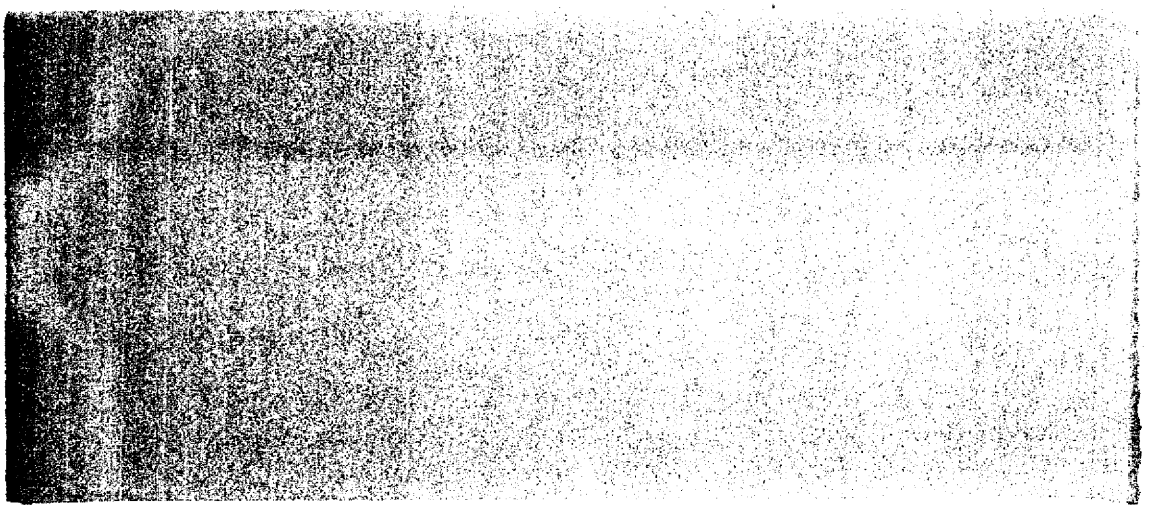
1. Enzyme inhibition; activated radicals,
2. Alterations in cell membrane permeability,
3. Generalized protein denaturation,
4. Inhibition of mitosis; chromosome changes,
5. Production and circulation of toxins
6. Adrenal cortical insufficiency,
7. Pancytopenia and its sequelae.

The syndrome is obviously the result of disturbances in the homeostasis of the animal produced by cellular injury of varying degrees in different organ systems. The fifth to seventh mechanisms are attempts to explain the clinical syndrome at a mammalian level. The seventh mechanism probably the result of the fourth, will explain most of the gross clinical and pathological observations seen in animals dying in the lethal range.

9.5.1 *Enzyme Inhibition.* The concept of enzyme inhibition has been carefully and extensively studied by Barron and associates. Initially it was thought that enzyme inhibition was not considered important because the doses necessary to inactivate concentrated enzyme solutions were 10 to 1000 times greater than those that seriously injure living tissues. The present status of the enzyme inhibition concept may be summarized as follows:

As a result of the work of Fricke, 1934, and of Dale, 1943, and others, it has been shown that in dilute solutions the number of molecules brought into reaction is proportional to the number of ions produced in the solution, and is independent of the concentration of the solution. This led to the concept that the action of the radiation is not primarily on the dissolved





substance, but on the solvent. The activation of water consists of the production of highly reactive oxidizing substances (OH, H_2O_2 and other complexes) as the result of ionizing radiation. The active products presumably oxidize the sulfhydryl groups (SH) of many enzymes to the enzymatically inactive disulfide form. This inactivation is generally reversible in the lower dose range. With larger amounts of radiation, the enzyme inhibition is also produced by protein enzyme denaturation by direct rupture of chemical bonds. This type of denaturation is irreversible. Reversible enzyme inhibition may play a part in the initiation of the syndrome of radiation illness, particularly in the lethal range, but is probably not the only and may not be the most important initiating mechanism.

Recently Pajewski and Pauly have studied the effects of radiation on enzymes in impure solution, and finds the doses required for inactivation to be quite high. This may be explained on the basis that while enzymes in pure dilute solution may interact with essentially all radicals produced in the water, in the presence of relatively inert competing substances, very high doses may be required for significant inactivation. Thus while enzyme inhibition may play a role in producing damage, there is at present no conclusive proof that this mechanism is of major importance in producing the acute radiation syndrome.

9.5.2 *Alterations in the Permeability of Cell Membranes* have been postulated. Absorption of water and vacuole formation can be observed within nuclei. This may result in alterations in the permeability of cell membranes or an increased intranuclear osmotic pressure (Failla).

9.5.3 *Denaturation of Proteins.* In general, in addition to the protein enzymes already considered, denaturation has been postulated as being responsible for some of the phenomena that are observed. Denaturation is known to occur at higher dose ranges; however, it appears unlikely that it plays a significant role at dose levels of most interest biologically.

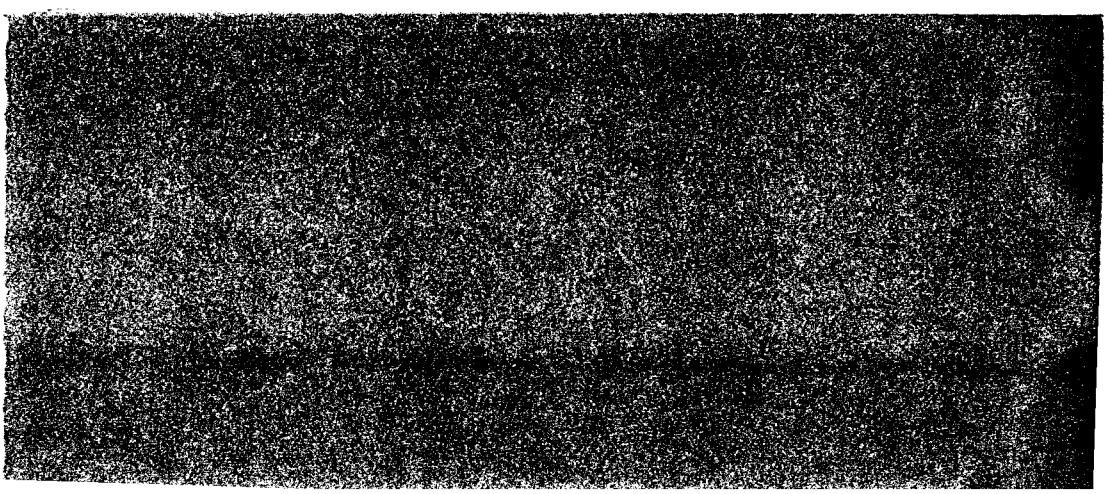
9.5.4 *Inhibition of Mitosis; Chromosome Changes.* Mitotic inhibition occurs at relatively low dose levels. Apparent recovery may result, and the mitotic index may return to normal within a short time (Fliedner *et al.*). However, even at doses as low as 100 or 200 r, a large number of mitotic figures may show obvious abnormalities (Puck; Bender; Fliedner, Bond, Cronkite). These abnormalities may range in severity from gross disruption of the chromosome pattern with fragmentation of individual chromosomes to chromosome "stickiness," and undoubtedly to damage too subtle for detection by cytological means. The cell so affected may die essentially immediately, it may fail to divide and become a "giant" cell, or it may be able to go through a limited number of subsequent divisions before all progeny die. The net result is that the proliferative potential of organs composed of rapidly dividing cells is reduced, and thus cellularity is reduced.

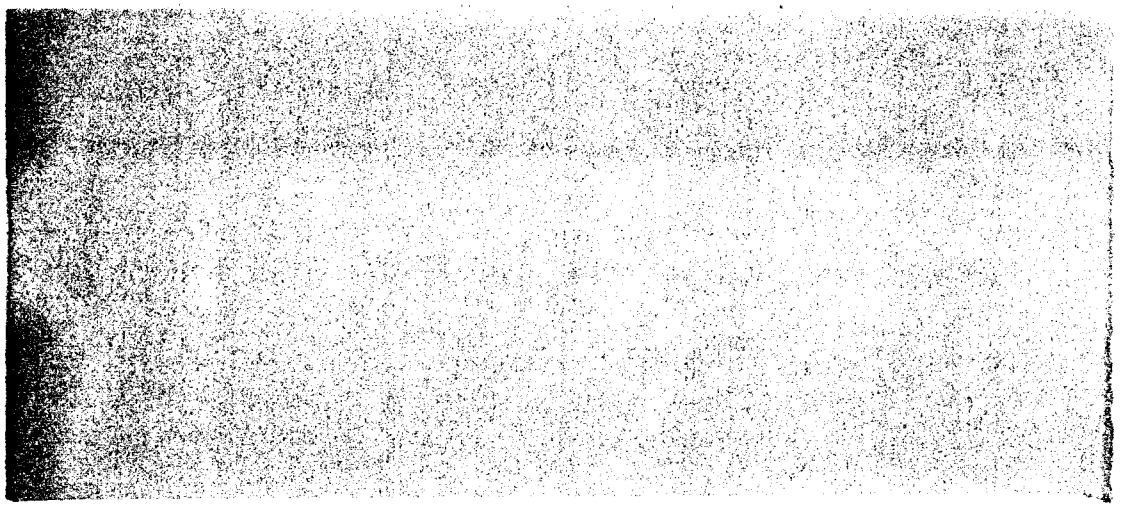
In normally nondividing cell systems as in the liver, chromosome damage can be "unmasked" by inducing cell division as a result of partial organ extirpation. It is still an assumption that the chromosome damage known to occur is responsible for decreased proliferative capacity—such damage could be present concomitantly with other lesions responsible for the defect.

9.5.5 *Circulating Toxins.* The production and/or absorption and circulation of toxic substances from irradiated tissues or absorption from the bowel whose selective permeability has been changed, have been considered by some as contributing to the development of radiation illness. Others doubt its importance. Bacterial pyrogenic substances, digestive enzymes, and "enterotoxins" from the bowel and histamine-like substances from tissue in general have been considered by various investigators as playing some role in the pathogenesis of radiation illness. To date, the available evidence in favor of indirect effects upon the blood-forming organs by circulating toxic substances has not been conclusive (Lawrence; Valentine and Dowdy; Campo, Bond and Cronkite).

The histamine theory of radiation illness has been advocated by Ellinger, who considers that many of the effects of radiation are due to the production of histamine-like substances. Other investigators have failed to demonstrate significantly increased amounts of histamine in the blood and in tissues. Weber and Steggerda have obtained convincing information showing that there is a correlation between the increase in histamine levels of rat plasma and depression in the blood pressure following x-irradiation. Techniques for detecting histamine are difficult and failure of some investigators may have been due to technical difficulties. In addition, the presence of increased levels of histamine does not necessarily mean that histamine is the cause of the various phenomena that are seen after irradiation but may simply be a result of the fundamental defect produced by the effects of ionizing radiation on tissue. Conard has shown in a study of the motility, tonus, and contraction of the bowel immediately after irradiation locally that the behavior of the bowel is not identical to that produced by histamine baths or injections. Other evidence which suggests that histamine may play an important part in the pathogenesis of radiation illness is the fact that conditions that increase the histamine content of tissues may also increase the lethality rate from x-rays. For example, induced hyperthyroidism increases the histamine content of tissues (Parrot) and increases the lethality of total body x-rays in mice (Blount and Smith). Adrenalectomy also increases the histamine content of tissues of the rat (Rose and Brown) and definitely increases the lethality of x-rays (Cronkite and Chapman; Kaplan; Edelman and Campo).

9.5.6 *The Role of the Adrenals in the Acute Radiation Syndrome.* The





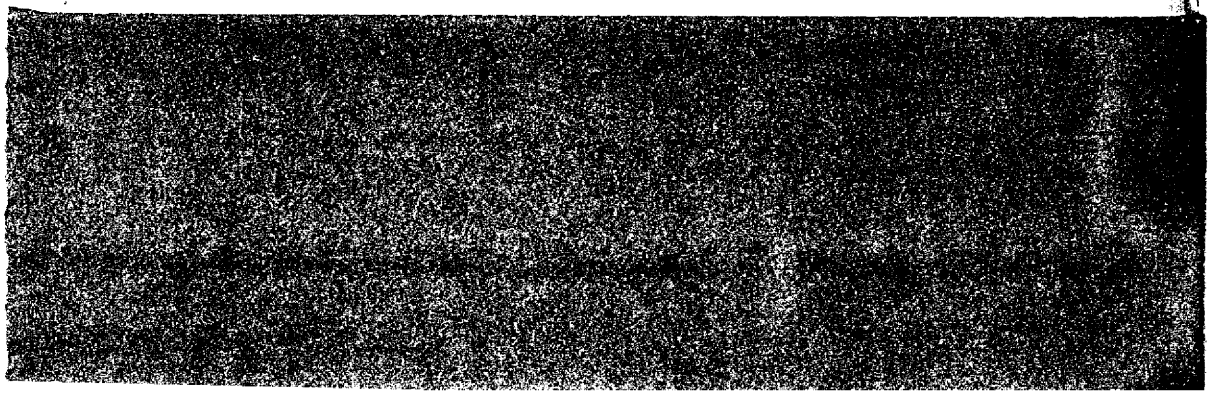
adrenals have been shown to play a role in the acute radiation syndrome; however, the importance of this role has received widely different evaluations. Certain similarities between adrenal cortical insufficiency and acute radiation injury, such as changes in blood chlorides, water metabolism, blood cholesterol, fat deposit in the liver and blood sugar, have been claimed. There is no doubt that polydipsia and polyuria follow heavy exposure, and that there may be a redistribution of fluids as indicated by blood volume, plasma and hematocrit changes, and some edema. The changes in blood chemistry are small and apparently inconsistent. The fluid balance changes noted following acute totalbody exposure can be explained on the basis of vomiting and/or diarrhea, with the resulting fluid and electrolyte losses, as well as the eventual failure to eat and drink. Many of the changes may be explained as resulting from the stress accompanying the disease. Patt and associates have described a series of characteristic changes in the adrenals of the rat exposed to various dosages of x-radiation, which were prevented by hypophysectomy. Evidence has since been presented that indicates radiation is not an exception to the general rule that adrenalectomy sensitizes to all stresses (Cronkite and Chapman; Kaplan). Nims and Sutton presented data on the rat which indicated that the polydipsia and decrease in adrenal cholesterol level following WBR were the result of increased activity of the pituitary-adrenal system, and that the initial fall in liver glycogen was principally the result of lowered food intake. Lasser and Stenstrom, in a clinical study of patients following pelvic area irradiation, found the degree and time course of "radiation sickness" to correlate with changes in the absolute peripheral eosinophile count, but not with the Thorn ACTH-eosinophile, 4-hours response test. They concluded that the adrenal cortex underwent definite changes in the course of irradiation, but that the changes probably were not related to clinical "radiation sickness." Santisteban *et al.* showed that cortisone replacement therapy progressively restored the resistance of irradiated-adrenalectomized mice. However, events causing death in the irradiated-intact animals differed from those in the x-irradiated adrenalectomized group despite cortisone treatment, indicating that cortisone may only partially restore resistance. Bond *et al.* obtained highly selective irradiation of various small portions of the rat with a "pencil" beam of 190 mev deuterons, and found that the thymus, spleen, and adrenal weights characteristic of pituitary-adrenal stimulation resulted only if and when the irradiation given imposed severe stress on the animal, as indicated by the gross symptoms of illness and body-weight loss. Such changes could not be elicited by irradiation of the adrenals alone, nor were they prevented by adrenal irradiation if additional radiation damage to other tissues sufficient to put the animal under "stress" were present. The isolated, perfused calf's adrenal gland was used to study the effects of

gamma radiation on the secretion of adrenal cortical hormones (Rosenfeld *et al.*). Secretion was markedly reduced; however, it should be noted that the doses used were in excess of 2000 r (some five times the LD_{50} and always supralethal), and that the isolated organ was removed from secretory stimuli that may be present in the intact animal following acute total body irradiation. Thus, the author's conclusion that the adrenal cortex must be considered a radio-responsive tissue cannot be considered to characterize the role of the adrenal in acute total body irradiation. French *et al.* have demonstrated early changes in plasma hydroxycorticosteroid levels, as well as changes in the peripheral neutrophile, lymphocyte, and eosinophile counts of monkeys given from 50 to 400 r total body radiation. The changes were maximal at 4 to 8 hours, and values were again normal by 12 hours. Shielding of the head or adrenals did not modify these early changes, implying that they were not the result of a direct effect on the pituitary-adrenal axis. Brayer *et al.* found, after a supralethal dose of WBR (1000 r) in swine, that a marked increase in urinary excretion of total adrenal cortical steroids occurred, which was most pronounced in the first 24 hours. In the case of the irradiated animal in the lethal dose range where pancytopenia is followed by its common sequelae of infection and hemorrhage, there is a depletion of the adrenal lipid and by inference one might say that this represents the stage of exhaustion in the adaptation syndrome. The present writers are inclined to interpret this terminal state as being simply the reaction of the organism to an overwhelming infection and not primarily to the initial radiation injury.

In view of our present knowledge, it appears quite certain that the role of the adrenal cortex is secondary to the stress of radiation in the development of the acute radiation syndrome. The previously quoted biochemical changes, the complications of hemorrhage, anemia and infections, the biological complexities of various mammals, and the simultaneous operation of factors which may change electrolyte and water metabolism in opposite directions at the same time point out the hazards that are contingent upon drawing conclusions that adrenal insufficiency exists because some of these changes are observed. The recent review of Sayers on the adrenal cortex and homeostasis points out this problem in great clarity. The problem is also discussed by Mole.

9.5.7 *Pancytopenic Sequelae, Infection.* The sequelae of pancytopenia are infection, hemorrhage and anemia. The latter two are discussed in Chapter 8. Infection here will be discussed as it relates to the lethal range of exposure, i.e., the range where some, but not all, of those exposed will die within a period of several weeks and to the sublethal range.

Evidence that infection is of importance in the acute radiation syndrome falls into several categories: (a) Clinical observations on human beings ex-



posed to large doses of radiation in the Japanese bombings and in reactor accidents and similar observations on large animals dying from radiation exposure. (b) Correlative studies on mortality rate, time of death, and incidence of positive blood cultures in animals. (c) Challenge of irradiated animals with virulent and normally nonvirulent organisms. (d) Studies on germ-free animals. (e) Studies of the effectiveness of antibiotics in reducing radiation mortality rate. (f) Studies on the effectiveness of agents that will augment or restore natural antimicrobial defenses on mortality rate in irradiated animals. A brief word on each of these lines of evidence is given below.

The Japanese dying of "atombombendisease" and human beings heavily exposed at the Los Alamos accident (Hempleman *et al.*) and Yugoslav (Mathé *et al.*) showed unmistakable evidence of infection. Signs and symptoms included high fever, Ludwig's angina and other mucosal and cutaneous infections, cellulitis, pneumonia and septicemia. Autopsy findings bore out the clinical picture. Similarly with large animals, particularly dogs, the temperature begins to rise 3 to 4 days before death, and is usually quite high prior to death. Orocutaneous lesions are common. At autopsy, pneumonia is the rule, as well as other evidence of infection.

At doses of total body radiation even in the high sublethal range, however, (Marshallese exposed to fallout gamma radiation, Cronkite *et al.*) no evidence of increased susceptibility to infection may be manifest. The Marshallese, in some of whom the neutrophile counts fell below 1000 per $mm.^3$, showed no increase in the incidence of infectious diseases over control groups. Epidemics of upper respiratory infection, measles and chicken pox, that occurred were no more pronounced in extent or severity in the exposed population compared to unexposed Marshallese in whom similar epidemics occurred at the same time. Similarly, the heavily-exposed individuals in the Y-12 accident (Andrews *et al.*) showed no infections that could be attributed definitely to radiation exposure.

The time of peak incidence of bacteremia in irradiated animals has been correlated with the time of peak incidence of mortality in the extensive studies of C. P. Miller and his group. The organisms are chiefly enteric in origin, and apparently gain access to the blood stream through the bowel wall. A positive correlation, of course, does not prove cause and effect, and it has been stated that such organisms represent agonal invasion and thus may be "incidental." A cause and effect relationship seems highly probable, particularly in the light of evidence from antibiotic therapy studies outlined below. Total body irradiation has been shown to activate infections that otherwise remained "latent" (Bond *et al.*).

Challenge of irradiated animals with virulent, or normally nonvirulent bacilli results in death at infective levels that produce no mortality in non-

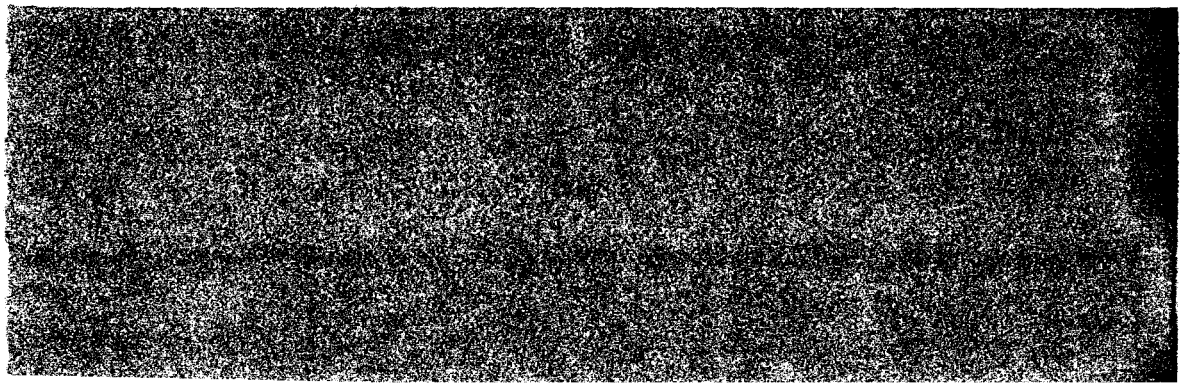
irradiated control animals. With virulent organisms, an appreciable increase in mortality rate is seen at x-radiation dose levels below those producing mortality in the absence of challenge (Shechmeister *et al.*). With normally nonvirulent organisms, the mortality rate following exposure in the lethal range is appreciably enhanced. Increased susceptability to viruses, Rickettsia, parasites such as *Trichinella spiralis*, and bacterial toxins in the irradiated animal have been reported. A synergistic effect of x-radiation and cortisone in increasing susceptibility to administered bacteria and viruses has been reported (Friedman *et al.*).

It is of importance to point out, however, that there is considerable variation in the degree of increased sensitivity to different microorganisms or toxins, and in the degree of effects depending on the route of administration (see under mechanisms of increased susceptibility below). Specifically, Hale and Stoner have shown that although a marked increase in susceptibility to pneumococci is evident in the irradiated mouse, no such increase is found for mice challenged with a virulent influenza virus. With the virus innoculation, the animals were protected against secondary bacterial invasion with antibiotics. The degree to which the reported increased susceptibility to viruses in irradiated individuals is due to secondary bacterial invasion is not known. Neutrophiles play a large role in resistance against bacterial, but not viral diseases (Wood). The peripheral neutrophile count is profoundly affected by irradiation, and thus a greater degree of altered immunity to bacterial, rather than viral infections might be expected. At any rate, blanket statements relating to susceptibility of the irradiated host are not warranted, and specific consideration in each instance must be given to the infecting agent, the host, the physiological state of the host and the degree of exposure to both radiation and the infectious agent.

Germ-free animals die following total body exposure to x-radiation (Reyniers). The dose required to kill, however, is somewhat higher than for "normal" animals, and the survival time is increased. These results can be taken as indicating that infection may be responsible for death in the irradiated animals in certain dose ranges. At higher doses, animals die even in the absence of infection. Extensive hemorrhage probably is a major cause of death in such animals; however, undoubtedly other poorly understood biochemical changes contribute.

Antibiotics administered following radiation exposure have been shown definitely to enhance survival under some circumstances. The incidence of spontaneous mortality has been shown to be reduced, and mortality in x-irradiated mice subsequently challenged with virulent organisms has been decreased.

Antibiotics, however, should not be considered to be necessarily lifesaving following severe exposure in the human being. Two human beings



exposed in the Los Alamos reactor accidents and one exposed in the Yugoslav accident died despite vigorous antibiotic therapy. It is possible that improved results would be obtained with a schedule of administration designed to avoid the development of resistant bacteria (Coulter and Miller). Of significance in this regard is the recent report (Hammond *et al.*) showing that mice exposed to neutron radiation are protected from death by antibiotics during the first 10 days, but not in the 11- to 30-day period when most mice die following gamma or x-radiation. This would indicate that under some conditions, at least, infection alone does not account for the mortality observed.

Thus, there is no doubt that infection contributes greatly to the disease process, and mortality following exposure to total body radiation. However, it is equally clear that acute radiation illness is not an infectious disease in the usual sense; rather infection is a complication of a serious debilitating underlying disease which specifically interferes with defense mechanisms against bacterial invasion. Death may occur in some individuals whether infection is present or not, at high dose levels. Thus antibiotics cannot be expected to be curative as with primarily infectious diseases, and dramatic cures cannot be expected from this type of therapy. However, as with any debilitating disease, antibiotics definitely will prevent death in a certain number who might otherwise die—prevent death until regeneration and restoration of functions allows normal defense mechanisms to again protect the exposed individual.

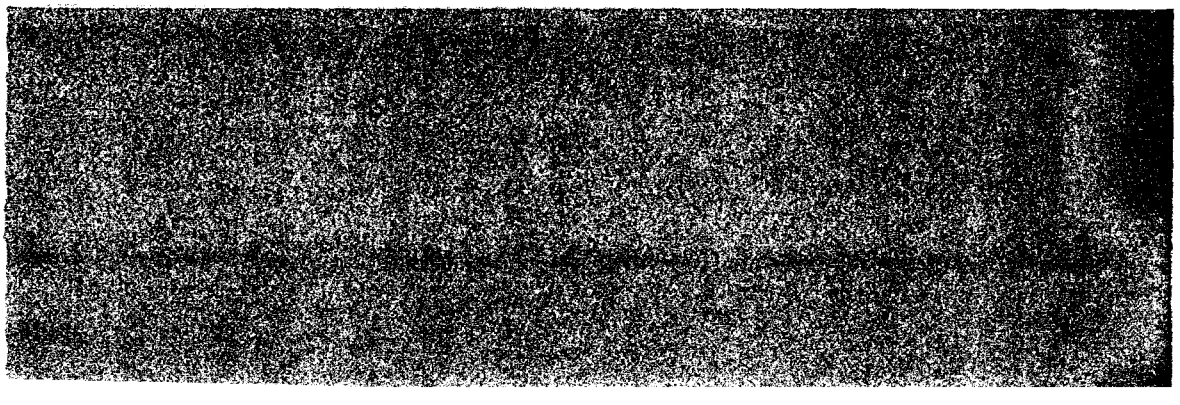
9.5.7.1 *Mechanisms of increased susceptibility to infection.* Nearly all known body defenses against bacterial invasion have been reportedly impaired by large doses of total body radiation. Thus the skin and mucous membranes may show small eroded areas, frequently secondary to hemorrhage, that provide portals of entry for bacteria. It has been shown that the number of bacteria able to cross the intestinal barrier does not increase following irradiation; however, those that cross are able to multiply and produce a fatal bacteremia in the host whose defenses in general are lowered (Gordon *et al.*). The leukopenia and impaired antibody production contribute greatly to the increased susceptibility to infection, and a failure to adequately clear the blood stream of bacteria indicates functional impairment of the phagocytic cells. Radiation mortality correlates well with the degree of granulocytic leukopenia (Smith *et al.*). Antibody production is seriously impaired (Stoner).

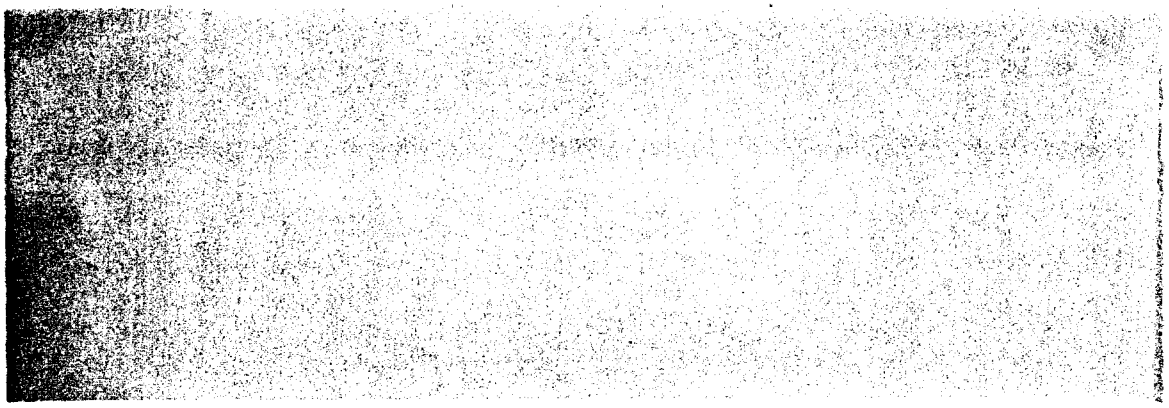
9.6 Résumé of Acute Radiation Effects

To recapitulate and summarize, it is apparent that diffuse cellular injury of different degrees is sustained by all tissues at the time of exposure to radiation. The exact mechanism by which this injury is produced remains

poorly understood. The degree of injury of various organs is the function of the amount of ionization produced within the organ and it is apparent, without extensive discussion, that clinical pictures will vary with the relative degree of injury to various organs and the importance of the organ in the over-all economy of the animal. For example, epilation may be very prominent, if conditions are such that the skin absorbs more radiation than deeper structures. This may occur if a combination of penetrating and slightly penetrating radiations are simultaneously received. The protoplasmic injury itself, wherever the cells may be located, is probably produced by a combination of enzyme inhibition, alteration in cellular permeability, mitotic inhibition and chromosome damage. Concomitant with or shortly after the diffuse cellular injury, "toxic" symptoms (nausea, vomiting, perhaps diarrhea, malaise, headache, anorexia, etc.) develop. These "toxic symptoms" subside within 24 to 48 hours, and during a variable latent period, depending on the dosage, only the hematological signs are easily found. With higher doses of radiation following which there is a very short survival time, there is no latent period, no subsidence of the initial toxic reaction. The vomiting continues, diarrhea develops, prostration occurs and is followed by death within a few days. In this high dose range, in excess of the minimal amount that will kill 100 per cent of the animals, the death is well correlated symptomatically and histologically with severe gastrointestinal injury which is not reversed during the survival period. At lower doses, complete histological recovery takes place within 4 to 5 days (Brecher and Cronkite; Tullis). During the latent period, a series of cellular and histological phenomena are occurring. In the opinion of the authors, the main reason for recurrence of symptoms and ultimate death in the lethal range is the failure of adequate regeneration of hemopoiesis. There may be an adrenal component or other as yet unknown factors contributing to the lethality but all evidence to date points towards the importance of hemopoiesis and its regeneration in survival from potentially lethal radiation injury. At any rate, the latent period is terminated with the recrudescence of symptoms and signs. The latter are well known, and in the mechanism of development can be fairly well explained as follows.

The panleukopenia is severe and progressive. In the granulopenic state, necrotizing, nonpurulent reactions develop at the site of infections. Hemorrhagic manifestations appear and may progress. The hemorrhage is most likely due to a combination of many factors, however, thrombocytopenia with a concomitant poor clot retraction, poor hemostasis, impaired prothrombin utilization, and the prolonged clotting time, probably can adequately explain all the phenomena. It is not necessary to introduce the concept of release of anticoagulants by irradiation in order to explain the prolongation of the whole-blood clotting time.





The anemia develops slowly, results from a partial or complete cessation of blood formation, from hemorrhage and perhaps from increased blood destruction (Lawrence, Dowdy and Valentine; Cronkite, 1948; Young).

In the animals that ultimately die, a severe cachexia is usually apparent before death. The extensive necrosis, ulceration, and edema of the bowel which is apparently secondary to the pancytopenia and extensive hemorrhage into the bowel, may contribute significantly to malnutrition. As a general rule, animals that cease to eat, particularly the mouse, die within 48 hours. The food intake and weight of all animals decreases in the first few days after irradiation, the survivors regain some of their weight and may not have a secondary drop. Those animals which fail to start eating again or who have a secondary occurrence of anorexia lose weight rapidly and die (Chapman and Cronkite; Smith *et al.*). Radiation death is not the result of simple starvation, however, as evidenced by the fact that obese mice die at the expected time (Smith, Chapman, and Alderman).

9.7 Factors Modifying the Response to Whole Body Irradiation

Various factors may favorably or unfavorably influence the lethality of total-body exposure to ionizing radiation or the sensitivity of various structures to ionizing radiation (see also Chapter 12). These factors may conveniently be grouped into preirradiation and postirradiation factors.

Before taking up those factors which are specifically proved to modify or not to modify the response, the following generalities have been assumed true by most, though not necessarily proved.

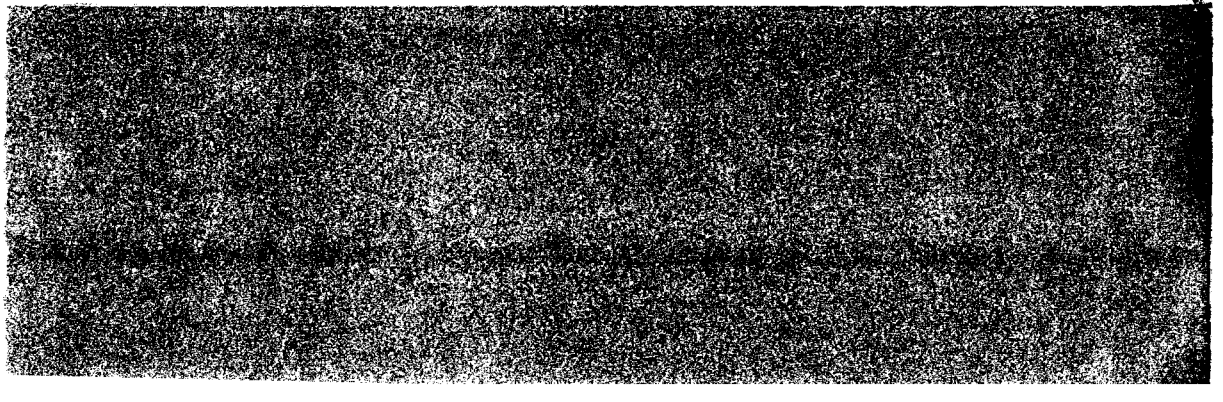
9.7.1 *Age and Sex.* The very young appear to be more sensitive to radiation (Abrams, Kohn and Kallman). Some evidence for increased sensitivity of children was seen in the exposed Marshallese (Cronkite *et al.*). There seems to be little dependence of sensitivity on age in the mature animal (Kohn and Kallman); however, the rat shows increasing sensitivity with increasing age. There is evidence that the female may be more resistant than the male (Cronkite *et al.;* Carter *et al.*); however, the difference is small and is not found consistently, particularly with small populations.

9.7.2 *Environment.* There is some evidence that cold, trauma, hunger, muscular exertion, and noise will increase the lethality of a given dose of radiation. Since a major cause of death following potentially lethal irradiation is infection, it is not unreasonable to expect that anything that would increase the susceptibility to infection would increase the mortality.

9.7.3 *Allergy, Immunity, Metabolic Disorders, and Dietary Deficiencies.* There is little known about the influence of these factors on the survival of man. However, mice with induced hyperthyroidism are more sensitive (Blount and Smith). Dietary deficiencies of vitamins and proteins generally seem to increase the incidence of radiation illness after x-ray therapy, par-

ticularly over the abdomen. However, the data that have been presented are not statistically conclusive.

9.7.4 *Preradiation Factors that Increase the Survival Rate.* In this section is included a discussion of a number of procedures and agents that must be carried out or be present prior to and or during actual exposure to radiation in order to afford protection. Perhaps the most widely known procedure is a lowering of oxygen tension, or hypoxia, first shown by Lacassagne in 1942. This finding has been confirmed extensively, and protection is afforded not only against early effects (Limperos; Dowdy *et al.*) but late effects as well (Lamson, Billings *et al.*). Although hypoxia during irradiation is easily accomplished by means of exposure in an atmosphere containing little or no oxygen, a number of other procedures or agents that produce a lowering of oxygen tension in the tissues appear to protect *via* this mechanism. Thus hypothermia protects presumably by virtue of the fact that it results in hypoxia. Carbon monoxide (Konecci, Taylor and Wilks) and cyanide (Bacq and Herve) are capable of increasing the survival rate. Agents that produce methemoglobinemia such as *p*-aminopropiophenane or PAPP (Storer and Coon) and nitrate (Cole, Bond and Fishler) are active. A variety of substances afford protection if injected prior to exposure, and Hektoen apparently was the first to report such protection in 1918 by the injection of foreign protein 10 days prior to irradiation. Estradiol was shown to decrease mortality if injected 10 days before irradiation of mice (Treadwell, Gardner, and Lawrence; Patt *et al.*). Interest in chemical preprotection was heightened in 1949 by the finding that SH-containing compounds such as cysteine (Patt) and glutathione (Cronkite *et al.*) yield considerable protection. The list of compounds that afford some degree of protection has grown steadily, and the subject has been reviewed extensively (Alexander and Bacq; Bond and Cronkite; Bond and Robertson; Report of the United Nations Scientific Committee). Some dozen *N*-alkyl, *N*-aryl or *N*-acyl derivatives of cysteine have been reported to be protective, as well as other sulfur-containing compounds, e.g., thiourea. Certain compounds with branched or prolonged carbon chains such as 3-mercaptopropylguanidine are effective, as are a number of compounds with pronounced pharmacological and toxicological activity such as histamine, serotonin, DOPA, epinephrine, oxytocin, reserpine and apresoline, anesthetic agents, and ethyl alcohol. Other substances include salicylic acid, zinc, cobalt, magnesium, sulfate, chlorpromazine, chelating agents, morphine, linoleate, oxypolygelatin, and certain vaccines. Reported protection by flavanones (Rekers and Field; Clark *et al.*) was not found by others (Cronkite *et al.*; Buchanan *et al.*). To date no preprotective agent has proved suitable for practical preprotection in the human being, and any such agent of course would have to be given prior to exposure to be effective.



One compound, S2, β-amino-ethylisothiouronium·Br·HBr (AET), has shown some promise in this regard because of its high degree of effectiveness and low toxicity when given orally to rodents. These favorable qualities have been less pronounced in higher species; however, the mechanisms by which preprotective agents act are not clear and are controversial. Hypoxia and hypoxia-inducing agents are effective presumably by a reduction in the formation of free radicals, and it is not clear how many of the protective agents may act at least in part *via* this mechanism. A number of compounds are presumed to act through a free radical scavenging mechanism, i.e., by competing for intracellular free radicals produced by the radiation. Thiol compounds are known to have a great affinity for free radicals. These mechanisms would not explain protection against the direct effects of radiation, although it is not established what proportion of the total effect is direct or indirect under various circumstances. Some agents apparently protect by induction of metabolic changes; others presumably by restoration of injury in the primary target.

9.7.5 *Shielding Effects* (also see section 9.8.2). The prototype of shielding experiments was initiated by Chiari who in 1912 demonstrated that bone marrow of the rabbit when transplanted to the spleen would grow only if the spleen were shielded and the rest of the animal were irradiated. Fabricius-Möller clearly demonstrated that shielding of portions of the skeleton prevented the fall in blood platelets and hemorrhage from doses which uniformly killed his unshielded animals. Chrom (1935) reported a series of experiments on shielding portions of the abdomen and its influence on phagocytosis of bacteria. The technique of shielding has been elaborated and exploited by Jacobson *et al.* in a large series of articles in the past few years. Jacobson and his group have shown a very striking protection of mice to an approximate 100 per cent lethal dose of radiation when the mouse spleen* and the other organs are shielded with lead. Shielding of these organs resulted in a very marked increase in rate of hemopoietic regeneration.

Other shielding experiments have demonstrated protection; for example, shielding of the adrenals (Edelmann) and the head (Allen *et al.*). Bond *et al.* have shown that the time sequence, survival time and nature of death is different when the abdomen is shielded than when the skeleton is shielded. It requires a larger dose in r to kill when the abdomen is shielded and less when only the abdomen is exposed, and thus a good part of the skeleton is shielded. Abdomen-exposed animals die more quickly. Protection is conferred if one-half of the body only is exposed, followed in a matter of min-

* The mouse spleen shows extensive myelopoiesis under normal conditions; hence the protective effect of splenic shielding in the mouse is not necessarily something that is unique to the splenic tissue *per se*.

utes by exposure of the remaining half with shielding of the previously exposed portion (Swift *et al.*).

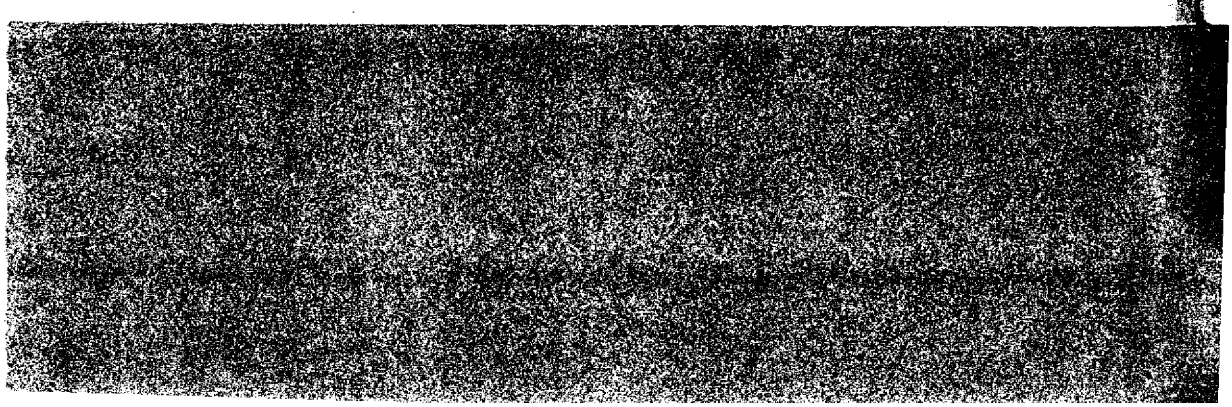
9.7.6 *Parabiosis.* Parabiosis accomplished some time prior to irradiation (Huff *et al.*; Brecher and Cronkite; Finerty *et al.*) markedly decreased mortality of animals exposed to an otherwise fatal dose of radiation.

9.8 Postradiation Factors

The factors that modify the radiation response after irradiation can be divided into those that increase the mortality rate, and those that favorably influence the mortality rate and survival time. The former will be considered first.

9.8.1 *Unfavorable Postirradiation Factors.* Smith and Smith showed that moderate exercise only slightly decreased the survival rate of mice. Strenuous exercise in the form of forced swimming after irradiation increased the mortality rate strikingly in rats (Kimmeldorf; Newry). Smith and Smith presented evidence showing that induction and maintenance of a hypermetabolic state by the administration of dinitrophenol after irradiation for the full observation period increased mortality. Anti-thyroid therapy with thiouracil and propyl-thiouracil did not influence the mortality rate. Ellinger reports that testosterone proprionate administered in daily doses of 0.25 and 0.5 mg. to mice after irradiation with an LD_{50} increases the mortality rate. Smith *et al.* concluded that ACTH and cortisone do not increase the survival rate and that ACTH after irradiation may be harmful. It appears that synkavit and other related compounds of the vitamin K group will increase the mortality of irradiated animals. The material tends to concentrate in some tumors following intravenous injection (Mitchell *et al.*).

9.8.2 *Postradiation Factors that Increase the Survival Rate.* In general, one can divide postradiation modification of radiation injury into three general categories: (a) the striking and rapid restoration of severely damaged, hemopoictic tissues by shielding of bone marrow or spleen, parabiosis, injection of bone marrow, or splenic homogenate, etc., which are effective following usually lethal doses of irradiation from which spontaneous recovery is rare; (b) the less striking effect of postradiation stimulation of myelopoiesis and erythropoiesis. Myelopoiesis can be stimulated by sterile inflammation (Cronkite and Brecher) in the midlethal or sublethal, but not in the absolute lethal zone. Erythropoiesis is stimulated by anoxic stimuli or by normal anemic plasma in the sublethal range only; (c) modification of the histological and clinical picture by substitution (red cell, white cell, and platelet transfusion with or without use of antibiotics) with moderately increased survival rate or induced restoration of hemopoietic tissues (Sorensen *et al.*). The last category simply represents sub-



stitution of elements that are no longer being produced. In the second category, one can imagine the mechanism as being due to the stimulation of precursor cells that are injured, but still capable of responding to physiological stimuli (erythropoietin, leukocytosis promoting factor, etc.) that are known to exist, although not yet adequately characterized. Interest has centered mainly around the mechanism of the restorative effect in the first category, and this will be pursued in some detail here (for reviews of this subject, see Cronkite and Bond; Bond and Cronkite; Jacobson; Report of U. N. Scientific Committee; Tissue Homotransplantation Conference).

Studies on measures to induce accelerated restoration of tissues had their genesis in shielding experiments. Restoration or regeneration of most tissues occurs in the absence of special measures if the radiation dose is low enough to allow spontaneous survival (it is possible to have permanent atrophy of some tissues that are not essential to life, e.g., reproductive cells, or of portions of tissues that are essential to life). Of most importance for immediate survival at radiation doses in the lethal range is restoration of the hematopoietic tissues, and the degree to which shielding or allied procedures accelerates restoration of other tissues, or influences ultimate longevity, genetic damage or tumor induction, is not well defined. Shielding or parabiosis apparently does not protect against most types of radiation-induced neoplasms (Maisin; Brecher *et al.;* Court-Brown; Finerty), but does against lymphoma induction (Kaplan) or myelocytic leukemia (Upton *et al.*) in mice.

Early studies on shielding and restoration of irradiated tissues go back to Chiari (1912) and Fabricius-Möller (1921) (see Cronkite and Brecher). The later studies of Jacobson and his associates led to the concept that "humoral factors" were present in the shielded spleen of the irradiated mouse which induced rapid restoration of the irradiated hemopoietic tissues elsewhere in the body. Their work and concepts are summarized in reviews by Jacobson *et al.*

Studies on the mechanism of the protection afforded by parabiosis have been pursued by Finerty *et al.*, Schneider *et al.*, Binhammer *et al.*, and Metz *et al.*, and it was concluded that the effect was not mediated through spleen, adrenals, or hypophysis (Finerty *et al.*, Schneider *et al.*). Swift *et al.* successively irradiated portions of the body, followed after varying time intervals with irradiation of the entire remaining portion of the body. This procedure significantly increased the survival rate. These studies indicated strongly that the protective factor circulates and can be quickly picked up by tissues that have been irradiated.

Cole and associates have investigated the possible existence and subcellular location of the protective "spleen factor." Early in their work,

it became evident that age, strain and species were factors that influenced the results. The effectiveness of several subcellular fractions of spleen homogenates prepared by the Schneider-Hogeboom techniques was then tested. The experiments conclusively showed that there was no restorative effect connected with the mitochondria, microsomes or soluble supernatant fractions. The restorative effect was found only with the cell nucleus fraction. Since relatively few intact cells were found on stained smears of the nucleus fraction, it was believed that their experiments strongly supported the concept that the restorative effect was noncellular and associated with the nucleoproteins. Further studies on the splenic homogenates have shown that DNAase and trypsin inactivate the material, as does distilled water extraction under various conditions. Since enzymes are believed not to attack living intact cells, these experiments were interpreted as indicating that the active principle is associated with DNA and not necessarily with living cells. These contentions argued strongly for the noncellular concept.

It was thought early that studies with heterologous marrow might provide the definitive answer to the question of whether cell transfer is involved in these protective phenomena. Lorenz and Congdon, and Congdon and Lorenz reported that homologous and heterologous ground bone favorably modify lethal radiation injury in the mouse. Transplanted homologous bone developed bone marrow, but heterologous bone transplants did not show bone marrow formation. The same investigators reported protection of some strains of mice by intravenous injections of rat bone marrow emulsion from certain strains of rats. They interpreted the bone and bone marrow transplant studies as evidence in favor of the existence of a humoral factor. Cole *et al.* protected mice with rat bone marrow. Late deaths after 2 weeks were common.

A British group (Barnes and Loutit) have made a series of contributions on the nature of the restorative action of splenic implants and homogenates. Initially, they confirmed the effectiveness of splenic homogenates. Next, they showed that immunization of one strain of mouse (CBA) by strain A material prevents protection; whereas, short-lived protection of CBA mice could be obtained by use of strain A material in nonimmune mice. In general, their experience was the same as Cole *et al.* in that freezing, thawing, irradiation, and formalin-treatment inactivated the principle. Their studies, extensively confirmed for bone marrow, showed that the restorative principle of intact CBA mice spleens could be preserved when the spleens are equilibrated with glycerol serum and stored at -70°C. for as long as 83 days.

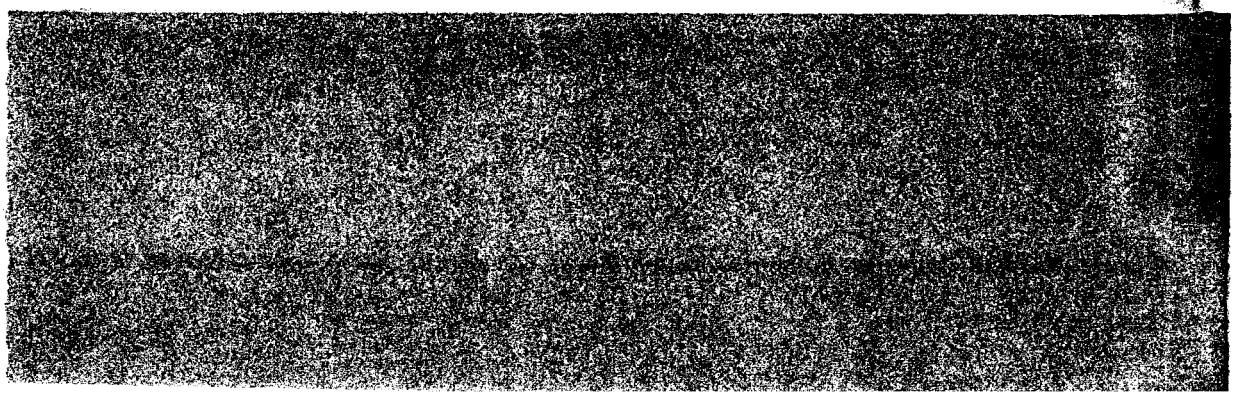
Recently very significant studies, incontrovertible when considered together, have been reported independently by several different laboratories

conclusively proving that cellular transplantation can and does take place. Lindsley *et al.* availed themselves of the blood type of certain strains of rats and proved that functional erythropoietic tissue of the donor animal was implanted in the irradiated host and was producing cells characteristic of the donor. As pointed out by Ford *et al.*, this might be comparable to transduction in bacteria. Nowell *et al.* took advantage of the fact that rat leukocytes give a strong positive alkaline phosphatase and mouse leukocytes give a negative reaction. Irradiated mice were injected with rat bone marrow. This increased the survival rate. Phosphatase-positive white blood cells were found in the peripheral blood and the bone marrow showing that transplantation had in all probability occurred. However, these authors do not rule out that the phenomenon may have been induced in the host cells; a rather unlikely explanation. Ford *et al.* have, without doubt, proved that transplantation of donor hemopoietic cells has occurred. They used a distinctive "marker chromosome" that had been induced by a radiation reciprocal translocation of chromosomes yielding a small distinctive easily detected chromosome. When spleen homogenates were prepared from the spleens of mice possessing this distinctive chromosome, the proliferative hemopoietic tissue of recipient mice consisted predominantly of the marked cells. Brocades *et al.* have demonstrated continued proliferation of rat lymphocytic cells in irradiated mice. Makinodan by quantitative immunological tests on red cells proved that irradiated mice heterologously protected by rat bone marrow eventually developed 100 per cent rat red cells and also confirmed Nowell *et al.* on the presence of rat granulocytes by the distinctive phosphatase reaction. It would appear that these four studies would have driven the last "coffin nail" into the "humoral theory of Jacobson"; however, proof of transplantation does not exclude a humoral contribution. In fact, Jaroslow and Taliaferro have apparently demonstrated that there is a noncellular factor associated with diverse materials such as mouse spleen, HeLa cells, and yeast autolysate that restores the ability to produce antibodies. C. L. Miller has also demonstrated a heat labile serum factor that is necessary to retain the protective effect of cells of embryo spleen or liver in tissue cultures, although the fact is not necessary for viability of the culture.

As indicated earlier, while protection is afforded under some circumstances in which the injected cells are not genetically identical to those of the host, such protection is usually short-lived. Survival of the graft and host is dependent on the histocompatibility of the antigenic pattern of the donor and host. Histoincompatibility is associated with two groups of antigens, the H-antigens that result in production of humoral antibodies, and T-antigens that produce tissue immunity but not detectable circulating antibodies. If the dose of radiation is not sufficiently high,

the immunological response of the host may be restored with early rejection of a noncompatible graft. At higher dose levels the graft may develop a lethal syndrome characterized by skin lesions, gastrointestinal dysfunction, lymphoid tissue atrophy and generalized wasting away of tissues (Congden). This reaction is frequently termed "secondary disease," and is believed to be chiefly the result of a reverse immunological reaction, i.e., reaction of the grafted tissue against that of the host. The reaction is potentiated if even small amounts of lymphocytic cells are transfused with the marrow. The secondary disease has been demonstrated in several animal species including mice, rats, guinea pigs, hamsters, rabbits, monkeys and dogs. There appears to be little question that an individuals' own bone marrow, or that from an identical twin will "take" if infused into the irradiated human being and may be life-saving. Long-term survival of antigenetically nonidentical (homologous) marrow has been reported in a human being who had received chemotherapy for a blood dyscrasia (Beilby). Mathé has reported a temporary "take" of homologous marrow given to several individuals who received high doses of radiation in a reactor accident, and has reported successful transplantation and "secondary disease" in leukemic children given high doses of whole body radiation followed by infusion of homologous marrow. The procedure has not been curative when applied to individuals with leukemia. However, radiation apparently has allowed successful transplantation of homologous kidneys in the human being (Merrill *et al.*) and more practical applications may be expected in the rapidly developing field of tissue homotransplantation (see Report of Tissue Homotransplantation Conference).

Thus it must be accepted that transfer of viable cells with the potential of restoring hematopoietic tissues (and the immune response) does occur. However, the identity of the stem cell or cells transferred remains unknown. It must be recalled that with shielding of the spleen or marrow, apparently cells capable of stem cell activity are carried *via* the blood stream and initiate repopulation of the depleted marrow areas. Injected peripheral blood cells and cells from peritoneal washings will proliferate as will bone marrow in the irradiated host. It is known that a small percentage of cells normally present in the peripheral blood are capable of DNA synthesis and thus presumably of proliferation. Evidence has been presented indicating that these may not be the same cells that give rise to mitotic figures when normal peripheral blood is cultured under appropriate conditions. The problem appears to blend into, and may answer at least in part the more general old hematological problem of the origin of extramedullary hematopoiesis. Is it autochthonous or metastatic? Proof of cell transplantation does not rule out or exclude completely a humoral contribution with stimulus for autochthonous growth. However, it does seem clear



that not only can the marrow stem cells be transplanted by intravenous injection, but that there also exists a mobile pool of pluripotential or totipotential cells that circulate in the blood stream and are available to initiate hematopoietic and perhaps other activity where required.

REFERENCES

ABRAMS, H. L., AND KAPLAN, H. S.: The effect of shielding on mortality following irradiation. *Stanford M. Bull., 9:* 165–167, 1951.

ABRAMS, H. L.: Influence of age, body weight and sex on susceptibility of mice to the lethal effects of x-radiation. *Proc. Soc. Exper. Biol. & Med., 76:* 729–732, 1951.

ALPEN, E. L., AND SHELINE, G. E.: The combined effects of thermal burns and whole body x-irradiation on survival time and mortality. *Ann. Surg., 140:* 113–118, 1954.

ANDREWS, G. A., SITTERSON, W. S., KRETCHMAR, A. L., *et al.* Accidental radiation excursion in the Oak Ridge Y-12 plant. Part IV. Preliminary report on the clinical and laboratory effects in the irradiated employees. *Health Physics, 2:* 139–156, 1959.

BACQ, Z. M., AND HERVE, A.: Cyanure et rayons-x. *J. Physiol., 41:* 124–125, 1949.

BARNES, D. W. H., AND LOUTIT, J. F.: Protective effects of implants of spleen. *Proc. Roy. Soc. Med., 46:* 251–252, 1953.

BARNES, D. W. H., AND LOUTIT, J. F.: *Proceedings of the International Conference on Peaceful Uses of Atomic Energy*, pp. 291-296. New York: United Nations, 1956.

BARRON, E. S. G., DICKMAN, S., MUNTZ, J. A., AND SINGER, T. P.: Studies on the mechanism of action of ionizing radiations. I. Inhibition of enzymes by x-rays. *J. Gen. Physiol., 32:* 527–552, 1949.

BARRON, E. S. G., AND DICKMAN, S.: Studies on the mechanism of action of ionizing radiations. II. Inhibition of sulfhydryl enzymes by alpha, beta, and gamma rays. *J. Gen. Physiol., 32:* 595–605, 1949.

BARROW, J., AND TULLIS, J. L.: The sequence of cellular response to injury in mice exposed to 1100 r total body x-radiation. *A.M.A. Arch. Path., 53:* 391–407, 1952.

BAXTER, H., DRUMMOND, J. A., STEPHENS-NEWSHAMM, L. G., AND RANDALL, R. G.: Reductions of mortality in swine from combined total body radiation and thermal burns by streptomycin. *Ann. Surg., 137:* 450–455, 1953.

BEILBY, J. O. W., CADE, I. S., JELIFFE, A. M., PACKIN, D. M., AND STEWART, J. W.: Prolonged survival of a bone marrow graft resulting in a blood-group chimera. *Brit. M. J.*, 96–99, January 9, 1960.

BENDER, M. A., AND GOOCH, P. C.: Somatic chromosomal aberrations in normal and irradiated humans. *Radiation Res., 14:* 451, 1961.

BINHAMMER, R. T., SCHNEIDER, M., AND FINERTY, J. C.: Time as a factor in post-irradiation protection by parabiosis. *Am. J. Physiol., 175:* 440–442, 1953.

BLOUNT, H. C., JR., AND SMITH, W. W.: The influence of thyroid and thiouracil on mice exposed to roentgen radiation. *Science, 109:* 83, 1949.

BOND, V. P., *et al.*: Sensitivity of abdomen of rat to x-irradiation. *Am. J. Physiol., 161:* 323–330, 1950.

BOND, V. P., SWIFT, M. N., TAKETA, S. T., AND TOBIAS, C. A.: Indirect effects of deuteron irradiation in rats. *Am. J. Physiol., 174:* 259–263, 1953.

BOND, V. P., SILVERMAN, M. S., AND CRONKITE, E. P.: Pathogenesis and pathology of post-irradiation infection. *Radiation Res., 1:* 389–400, 1954.

Bond, V. P., Shechmeister, I. L., Swift, M. N., and Fishler, M. C.: The effects of x-irradiation on a naturally occurring endemic infection. *J. Infect. Dis., 91:* 26–32, 1952.

Bond, V. P., and Cronkite, E. P.: Effects of radiation on mammals. *Ann. Rev. Physiol., 19:* 299–328, 1956.

Bond, V. P., and Robertson, J. S.: Vertebrate radiobiology (lethal actions and associated effects). *Ann. Rev. Nucl. Sci., 7:* 135–162, 1957.

Bond, V. P., Cronkite, E. P., Sandhaus, C. A., Robertson, J. S., and Borg, D. C.: Geometrical and energy factors influencing the effect of penetrating radiations on man. *Radiation Res., 6:* 554–572, 1957.

Bowers, J. Z., and Scott, K. G.: Distribution and excretion of electrolytes after acute whole body irradiation injury. I. Studies with radiopotassium. *Proc. Soc. Exper. Biol. & Med., 78:* 645–648, 1951.

Brayer, F. T., Glasser, S. R., and Duffy, B. J., Jr.: Effect of x-irradiation on the adrenal cortical steroid excretion in urine. *Science, 120:* 112, 1954.

Brecher, G., and Cronkite, E. P.: Lesions of the alimentary tract in dogs exposed to whole body irradiation of 300 to 3000 r. Presented before American Association of Pathology and Bacteriology, Cleveland, April 26, 1951.

Brecher, G., and Cronkite, E. P.: Post-radiation parabiosis and survival in rats. *Proc. Soc. Exper. Biol. and Med., 77:* 292–294, 1951.

Buchanan, D. J., Pearson, W. N., Amarisingham, C., Hudson, G. W., and Darby, W. J.: Citrovorum and irradiation injury. *Am. J. Physiol., 175:* 437–439, 1953.

Carsten, A.: Partial-body irradiation. In *Report on Conference on Physical Factors Modifying Response to Radiation.* Ann., New York Acad. Sci., November, 1962.

Carter, R. E., Bond, V. P., and Seymour, P. H.: The relative biological effectiveness of fast neutrons in mice. *Radiation Res., 4:* 423, 1956.

Chapman, W. H., and Cronkite, E. P.: Further studies on the beneficial effect of glutathione on x-irradiated mice. *Proc. Soc. Exper. Biol. & Med., 75:* 308–322, 1950.

Chapman, W. H., and Jerome, E. A.: An analysis of the effects of total-body x-irradiation on the body weight of white Swiss mice. *Radiation Res., 4:* 519–531, 1956.

Chiari, O. M.: Vorläufigen Mitteilung über Knochenmarkstransplantation. *München. med. Wchnschr., 59:* 2503, 1912.

Chron, S. A.: Studies on the effects of roentgen rays upon the intestinal epithelium and upon the reticuloendothelial cells of the liver and spleen. *Acta radiol., 16:* 641–650, 1935.

Clapper, W. E., Roberts, J. E., and Meade, G. H.: Radiation effects on pneumococcol infection produced by subcutaneous injections into white mice. *Proc. Soc. Exper. Biol. & Med., 86:* 420–422, 1954.

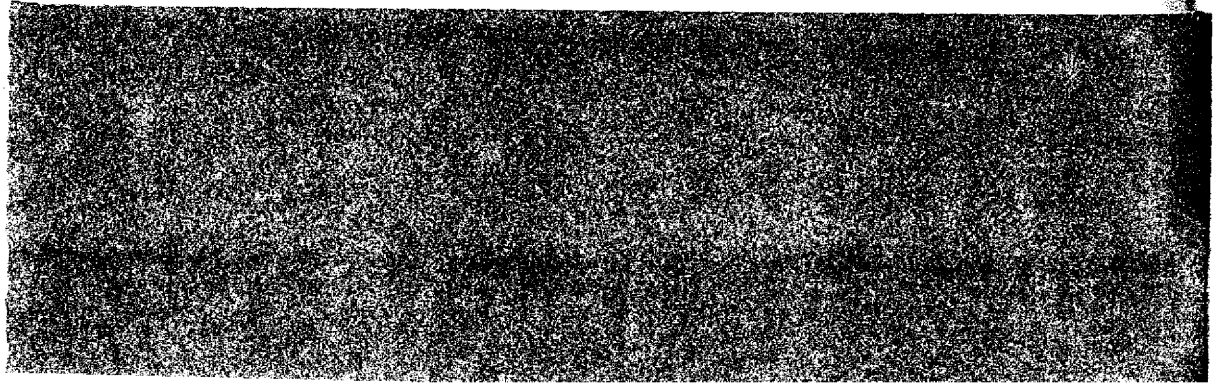
Clark, W. G., Uncapher, R. P., and Jordan, M. L.: Effect of flavonoids (vitamin P) on mortality from total body roentgen irradiation. *Science, 108:* 629–630, 1948.

Cole, L. S., Bond, V. P., and Fishler, M. C.: Protection against radiation by sodium nitrite. U. S. Navy Radiological Defense Laboratory Report, San Francisco, 1952.

Cole, L. J., and Ellis, M. E.: Age, strain and species factors in postirradiation protection by spleen homogenates. *Am. J. Physiol., 173:* 487–494, 1953.

Cole, L. J., Fishler, M. C., and Bond, V. P.: Subcellular fractionation of mouse spleen radiation protection activity. *Proc. Nat. Acad. Sci., 39:* 759–772, 1953.

Cole, L. J., and Ellis, M. E.: Studies on the chemical nature of the radiation protective factor in mouse spleen. *Radiation Res., 1:* 347–357, 1954.



COLE, L. J., AND ELLIS, M. E.: On the nature of the spleen-bone marrow radiation recovery factor. In *Fundamentals of Radiobiology*, edited by Z. M. Bacq, and P. Alexander. 389 pp.: Butterworth Scientific Publications, 1955.

COLE, L. J., FISHLER, M. C., AND ELLIS, M. E.: Studies on the nature of the radiation protection factor in mouse spleen. *Radiology, 64:* 201–207, 1955.

CONARD, R. A.: Cholinesterase activity, weight, water content and pathology of small intestine of rats subjected to x-radiation. *Am. J. Physiol., 170:* 425–428, 1952.

CONARD, R. A.: Effect of x-irradiation on intestinal motility of the rat. *Am. J. Physiol.*, 1951.

CONARD, R. A., CRONKITE, E. P., BRECHER, G., AND STROME, C. P. A.: Experimental therapy of the gastrointestinal syndrome produced by lethal doses of ionizing radiation. J. Appl. Physiol., *9:* 227–240, 1956.

CONARD, R. A.: Some effects of ionizing radiation on the physiology of the gastrointestinal tract. *Radiation Res., 5:* 167–188, 1956.

CONGDON, C. C., AND LORENZ, E.: Humoral factor in irradiating protection. Modification of lethal radiation injury in mice by injection of rat bone marrow. *Am. J. Physiol., 176:* 297–300, 1954.

CONGDON, C. C., AND URSO, I. S.: Pathologic findings in the delayed heterologous bone marrow section. *Radiation Res., 7:* 310, 1957.

CRONKITE, E. P.: The clinical manifestations of acute radiation illness produced in goats by exposure to an atomic bomb, Test Able, Bikini, 1946, with comments on therapy. *U. S. Naval M. Bull., 49:* 199–215, 1949.

CRONKITE, E. P., AND BRECHER, G.: The experimental therapy of the hemorrhagic phase of the radiation syndrome with platelet transfusions. *Acta radiol. (suppl.), 116:* 376–380, 1954.

CRONKITE, E. P., BOND, V. P., CONARD, R. A., SHULMAN, N. R., FARR, R. S., COHN, S. H., DUNHAM, C. L., AND BROWNING, L. E.: Some effects of ionizing radiation on human beings. Atomic Energy Document TID 5358, 1956. U. S. Government Printing Office, Washington 25, D. C. Shortened version in *J.A.M.A., 159:* 430–434, 1955.

CRONKITE, E. P., AND CHAPMAN, W. H.: A critical analysis of the syndrome of acute total body irradiation illness, its role in atomic warfare and its influence in the future practice of military medicine. *Mil. Surgeon, 104:* 7–21, 1949.

CRONKITE, E. P., AND CHAPMAN, W. H.: The effect of adrenalectomy and glutathione on x-ray induced mortality in mice. *Fed. Proc., 9:* 329, 1950.

CRONKITE, E. P., AND CHAPMAN, W. H.: The effect of adrenalectomy on radiation-induced mortality of the mouse. *Proc. Soc. Exper. Biol. & Med., 74:* 337, 1950.

CRONKITE, E. P., CHAPMAN, W. H., AND CHAMBERS, F. W.: Failure of a flavonoid (vitamin P) to reduce radiation mortality in mice. *Proc. Soc. Exper. Biol. & Med., 76:* 282–284, 1951.

CRONKITE, E. P., JACKSON, D. P., LEROY, G. V., AND LUNDY, A. R. T.: The present status of the hemorrhagic phase of radiation injury. *Proceedings of the International Society of Hematology*, May, 1951.

CRONKITE, E. P., HALPERN, B., JACKSON, D. P., AND LEROY, G. V.: A study of the hemorrhagic state in dogs after lethal dose of 2-million volt x-rays. *Proc. Central Soc. Clin. Res., 23:* 26, 1950.

CRONKITE, E. P., AND BRECHER, G.: The protective effect of granulocytes in radiation injury. *Ann. New York Acad. Sci., 59:* 815–833, 1955.

CRONKITE, E. P., BRECHER, G., AND CHAPMAN, W. H.: Studies on the mechanism

of the protective action of glutathione against radiation injury. *Mil. Surgeon, 109:* 296-307, 1951.

CRONKITE, E. P., JACOBS, G., BRECHER, G., AND DILLARD, G.: The hemorrhagic phase of the acute radiation syndrome due to exposure of the whole body to penetrating ionizing radiation. *Am. J. Roentgenol., 67:* 796–803, 1952.

CRONKITE, E. P., AND BRECHER, G.: Defects in hemostasis produced by whole body irradiation. 5th Annual Conference—Blood Coagulation and Allied Subjects. *Trans. Josiah Macy Foundation*, New York, 1952.

CRONKITE, E. P., BOND, V. P., CHAPMAN, W. H., AND LEE, R. H.: Biological effects of atomic-bomb gamma radiation. *Science, 122:* 148–150, 1955.

DALE, W. M.: Effect of x-rays on aqueous solutions of biologically active compounds. *Brit. J. Radiol., 16:* 171–172, 1943.

DOUGHERTY, T. F., AND SCHNEEBELI, G. L.: Role of cortisone in regulation of inflammation. *Proc. Soc. Exper. Biol. & Med., 75:* 854–859, 1950.

DOWDY, A. H., BENNETT, L. R., AND CHASTAIN, S. M.: Protective effect of anoxic anoxia against total body roentgen irradiation of mammals. *Radiology, 55:* 879–885, 1950.

EDELMANN, A.: Adrenal shielding and survival of rats after x-irradiation. *Am. J. Physiol., 165:* 57–60, 1951.

EDELMANN, A.: Survival of adrenalectomized rats with and without replacement therapy following x-irradiation. *Am. J. Physiol., 167:* 57–60, 1951.

Effects of Nuclear Weapons, 1962 Washington, D. C.: U. S. Government Printing Office.

ELLINGER, F. P.: The influence of pharmacological agents on effects of irradiation. *Radiology, 50:* 234–243, 1948.

ELLINGER, F. P.: *Medical Radiation Biology*. Springfield, Ill.: Charles C Thomas, 1957.

ELLINGER, F. P., ROSWIT, D. B., AND GLASSER, S.: The treatment of radiation sickness with adrenal cortical hormones (desoxycorticosterone acetate). *Am. J. Roentgenol., 61:* 381–396, 1949.

ELLINGER, F.: Some effects of testosterone propionate on mice irradiated with x-rays. *Proc. Soc. Exper. Biol. & Med., 74:* 616–619, 1950.

ELLINGER, F.: Pharmacologic studies on irradiated animals. Effect of cortisone on x-ray mortality of mice. *Proc. Soc. Exper. Biol. & Med., 80:* 214–220, 1952.

ELLINGER, F.: Effect of cell-free aqueous extracts from normal and irradiated spleens on x-ray induced mortality in mice; a preliminary report. *Radiol. Clin., 23:* 229–239, 1954.

ESPLIN, D. W., MARCUS, S., AND DONALDSON, D. M.: Effects of x-irradiation and adrenalectomy on phagocytic activity. *J. Immunol., 70:* 454–460, 1953.

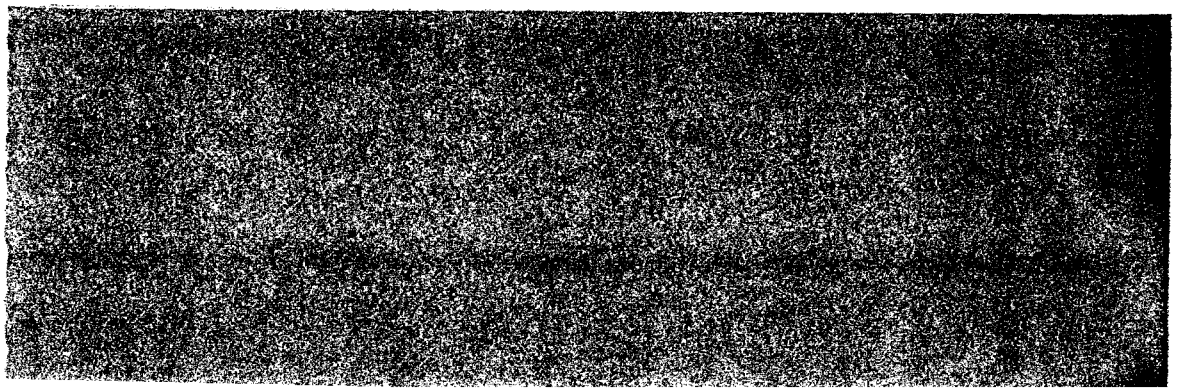
FABRICIUS-MOLLER, J.: *Experimental Studies of the Hemorrhagic Diathesis from X-ray Sickness*. Copenhagen: Levin and Munksgaards Forlag, 1922.

FAILLA, G.: A theory of the biological action of ionizing radiations. Occasional publications of American Association for the Advancement of Science, No. 4, 202–214. Supplement to *Science, 85:* June, 1933.

FINERTY, J. C., BINHAMMER, R. T., AND SCHNEIDER, M.: Survival of irradiated rats in parabiosis with hypophysectomized partners. *Science, 118:* 654–655, 1953.

FLIEDNER, T. M., BOND, V. P., AND CRONKITE, E. P.: Structural cytologic and autoradiographic changes in the bone marrow following total body irradiation. *Am. J. Path., 38:* 599–623, 1961.

FLIEDNER, T. M., CRONKITE, E. P., BOND, V. P., RUBINI, J. R., AND ANDREWS, G.:



The mitotic index of human marrow in healthy individuals and irradiated human beings. *Acta Haemat. 22:* 65-78, 1959.

FORD, C. E., LAMERTON, J. L., BARNES, D. W. H., AND LOUTIT, J. F.: Cytological identification of radiation chimaeras. *Nature, 177:* 452-454, 1956.

FORSTER, F. M., *et al.*: Degenerative changes in cerebral arteries following administration of desoxycorticosterone acetate. *J. Clin. Endocrinol., 6:* 77-87, 1946.

FRICKE, E.: Symposium. *Quantitative Biol. 2:* 241, 1934.

FRIEDMAN, J., WERDER, A. A., ROTH, F. J., GRAHM, A. B., OVIDIO, J. M., AND SYVERTON, J. T.: The synergistic effects of roentgen radiation and cortisone upon susceptibility of mice to pathogenic microorganisms. *Am. J. Roentgenol., 71:* 509-517, 1954.

GERSTNER, H. B.: Acute radiation syndrome in man. *U. S. Armed Forces Med. J., 9:* 313-354, 1958.

GOLDFELDER, A., *et al.*: Agents influencing experimental radiation injury; effects of folic acid and pyridoxine. *Proc. Soc. Exper. Biol. & Med., 67:* 272-278, 1948.

GORDON, L. E., RUML, D., HAHNE, H. J., AND MILLER, C. P.: Studies on the susceptibility of infection following ionizing radiation. IV. The pathogenesis of endogenous bacteremia in mice. *J. Exper. Med., 102:* 413-424, 1955.

GRAHAM, J. B., GRAHAM, R. M., AND GRAFFEO, A. J.: The influence of adrenal cortical hormones on sensitivity of mice to ionizing radiation. *Endocrinology, 46:* 434-440, 1950.

GRAHAM, J. B., AND GRAHAM, R. M.: The modification of resistance to ionizing radiation by humoral agents. *Cancer, 3:* 709-717, 1950.

HALE, W. M., AND STONER, R. D.: The effect of cobalt-60 gamma radiation on passive immunity. *Yale J. Biol. & Med., 25:* 327-333, 1953.

HALEY, T. J., MANN, S., AND DOWDY, A. H.: A comparison of the responses of normal and hypothyroid mice to acute whole-body roentgen radiation. *Science, 112:* 333-334, 1950.

HAMMOND, C. W., VOGEL, H. H., CLARK, J. W., COOPER, D. B., AND MILLER, C. P.: The effect of streptomycin therapy on mice irradiated with fast neutrons. *Radiation Res., 2:* 354-360, 1955.

HARRISON, H. E., AND DARROW, D. C.: Renal function in experimental adrenal insufficiency. *Am. J. Physiol., 125:* 631-643, 1939.

HAURANI, F. I., REPPLINGER, E., AND TOCANTIUS, L. M.: Attempts at transplantation of human bone marrow in patients with acute leukemia and other marrow depletion disorders. *Am. J. Med., 28:* 794-806, 1960.

HAYES, D. F.: A summary of accidents and incidents involving radiation in atomic energy activities, June 1945 through December 1955. U. S. Atomic Energy Commission, Report TID-5360, 1956.

HAYES, D. F.: A summary of incidents involving radioactive material in atomic energy activities. January–December 1956. U. S. Atomic Energy Commission Report TID-5366. (Suppl.) 1957.

Hearings before the Joint Committee on Atomic Energy, Congress of the United States, in 1957, 1959, 1960 and 1962. Washington, D. C.: U. S. Government Printing Office.

HEKTOEN, L.: Further studies on the effects of the roentgen ray on antibody production. *J. Infect. Dis., 20:* 28-33, 1918.

HENNESSEY, T. G., AND HUFF, R. L.: Depression of tracer iron uptake curve in rat erythrocytes following total body x-irradiation. *Proc. Soc. Exper. Biol. & Med., 78:* 436-439, 1950.

HOLDEN, W. D., COLE, J. W., PORTMANN, A. F., AND STORAASLI, J. P.: Hypothromboplastinemia following total body irradiation. *Proc. Soc. Exper. Biol. & Med., 70:* 553–556, 1949.

HOLLINGSWORTH, J. W., AND FINCH, S. C.: Effect on cross-circulation with normal rats on experimental E. coli bacteremia in irradiated rats. *Clin. Res. Proc., 4:* 19, 1956.

HOWLAND, J. W., *et al.:* University of Rochester, U. S. Atomic Energy Commission Project, Report No. UR-94, 1949.

HOWLAND, J. W., INGRAM, M., MERMAGEN, H., *et al.:* "The Lockport incident; accidental partial-body exposure of humans to large doses of x-irradiation," pp. 11–26. In *Diagnosis and Treatment of Acute Radiation Injury. WHO*, 1961.

International Commission on Radiological Units and Measurements (ICRU) Reports. *Radiology 62:* 106–109, 1954; *Handbook 62*, National Bureau of Standards, 1957; *Handbook 78*, 1959; *Handbook 84*, 1962.

JACKSON, D. P., CRONKITE, E. P., AND JACOBS, G.: Prothrombin utilization in fatal radiation injury. *Am. J. Physiol., 169:* 208–217, 1952.

JACKSON, D. P., CRONKITE, E. P., LEROY, G. V., AND HALPERN, B.: Further studies on the nature of the hemorrhagic phase of radiation injury. *J. Lab. and Clin. Med., 39:* 449–461, 1952.

JACOBSON, L. O., ROBSON, M. J., AND MARKS, E. K.: The effects of x-irradiation on antibody formation. *Proc. Soc. Exper. Biol. & Med., 75:* 145–152, 1950.

JACOBSON, L. O., *et al:* The role of the spleen in radiation injury. *Proc. Soc. Exper. Biol. & Med., 70:* 740–742, 1949.

JACOBSON, L. O.: Recovery from radiation injury. *Blood, 6:* 769–770, 1951.

JACOBSON, L. O., SIMMONS, E. L., MARKS, E. K., AND ELDREDGE, J. H.: Recovery from radiation injury. *Science, 113:* 510–511, 1951.

JACOBSON, L. O.: Janeway Lecture, *Am. J. Roentgenol., 72:* 543–555, 1954.

JAROSLOW, B. N., AND TALIAFERRO, W. H.: The restoration of hemolysin-forming capacity in x-irradiated rabbits by tissue and yeast preparations. *J. Infect. Dis., 98:* 75–81, 1956.

JENNINGS, F. L.: Effect of protein depletion upon susceptibility of rats to total body irradiation. *Proc. Soc. Exper. Biol. & Med., 72:* 487–491, 1949.

JOINT COMMITTEE, Public hearings on the hazards of ionizing radiations. Congressional Record, 1957.

KAPLAN, H. S.: Influence of age on susceptibility of mice to the development of lymphoid tumors after radiation. *J. Nat. Cancer Inst., 9:* 55–56, 1948.

KAPLAN, H. S., BROWN, M. B., AND PAULL, J.: Influence of bone-marrow injections on involution and neoplasia of mouse thymus after systemic irradiation. *J. Nat. Cancer Inst., 14:* 303–316, 1953.

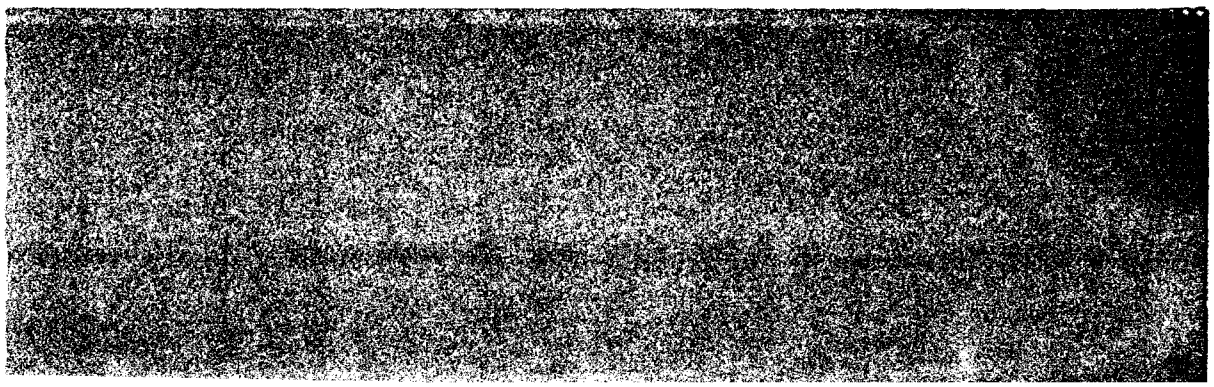
KIMELDORF, D. J. *et al.:* The effect of exercise upon the lethality of roentgen rays for rats. *Science, 112:* 175–176, 1950.

KOHN, H. I.: Changes in blood plasma of guinea pig during acute radiation syndrome. *Am. J. Physiol., 162:* 703–708, 1950.

KOHN, H. I.: Effect of immaturity, hypophysectomy, and adrenalectomy upon changes in blood plasma of rat during acute radiation syndrome. *Am. J. Physiol., 165:* 43–56, 1951.

KOHN, H. I., AND KALLMAN, R. F.: Age, growth and the LD_{50} of x-rays. *Science, 124:* 1078, 1956.

LACASSAGNE, A.: Chute de la sensibilite aux rayons X chez la souris nouveaunee en etat d'asphyxie. *Compt. Rend. Acad. Sci. Paris, 215:* 231–232, 1942.



LAMSON, B. G., AND TULLIS, J. L.: The progression of morphologic lesions in Swiss mice exposed to 625 r, 2000 KVP, total body x radiation. *Mil. Surgeon, 109:* 281–295, 1951.

LAMSON, B. G., BILLINGI, M. S., EWELL, L. H., *et al.*: Late effects of total body roentgen radiation. V. Hypertension and nephrosclerosis in female Wistar rats surviving 1000 r hypoxic total-body irradiation. *A.M.A. Arch. Pathol., 66:* 322–329, 1958.

LANGHAM, W., WOODWARD, K. T., ROTHERMAL, S. M., HARRIS, P. S., LUSHBAUGH, C. C., AND STORER, J. B.: Studies on the effect of rapidly delivered, massive doses of gamma rays on mammals. *Radiation Res., 5:* 404–432, 1956.

LASSER, B. C., AND STENSTROM, K. W.: Radiation sickness. A study of its relation to adrenal cortical function and absolute eosinophile count. *Am. J. Roentgenol., 72:* 474–487, 1954.

LARKIN, J. C.: Effect of atropine on acute irradiation sickness in mice. *Am. J. Roentgenol., 62:* 547–549, 1949.

LAWRENCE, G. H.: The effect of total body x-irradiation 17-ketosteroid excretion in dogs. *Endocrinology, 45:* 383–388, 1949.

LAWRENCE, J. S., DOWDY, A. H., AND VALENTINE, W. N.: The effects of radiation on hemopoiesis. *Radiology, 51:* 400–413, 1948.

LAWRENCE, J. S., VALENTINE, W. N., AND DOWDY, A. H.: The effect of radiation on hemopoiesis. Is there an indirect effect? *Blood, 3:* 593–611, 1948.

LEA, D. E.: *Actions of Radiations on Living Cells.* Ed. 2, p. 195. New York: Cambridge University Press, 1944.

LEROY, G. V.: The medical sequelae of the Atomic Bomb Explosion. *J.A.M.A., 134:* 1143–1148, 1947.

LIEBOW, A. A., WARREN, S., DECOURSEY, E.: Pathology of atomic bomb casualties. *Am. J. Path., 25:* 853–1028, 1949.

LIMPEROS, G.: Effect of varying tension on mortality of x-rayed mice. *J. Franklin Inst., 249:* 513–514, 1950.

LIMPEROS, G., AND MOSHER, W. A.: Protection of mice against x-radiation by thiourea. *Science, 112:* 86–87, 1950.

LINDSLEY, D. L., ODELL, T. T., JR., AND TAUSCHE, F. G.: Implantation of functional erythropoietic elements following total-body irradiation. *Proc. Soc. Exper. Biol. & Med., 90:* 512–515, 1955.

LORENZ, E., AND CONGDON, C. C.: Modification of lethal irradiation injury in mice by injection of homologous or heterologous bone. *J. Nat. Cancer Inst., 14:* 955–964, 1954.

LORENZ, E., CONGDON, C., AND UPHOFF, D.: Modifications of acute irradiation injury in mice and guinea pigs. *Radiology, 58,* 863–877, 1952.

LYON, G. M.: Radiological aspects of civil defense. *J.A.M.A., 146:* 465–471, 1951.

MAISIN, J., MAISIN, H., DUNJIC, A., AND MALDAGUE, P.: *Proceedings of the International Conference on Peaceful Uses Atomic Energy,* pp. 315–29. New York: United Nations, 402 pp. 1956.

MAKINODAN, T.: Circulating rat cells in lethally irradiated mice protected with rat bone marrow. *Proc. Soc. Exper. Biol. & Med., 92:* 174–179, 1956.

MARCUS, S., AND DONALDSON, D. M.: Suppression of normal bactericidal action of rabbit serum following whole body x-irradiation. *Proc. Soc. Exper. Biol. & Med., 83:* 184–187, 1953.

MATHÉ, G., *et al.*: Nouveaux essais de greffe de moelle osseuse homologue apres irradiation totale chez des enfants attients de leucemie aigue en remission. *Rev. hémat., 15:* 115–161, 1960.

MATHÉ, G., JAMMET, H., PENDIC, B., *et al.*: Transfusions et greffer de moelle osseuse homologue chez des humains irradies a haute dose accidentellement. *Rev. Franc. Etudes Clin. Biol., 4:* 226–238, 1959.

MERRILL, J. P., MURRAY, J. E., HARRISON, J. H., FRIEDMAN, E. H., DEALY, J. B., JR., AND DAMMIN, G. S.: Successful hemotransplantation of the kidney between nonidentical twins. *New England J. Med., 262:* 1251–1260, 1960.

METZ, G., BINHAMMER, R. T., SCHNEIDER, M., AND FINERTY, J. C.: Hematologic changes in rats protected from lethal x-radiation by post-irradiation parabiosis. *Radiation Res., 2:* 159–165, 1955.

MILLER, C. P., HAMMOND, C. W., AND TOMPKINS, M.: The incidence of bacteremia in mice subjected to total body x-radiation. *Science, 111:* 540–541, 1950.

MILLER, C. P., HAMMOND, C. W., AND TOMPKINS, M.: The role of infection in radiation injury. *J. Lab. & Clin. Med., 38:* 331–343, 1951.

MILLER, C. P., HAMMOND, C. W., TOMPKINS, M., AND SHORTER, G.: The treatment of postirradiation infection with antibiotics, an experimental study on mice. *J. Lab. & Clin. Med., 39:* 462–479, 1952.

MILLER, C. L.: Recovery from irradiation following the administration of cultured tissues. *Nature, 178:* 142, 1956.

MILLER, L. S., FLETCHER, G. H., AND GERSTNER, H. B.: Systemic and clinical effects induced in 263 cancer patients by whole-body x-irradiation with normal air doses of 15 to 200 r. *School of Aviation Medicine, USAF,* Report 57-92, 1957.

MOLE, R. H., PHILPOT, J. ST. L., AND HODGES, G. R. V.: Reduction in lethal effect of x-radiation by pretreatment with thiourea or sodium ethane dithiophosphonate. *Nature, 166:* 515, 1950.

MOLE, R. H.: Whole body irradiation and the idea of stress. *Brit. J. Exper. Path., 37:* 528–531, 1956.

NIMS, L. F., AND SUTTON, E.: Adrenal cholesterol, liver glycogen and water consumption of fasting and x-irradiated rats. *Am. J. Physiol., 177:* 51–54, 1954.

NOWELL, P. C., COLE, L. J., HABERMEYER, J. G., AND ROAN, P. L.: Growth and continued function of rat marrow cells in x-irradiated mice. *Cancer Res., 16:* 258–261, 1956.

PAINTER, E. E., AND COOLEY, M. A.: Fluid volume studies in gut, muscle, and skin of rats after total body x-radiation. *Fed. Proc., 10:* 100, 1951.

PARKER, D. B.: Engineers in atomic offense and defense. *Mil. Engineer, 42:* 257–259, 1950.

PATT, H. M., *et al.*: X-irradiation of the hypophysectomized rat. *Science, 108:* 475–476, 1948.

PATT, H. M., *et al.*: Adrenal response to total body x-radiation. *Am. J. Physiol. 150:* 480–487, 1947.

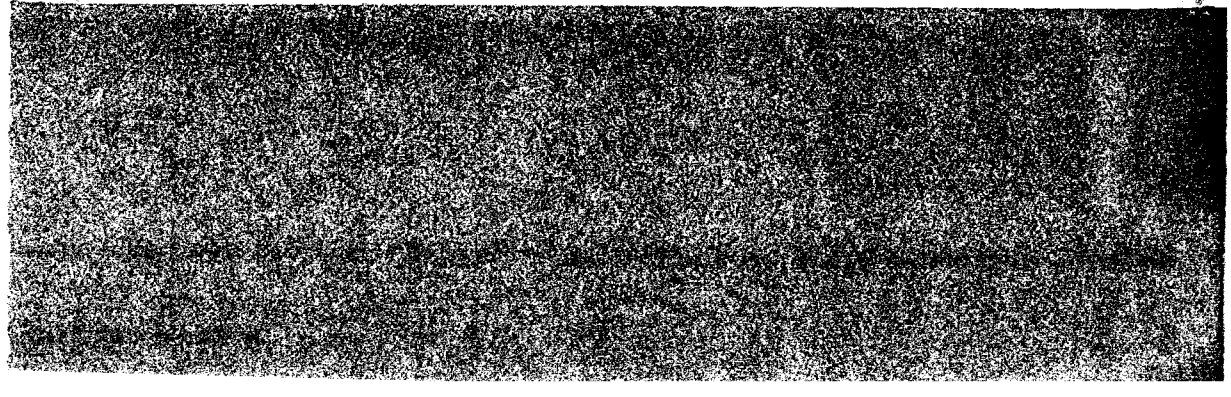
PATT, H. M., SMITH, D. E., AND JACKSON, E.: The effect of cysteine on the peripheral blood of irradiated rat. *Blood, 5:* 758–763, 1950.

PATT, H. M., TYREE, E. B., STRAUBE, R. L., AND SMITH, D. E.: Cysteine protection against x-irradiation. *Science, 110:* 213–214, 1949.

PAULY, H.: X-ray sensitivity and target volume of enzyme induction. *Nature, 174:* 1570–1571, 1959.

PEARSE, H. E., AND PAYNE, J. L.: Medical progress, mechanical and thermal injury from atomic bomb. *New England J. Med., 241:* 647–563, 1949.

PILLEMER, L., BLUM, L., LEPOW, I. H., ROSS, O. A., TODD, E. W., AND WARDLAW, A. C.: The properdin system and immunity. I. Demonstration and isolation of a new serum protein, properdin, and its role in immune phenomena. *Science, 120:* 279–285, 1954.



PROSSER, C. L., *et al.*: Plutonium project: the clinical sequence of physiological effects of ionizing radiation in animals. *Radiology, 49:* 299-313, 1947.

PUCK, T. T.: Action of radiation on mammalian cells. III. Relationship between reproductive death and induction of chromosome anomalies by x irradiation of euploid reproductive human cells *in vitro*. *Proc. Nat. Acad. Sci., 44:* 772-780, 1958.

QUASTLER, H., LANZL, E. F., KELLER, M. E., AND OSBORNE, J. W.: Acute intestinal radiation death. Studies on roentgen death in mice. III. *Am. J. Physiol., 164:* 546-556, 1951.

RAJEWSKY, B., GERBER, G., AND PAULY, H.: X-ray inactivation of the components of the succinic acid dehydrogenase-cytochrome-cytochrome oxidase system. In *Advances in Radiobiology*, edited by G. Henesy, A. Forrsborg, and J. Abbott. London: Oliver & Boyd, Ltd., 5, 1957.

RAPER, J. R.: Effects of total surface beta irradiation. *Radiology, 49:* 314-324, 1947.

REID, J. D., BROOKS, J. W., HAM, W. T., AND EVANS, E. I.: The influence of x-radiation on mortality following thermal flash burns: the site of tissue injury as a factor of determining the type of invading bacteria. *Ann. Surg. 142:* 844-850, 1955.

REKERS, P. E., AND FIELD, J. B.: Control of hemorrhagic syndrome and reduction in x-irradiation mortality with a flavonone. *Science, 107:* 16-17, 1948.

REKERS, P. E.: University of Rochester, Atomic Energy Project Report UR-104, 1951.

REKERS, P. E., COULTER, M. P., AND WARREN, S. L.: Effect of transplantation of bone marrow into irradiated animals. *Arch. Surg., 60:* 635-667, 1950.

Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. General Assembly, 17th session, supplement No. 16 (A/5216).

REYNIERS, J. A., In: *LOBUND-ONR-AEC Report III*. Lobund study on comparative effects of total-body radiation. November 16, 1953.

ROBBINS, L. L., *et al.*: Superficial "burns" of skin and eyes from scattered cathode rays. *Radiology, 46:* 1-23, 1946.

ROSE, B., AND BROWNE, J. S. L.: Effect of adrenalectomy on histamine content of tissues of rat. *Am. J. Physiol., 131:* 589, 1941.

ROSENFELD, G., UNGAR, F., DORFMAN, R. I., AND PINCUS, G.: Irradiation and adrenal steroidogenesis. Steroid transformation by irradiated isolated perfused calf adrenals. *Endocrinology, 56:* 24-29, 30-36, 1955.

ROSENTHAL, R. L., AND BENEDEK, A. L.: Blood coagulation and hemorrhage following total body x-irradiation in the rabbit. *Am. J. Physiol., 161:* 505-515, 1950.

ROSS, M. H., AND ELY, J. O.: Effects of Large Doses of Neutrons on Dogs. In *Neutron Effects on Animals*. Baltimore: The Williams & Wilkins Co., 1947.

SALISBURY, P. F., *et al.*: Effect of early cross-transfusion on x-irradiation disease. *Science, 113:* 6-7, 1951.

SARGEANT, J. C.: Civil defense organization and medical and health services in civil defense. *J.A.M.A., 145:* 897-900, 1951.

SANTISTABAN, G. A., BOWERS, J. Z., AND DOUGHERTY, T. F.: Influence of cortisone on the mortality of x-irradiated adrenalectomized mice. *Endocrinology, 55:* 794-807, 1954.

SAVITSKY, J. P.: Control of radiation hemorrhage with splenic extracts. *Blood, 10:* 52-61, 1955.

SAYERS, GEORGE: The adrenal cortex and homeostasis. *Physiol. Rev., 30:* 241-320, 1950.

SCHADE, F. F.: Medical defense plan of a metropolitan area. *J.A.M.A., 145:* 457–460, 1951.

SCHNEIDER, M., WYBOURN, R. C., BINHAMMER, R., AND FINERTY, J. C.: Protection of irradiated rats by parabiosis with adrenalectomized or splenectomized partners. *Radiology, 62:* 234–240, 1954.

SELYE, H.: The general adaptation syndrome and the diseases of adaptation. *J. Clin. Endocrinol., 6:* 117–230, 1946.

SHECHMEISTER, I. L., BOND, V. P., AND SWIFT, M. N.: The susceptibility of irradiated mice to infection as a function of post-irradiation time. *J. Immunol., 68:* 87–95, 1952.

SHECHMEISTER, I. L.: Susceptibility of irradiated animals to infection. *Radiation Res., 1:* 401–410, 1954.

SINAIKO, E. S., AND NECHELES, H.: Liver damage by desoxycorticosterone. *Science, 109:* 37–39, 1949.

SMITH, D. E., PATT, H. M., TYREE, E. B., AND STRAUBE, R. L.: Quantitative aspects of the protective action of cysteine against x-irradiation. *Proc. Soc. Exper. Biol. & Med., 73:* 198–200, 1950.

SMITH, FALCONER, AND SMITH, WILLIE W.: Exercise effects on tolerance to radiation. *Am. J. Physiol., 165:* 662–666, 1951.

SMITH, F., SMITH, W. W., ANDREWS, H. L., AND GRENAN, M. M.: Effect of parenteral injections of particulate matter on survival of x-irradiated animals. *Am. J. Physiol., 182:* 396–399, 1955.

SMITH, W. W., CHAPMAN, W. H., AND ALDERMAN, I. M.: Whole-body x-irradiation of obese mice. *Am. J. Physiol., 169:* 511–514, 1952.

SMITH, W. W., DOOLEY, R., AND THOMPSON, E. C.: Simulated high altitude following whole body radiation of mice. *J. Aviation Med., 19:* 227–237, 1948.

SMITH, W. W., AND SMITH, F.: Effects of thyroid and radiation on sensitivity to hypoxia. Basal rate of oxygen consumption and tolerance to exercise. *Am. J. Physiol., 165:* 639–650, 1951.

SMITH, W. W., GONSHERY, L., ALDEMAN, I., AND CORNFIELD, J.: Effect of granulocyte count and litter survival of irradiated mice. *Am. J. Physiol., 178:* 474–476, 1954.

SMITH, W. W., ALDEMAN, I., AND RUTH, H. J.: Functional studies of the hyperplastic spleen of mice recovering from radiation damage. *Am. J. Physiol., 182:* 403–406, 1955.

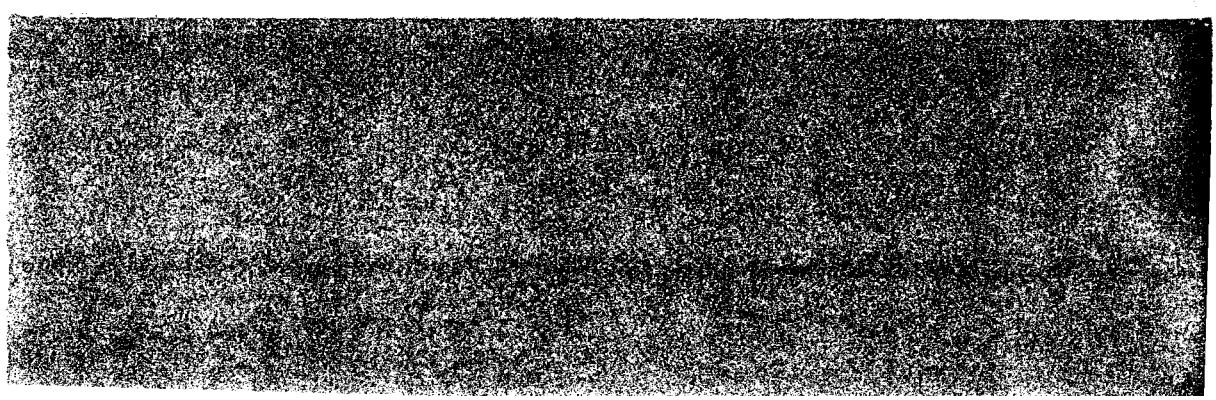
SMITH, F., AND GRENAN, M. M.: Effect of hibernation upon survival time following whole-body irradiation in the marmot (marmota monax). *Science, 113:* 686–688, 1951.

SMITH, W. W., SMITH, F., AND THOMPSON, E. C.: Failure of cortisone or ACTH to reduce mortality in irradiated mice. *Proc. Soc. Exper. Biol. & Med., 73:* 529–531, 1950.

SORENSEN, D. K., BOND, V. P., CRONKITE, E. P., AND PERMAN, V.: An effective therapeutic regimen for the hemopoietic phase of the acute radiation syndrome in dogs. *Radiation Res., 13:* 669–685, 1960.

STONER, R. D., AND HALE, M.: Radiation effects on primary and secondary antibody responses. Reprinted from *International Symposium on Effects of Radiations and Immune Processes.* University of Kansas, Sept. 1961, Scientific Papers, edited by C. A. Leone. p. 183–219. New York: Gordon and Breach, 1962.

STORER, J. B., HARRIS, P. S., FURCHNER, J. E., AND LANGHAM, W. M.: The relative biological effectiveness of various ionizing radiations in mammalian systems. *Radiation Res., 6:* 188–288, 1957.



STORER, J. B., AND COON, J. M.: Protective effect of paraaminopropiophenone against lethal doses of x-radiation. *Proc. Soc. Exp. Biol. & Med., 74:* 202–204, 1950.

STOREY, R. H., WISH, L., AND FURTH, J.: Changes in cell and plasma volumes produced by total-body x-radiation. *Proc. Soc. Exper. Biol. & Med., 74:* 242–244, 1950.

STRAUBE, R. L., PATT, H. M., TYREE, E. B., AND SMITH, D. E.: Influence of level of adrenal cortical steroids on sensitivity of mice to x-irradiation. *Proc. Soc. Exper. Biol. & Med., 71:* 539–541, 1949.

SWIFT, M. N., TAKETA, S. T., AND BOND, V. P.: Regionally fractionated x-irradiation equivalent in dose to total-body exposure. *Radiation Res., 1:* 241–252, 1954.

SWINGLE, W. W., AND REMINGTON, J. W.: The role of adrenal cortex in physiological processes. *Physiol. Rev., 24:* 89–127, 1944.

TALBOT, J. M., AND PINSONE, E. A.: The experimental use of bone marrow in acute radiation injury. *Mil. Surgeon, 108:* 312, 1951.

Tissue Homotransplantation Conference, Fifth, Report of. *Ann. of New York Acad. Sci., 999:* Art. 3, 1962.

THOMAS, E. D., LOCHTE, H. L., AND FERREBEE, J. W.: Irradiation of the entire body and marrow transplantation; some observations and comments. *Blood, 14:* 1–23, 1959.

TREADWELL, A. DEG., GARDNER, W. U., AND LAWRENCE, J. H.: The effect of combining estrogens with lethal doses of roentgen-ray in Swiss mice. *Endocrinology, 32:* 161–164, 1943.

TULLIS, JOHN L., CHAMBERS, F. W., JR., MORGAN, J. E., AND ZELLER, J. H.: Mortality in swine and dose distribution studies in phantoms exposed to supervoltage roentgen radiation. *Am. J. Roentgenol., 67:* 620–627, 1951.

TULLIS, J. L.: The sequence of pathologic changes in swine exposed to the $LD_{100/30}$ of total body super-voltage x-radiation. *Mil. Surgeon, 109:* 271–280, 1951.

U. S. ATOMIC ENERGY COMMISSION: *Effects of Atomic Weapons.* Superintendent of Documents. Washington 25, D. C.: U. S. Government Printing Office, 1950.

UPTON, A. C., WOLFF, F. F., AND FURTH, J. *et al.*: A comparison of the induction of myeloid and lymphoid leukemias in x-radiated RF mice. *Cancer Res., 18:* 842–848, 1952.

VANDYKE, D. C., AND HUFF, R. L.: Epilation in the non-irradiated member of parabiotically united rats. *Proc. Soc. Exper. Biol. & Med., 72:* 266–270, 1949.

WARREN, S.: Effects of radiation on normal tissue. *Arch. Path., 34:* 443, 501, 562, 749, 917, and 1070, 1942.

WARREN, S. L., AND WHIPPLE, G. H.: Roentgen ray intoxication. *Exper. Med., 35:* 1922; *38:* 1923.

WEBER, R. P., AND STEGGERDA, F. R.: Histamine in rat plasma; correlation with blood pressure changes following x-irradiation. *Proc. Soc. Exper. Biol. & Med. 70:* 261–263, 1949.

WORKS, L. *et al.*: Effect of BAL on radiation mortality rate in mice. *Quart. Bull. Northwestern Univ. M. School., 24:* 295, 1950.

WOOD, W. B.: *Harvey Lectures*, pp. 72–98, 1951–1952. New York: Academic Press, Inc. 271 pp.

VOLKIN, E., AND KOHN, H. I.: A factor in the plasma of the irradiated rat which changes the A/G ratio. *Arch. Biochem., 30:* 326–332, 1951.