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HANDBUCH DER MEDIZINISCHEN RADIOLOGIE
ENCYCLOPEDIA OF MEDICAL RADIOLOGY

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The radiation syndromes

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With 9 figures

I. Introduction

Until 1945 the question of radiation syndromes produced by exposure of the whole body or portions of the body to penetrating or poorly penetrating radiations was of little consequence except to the practising radiologist. Following the use of nuclear bombs in Japan, the entire world became vitally concerned with the effects of whole body exposure to penetrating gamma radiation. Later, with the development of the atomic energy industries and the application of nuclear energy in the production of electric power, injuries from exposure to combined gamma and neutrons were seen following criticality accidents in the processing of fissionable materials and in accidents involving nuclear reactors. There have been several deaths, and in the survivors the question of late effects of radiation constitutes important medical-legal problems. These are not trivial problems. The questions of monetary rewards for fractures, burns and other injuries are well established in the courts. The question of rewards for a statistical possibility of getting a disease at some future date remains unanswered.

On March 1, 1954, the world was again forcibly reminded of the hazards of radiation in the modern world when a fall-out accident occurred following the experimental detonation of a thermonuclear device. The exposure of numerous native Marshallese and American military personnel to fission products involved both exposure to penetrating gamma radiation and exposure to superficial beta radiation from the fissionable materials that were in contact with the skin.

Thus, in view of the contemporary possible exposures of human beings to harmful amounts of radiation, one can set up a general classification of radiation injuries to be covered in this chapter.

1. Classification

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. In this chapter the following will be considered.

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stance — tungstate of calcium is its repulsive name — which is potential, whatever that means, to the said rays. The consequence of which is that you can see other people's bones with the naked eye — on the revolting indecency there is no need to dwell. It would be best to burn the works on these rays, execute the discoverer and whelm all calcium tungstate into the ocean. Let the fish contemplate each other's bones if they like, but not us."

Oh roentgen, then the news is true
And not a trick or idle rumor
That bids us each beware of you
And of your graveyard humor
We do not want, like Dr. Swift
To take our flesh off and to pose in
Our bones, or show each little rift
And joint for you to poke your nose in.

— From PUNCH, January 25, 1896.

Ill effects were usually blamed on such things as ultraviolet from the Crookes tubes, platinum particles, cathode rays, electrostatic discharges, heat and so forth. It was soon noted that erythema was frequently seen involving the hands, arms and faces of people working with X-ray apparatus, but it appeared that this was considered of scarcely any more importance than sunburn. Thus, before long a tragic list of disastrous consequences began to unroll and many of the early workers appeared as victims, often fatally injured.

One of the early reports of superficial radiation injury is that of Dr. KASSABIAN, who wrote of X-rays as an irritant in 1900 and described his own case: "About five months ago the fingers, knuckles and dorsum of the left hand exhibited a general erythematous condition. This continued about a month; the itching became intense, the skin became tough, glossy, edematous and yellow." His condition became worse, and in 1903, he again wrote, "In order to effect a cure I have used every remedial agent mentioned in all the textbooks — but nothing seemed any good." In 1908 an area of ulceration showed malignant changes. In 1909, in spite of amputation, there were axillary metastases and death soon followed. This story with minor variations could be told of many others indeed.

BOND, FLIEDNER and ARCHAMBEAU (1965) quote HOLTHUSEN (1959) as saying of the 336 early fatalities ascribed to radiation exposure, 251 died from cancer induced by repeated radiation exposure of the skin, and 56 others died from blood dyscrasias such as anemia or leukemia. Of course, in this chapter we are more concerned with the depressive effects of radiation upon the blood forming tissues and the sequelae of prompt bone marrow depression or aplasia. The harmful effects of whole body irradiation on animals were documented early in the excellent studies of HEINECKE (1903 to 1905). Radiation hemorrhage was described by FERNAU *et al.* in 1913. FABRICIUS-MOLLER observed the relationship of the hemorrhagic diathesis from X-ray exposure in guinea-pigs to the depressed platelet count. In his classical initial study in 1922 he demonstrated that shielding of one leg by lead prevented the depression in platelets and thus the bleeding. Later ALLEN *et al.* (1948) ascribed radiation hemorrhage to heparinemia. This has been subsequently refuted by JACKSON *et al.* (1952) and CRONKITE and BRECHER (1952). In subsequent studies CRONKITE *et al.* (1952) have demonstrated that the radiation hemorrhage can be prevented solely by platelet transfusions. The importance of infection in pancytopenic states has long been appreciated by clinicians. The specific importance of infection in radiation pancytopenia was emphasized by the studies of MILLER *et al.* (1951) in their classic studies on the incidence of bacteriemia in mice subjected to total body X-irradiation and the improved survival rate by the treatment if mice with antibiotics after exposure. The critical role of the bone marrow in the development of radiation injury was emphasized by a series of studies by JACOBSON *et al.* (1949—1950) in which it was shown that shielding of the spleen

a) The early consequences of short-term exposure

α) *From penetrating radiation*

α_1) *Whole body exposure*

The acute illness produced by total body irradiation may occur in man from exposure to gamma and/or neutron radiation from a detonated atomic bomb, high gamma exposure from fall-out from atomic bombs, from accidents with radioactive materials, nuclear power sources, or in radiotherapy either for malignancy or as a means of depressing antibody response preparatory to organ transplantation.

β_1) *Partial body or markedly inhomogeneous exposures*

An acute illness may result from partial body exposure to penetrating radiations as is commonly seen in therapeutic radiation for cancer, and might again be seen following exposure in shielded criticality accidents and from radiation sources in radar devices.

β) *From poorly penetrating radiations*

In this situation acute injury of the skin or other body integuments may result from beta ray exposures of the skin as may occur in contact with fall-out radiation from military or experimental use of nuclear bombs or from accidents involving handling of radioactive materials. This injury is primarily limited to the surface of the skin.

b) Long-term exposure

α) Again, this must be sub-divided under injuries from penetrating radiation and those from poorly penetrating radiation. From penetrating radiation one may develop the following late effects: blood dyscrasias, namely leukemia; an increase in degenerative diseases; shortening of the life span; an increase in the incidence of cancer in general: retardation of growth and development in children; an increased incidence of cataracts; impaired fertility; and, of course, genetic effects in gererations yet unborn. In this chapter the question of leukemia, shortening of the life span, the question of thyroid cancer, and retardation of growth and development in children will be considered briefly.

β) Poorly penetrating radiation primarily produces injury of the skin, and this will be considered only in respect to exposure to fall-out or contact with radioactive materials.

γ) *Absorption of radioactive materials*

This will be considered only briefly and in the context of absorption of fall-out materials in the event nuclear warfare, laboratory radiation accidents and the results of past absorption of radium and mesothorium.

II. Historical

Although the early history is well known, certain humorous and tragic aspects serve well to introduce the subject. In the early days there was some little apprehension concerning the newly found and mysterious rays. Unfortunately, the early fears were largely absurd and misdirected. Since they are rather humorous in the light of our knowledge today, it is of interest to refresh one's memory. Scarcely anyone seemed to realize that there might be biological dangers. Instead, the public was treated to imbecilities. The Pall Mall Gazette considered X-rays revoltingly indecent. Punch poked fun at Roentgen and advised him to work on spooks. A New Jersey legislature later was concerned about the use of X-rays in opera glasses. In London X-ray proof underwear was offered for sale. Today the following from Punch, January 1896, is quite comic:

crease the survival of irradiated animals. There followed a long period of time in which it was argued whether the beneficial effect of splenic shielding, injection of splenic and bone marrow cell suspensions was due to transplantation or a humoral stimulation of host cells. It is now clear that the beneficial effect is predominantly due to transplantation of hemopoietic stem cells. The huge literature on this subject has conclusively demonstrated the role of transplantation of the hemopoietic stem cells in protection against radiation injury. It is not clear when the hemopoietic effects of whole body irradiation were first observed in human beings. However, an early detailed report on the effects upon depression of the blood in human beings without blood dyscrasias by Roentgen ray therapy was published by MINOT and SPURLING in 1924. A classical review of the effects of radiation on normal tissues of man and animals covering the period prior to 1942 was published by WARREN (1942).

The explosion of the nuclear bombs at Hiroshima and Nagasaki produced human radiation pancytopenia on a massive scale. Everything that had been observed in animals was abundantly observed in the Japanese. These observations are reported by OUGHTERSON and WARREN (1956). The potential hazardous effects of fall-out radiation were emphasized following the accidental exposure of a large number of human beings to fall-out radiation on March 1, 1954. The effects of radiation from fall-out in human beings is described by CRONKITE, BOND and DUNHAM (1956).

Two other aspects of radiation injury are also of importance. First, there is the question of severe injury to the nervous system either by whole body irradiation or exposure of the head alone. This produces a rapidly fatal syndrome amply described by GERSTNER. — This has subsequently been observed in part in human beings exposed to huge amounts of radiation in criticality accidents (PAXTON *et al.*, 1958). Another means by which animals can be killed is the acute intestinal radiation death that was initially described by QUASTLER *et al.* (1951).

III. Definitions of human exposure

A semantic problem exists. In the past various descriptive terms have been used to describe the types of exposure, such as acute, chronic, protracted, repetitive and continuous exposure, again sub-divided into various categories on the basis of the type of radiation, its energy or other specific characteristic. Much ambiguity existed in the use of the preceding approach. Exposure conditions should therefore be defined according to the method proposed by the United States National Academy of Sciences, National Research Council Sub-Committee on Hematologic Effects of Radiation. These are:

1. Short-term exposure

Short-term includes total body exposures to radiation over a short period of time (e.g. in nuclear warfare, nuclear reactor or accelerator accidents) and exposure of limited but substantial body areas when the radiation is delivered either as a single dose or fractionated over a few days or weeks (e.g. in therapeutic radiation, diagnostic radiology or tracer or therepeutic use of radioactive isotopes). In considering short-term exposure, a dose greater than 50 rads is defined arbitrarily as a high dose, less than 50 rads a low dose. These definitions are for prospective and retrospective classification and study of radiation effects.

2. Long-term exposure

Long-term exposure refers to continued or repeated exposure to radiation over long periods of time — months or years. The possibility of such exposure is greatest in certain

occupational groups and in persons having body burdens of radioactive isotopes with relatively long, effective half-lives. X-ray examinations repeated frequently over a long time were also considered long-term exposure, as are exposures to cosmic radiation, naturally occurring radioactive isotopes, and world wide fall-out.

Although the total dose of radiation is important in long-term exposure, it is more useful and convenient to indicate the degree of exposure in terms of dose per unit of time, usually cumulative dose per week.

1. Minimal weekly dose is less than 100 millirads.
2. Low weekly dose is 100 to 1000 millirads.
3. High weekly dose is greater than 1000 millirads.

The minimal dose is less than the maximum permissible dose (MPD) recommended most recently by the International Commission on Radiological Protection and the National Committee on Radiation Protection and Measurements. The dividing line between low and high dose corresponds to the first MPD recommendations of these groups in effect between 1936 and 1948.

IV. Effect of physical factors on radiation response of mammals

Superficially it would appear unnecessary to discuss the role of physical factors upon the response of the whole body to irradiation. However, problems are involved which are significantly different from those encountered in radiation therapy. Clearly the preferable measure of the amount of radiation is the absorbed dose (rad). This unit, as is well-known, is completely independent of the energy and type radiation. However, the expression of biological effects from whole body exposure or large parts of the body in terms of the rad is not completely satisfactory. The distribution of dose in respect to time and space is also a major determinant of response. It is necessary to know whether the dose is essentially instanteneous, fractionated, short-term or long exposure, because distribution of dose with time also significantly influences the biological response. As will be pointed out later in this chapter, the response, recovery and resistance to subsequent doses of radiation is significantly altered by prior exposure to radiation. Further, the spatial distribution of the absorbed dose anatomically in depth within an organ significantly influences the biological response of the whole animal. The quality of the radiation is another meaningful parameter to be considered. High energy protons, alpha, beta, gamma, X-ray and neutrons, all have properties which may influence the quantitative response per unit of absorbed dose. Generally the relative biological effectiveness (RBE) per rad is a function of the linear energy transfer (LET). However, with very high proton energies and stripped nuclei, as may be encountered in space flight, one must also consider the possible influence of spalation. A problem to which there is no satisfactory solution is the anatomic inhomogeneities in the distribution of absorbed dose within the body. With most conditions of human exposure the relative homogeneity of absorbed dose will be the exception rather than the rule. It is fair to say that after accidental exposures true homogeneity in absorbed dose has never been seen. The problem on unpredictable inhomogeneity in dose raises an important practical difficulty in assessing the hazard of accidental exposure of man. The inhomogeneities simply cannot be described by any single meaningful value for the dose distribution received by the critical organs within the body, hence the biological response is the key to management, not a physical dose estimate.

Although exposure due to absorbed radioisotopes will rarely be observed, it does constitute a problem of difficult dosimetry. For practical purposes, it is almost impossible to measure directly the dose from internal emitters. Therefore, it is necessary to rely on calculations of the dose from estimations of the average concentration of the radioisotope involved and the biological half-life of the substance. From the preceding two, one can

easily calculate the absorbed dose providing that there is uniformity in the deposition of the material within all of the organs involved. Since the distribution is always inhomogeneous, one can only estimate the average dose and rarely, if ever, is one able to determine at a microscopic anatomical level the range in dose from the minimum to the maximum, nor the influence of relatively uninjured tissues upon contiguous severely injured tissues.

The concept of the integral dose is very useful in radiotherapy. This refers to the total energy absorbed within the object. This unit of measurement of radiation is of very limited or no value considering the effects of radiation on the whole body of man or animals since it has been shown that gram roentgens or integral dose cannot be used to predict the degree of biological effect. This arises from the fact that the biological effect depends not only on the total dose absorbed, but also on the portion of the body receiving the dose, the relative homogeneity of the absorbed dose and, of most importance, the influence of non-irradiated or lesser irradiated hemopoietic tissue upon the recovery of the more heavily

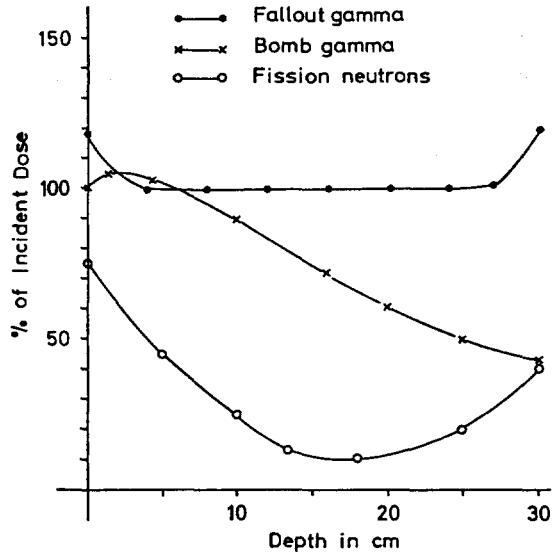

Fig. 1. Depth dose curves for three different types of radiation to which human being might be exposed

irradiated hemopoietic tissue. A very useful reference for a more technical and sophisticated discussion is the symposium on Physical Factors and their Modification of Biological Effects of Radiation (1964).

The relative biological effectiveness is analogous to the relative potency ratio for drugs in pharmacology. In radiation studies, a standard radiation, usually X-rays of prescribed characteristics, is used. The ratio of the dose in rads of X-rays to produce the same degree of biological effect to the dose of the test radiation is known as the RBE of the test radiation. When the targets are very small, one can obtain a precise estimate of the absorbed energy in each case and have a very scientific evaluation of the relative biological effectiveness. However, when one has larger targets, such as man, in a radiation field the problem is complicated by serious inhomogeneities in the distribution of absorbed dose. This is illustrated in Fig. 1. It will be noted that in the case of a diffuse field of gamma radiation coming from all directions at the individual, the surface dose is somewhat higher than the air dose due to back scatter, and the dose throughout the body is relatively uniform until the other side of the body is reached, at which point the dose again increases due to scatter and low energy components that are present. In the case of the penetrating initial bomb gamma radiation there is a very small increase in the absorbed dose in the first few centi-

metres, and then an attenuation with the unilateral irradiation, so that the exit dose is about 45 % of the entrance dose. In the case of fission neutrons, the first collision, absorbed dose at the surface is about 75 % of the incident dose. The absorbed dose is rapidly attenuated, reaching a low value of about 10 % of the entrance dose at 18 cm. Although the radiation is unidirectional, it is greater on the back surface of the body due to scattering from the air and entrance into the back side. These three examples of whole body exposure have three completely unique and different depth dose curves. Clearly, per rad of exposure there is a significantly different biological effect.

V. Qualitative and quantitative effects of radiation upon mammals

1. Dose mortality responses

Dose mortality responses have been used for decades to express the effect of radiation and to observe factors that modify the radiation response. All of the dose mortality curves have a characteristic sigmoidal appearance, as expressed in Fig. 2b. Generally, in respect to mammals most of the mortality is completed by 30 days and the mortality is scored at

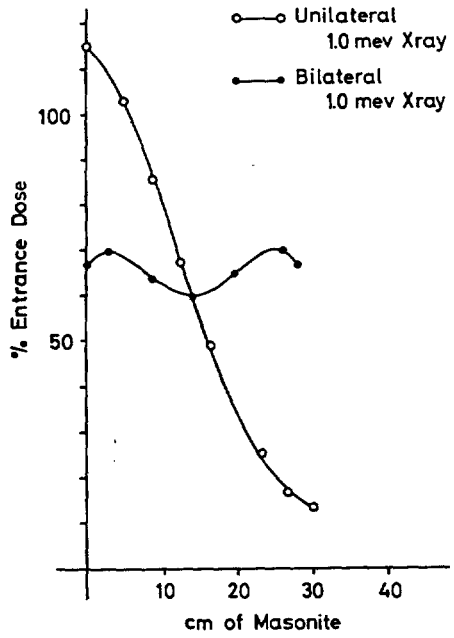

Fig. 2a. Depth dose curves for 1.0 MeV X-ray when all of the radiation is delivered to one side of the phantom and when half of the dose is delivered to both sides (bilateral)

this time. Note that the upper and lower portions of the curves are very poorly defined. It is theoretically impossible to ascertain the dose below which no individual would die or above which all individuals will die. However, these are in practice ascertained by exposure of large numbers of animals in the vicinity of zero and 100 % mortality. However, for comparative purposes the midpoint of the curve is used to characterize the entire dose response relationship. This dose is referred to as a median lethal dose, and is ordinarily

abbreviated LD_{50}. It is a derived dose and does not mean that an individual animal exposed to this dose will necessarily live or die. It indicates only that in a very large population one can expect half of those exposed to die within the stated time. Usually with mammals the range in dose between no deaths and 100 % mortality is of the order of 200 to 400 rads. Theoretically the lower end of the curve approaches the abscissa asymptotically and does not cross it until zero dose. In actuality it crosses the abscissa at a relatively high dose, creating effectively a threshold dose for mortality. A very useful means of expressing the dose mortality is to plot it on probability paper, by which the sigmoidal curve is transformed into a line. Then one determines the slope of the curve and the LD_{50} to characterise the whole system.

a) Influence of depth dose pattern upon dose mortality

This problem has been studied by numerous investigators, and is illustrated from the work of TULLIS *et al.* In Fig. 2a, the depth dose patterns of 2 MeV X-ray is plotted for a unilateral exposure and the depth dose pattern for bilateral exposure to the same total amount of radiation. In Fig. 2b the dose mortality curves for each type of exposure are

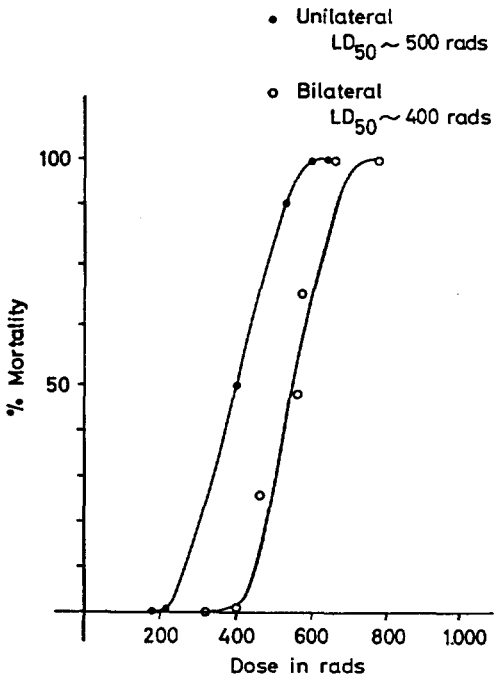

Fig. 2b

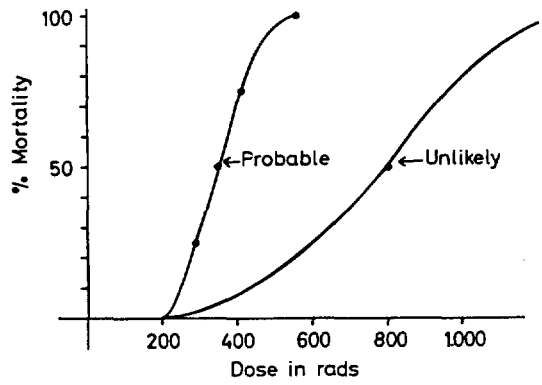

Fig. 3

Fig. 2b. X-ray dose mortality curves in swine when the radiation is given unilaterally or bilaterally showing the different killing effect of the same amounts of radiation when given so that depth dose is different as in Fig. 2b

Fig. 3. Schematic presentation of dose mortality curves for man indicating the most likely human response and an unlikely response. See text for rationale

plotted. Note that the estimated LD_{50} for the unilateral exposure is 500 rads and for the bilateral exposure is 400 rads. Furthermore, with bilateral exposure animals commence to die at approximately 200 rads exposure, whereas with the unilateral exposure deaths were not observed until 400 rads. Similar studies using very low energy radiation have shown that one can go to many thousands rads of unilateral exposure without any acute mortality, although serious skin injury is produced.

Earlier in this chapter, Fig. 1, the depth dose curves for different types of radiation to which human beings might be exposed were plotted. Other types of accidents in which human beings may be involved are criticality accidents that consist of a combination of mixed gamma and neutrons, and here there are also inhomogeneities in the absorbed dose. However, the influence of the inhomogeneities in depth dose illustrates in Fig. 2a and b cannot be extrapolated for purposes of prediction to other types of exposure.

b) The median lethal dose for human beings

There are certain general facts that are pertinent to attempting to answer this vital problem. First, as shown by BOND and ROBERTSON (1957), all small mammals have a relatively high LD_{50} when expressed as mid-line absorbed dose, and all large mammals (swine, burros, dogs etc.) have a relatively low LD_{50}. The slopes of most dose mortality curves are roughly the same. In general the LD_{50} for large mammals is of the order of 250 rads for X-rays with uniform dose distribution, and that for small species is approximately double this value. Some investigators have considered primates to be more closely related to human beings. However, the LD_{50} of monkeys is similar to the small mammals rather than the large mammals. Large animals exposed under silimar geometric conditions have rather uniform dose mortality curves, perhaps partly because large animals, unlike small animals, provide their own constant maximum scatter of radiation. The experimental determination of LD_{50} is usually based on animals of a clearly defined genetic background, age and sex. In general females are a little more resistant to radiation than males. When one is concerned with human populations, one is dealing with a spectrum of ages, sex and races.

Knowledge about the LD_{50} for man is clearly needed, both for evaluation of radiation accidents and from the standpoint of planning possible whole body radiation therapy for specific purposes. CRONKITE and BOND (1960) have approached the problem of estimation of the LD_{50} for man in the absence of any therapy for the injury in the following manner. A large number of human beings were exposed to 175 rads of gamma radiation from fall-out. As illustrated in Fig. 1, the depth dose below 1 cm is quite uniform from this type of radiation. These individuals had a severe hematologic depression and were on the verge of developing purpura and had a severe granulocytopenia. From data on animals, it can be assumed that an increment of 50 to 100 rads probably would have placed these exposed human beings into the lethal dose range. One can therefore anchor the lower end of the dose mortality curve for man in the vicinity of 200 rads. The next assumption asserts that the slope of the dose mortality curve for large animals and for human beings will be almost the same. With the preceding two assertions one can draw a dose mortality curve through the lower anchor with the slope similar to that of dogs, and obtains an estimated LD_{50} of about 360 rads for man. This is illustrated in Fig. 3. Other human data are consistent with this estimate. One out of five of the Yugoslavs exposed to about 350 rads in a nuclear accident died. The hematologic response of the individuals exposed to approximately 300 rads in another criticality accident was significantly greater than that in the Marshallese. Some of these individuals developed purpura, and the depression in their granulocyte count was also greater than in the Marshallese. Furthermore, extensive studies on clinical radiation therapy exposing the entire body has resulted in a severe hematologic depression of individual with metastatic cancer after exposure to 200 rads, and an occasional death in these diseased individuals has been observed (MILLER *et al.*, 1957). The dose of radiation received by the Japanese in Hiroshima and Nagasaki is under continuing study by the joint Japanese-American Atomic Bomb Casualty Commission. With further refinements of their estimates, one may be able to ascertain the dose to a sufficient number of human beings to get a rather precise estimate of the human LD_{50} exposed to this type of radiation and given no therapy.

in the mammal

A very sophisticated discussion of the role of disturbance in cellular kinetics of cell renewal systems as a basis for mammalian radiation lethality has been published by BOND, FLIEDNER and ARCHAMBEAU (1965). For our purposes in this chapter only a brief summary of the different types of organ systems within the body and their characteristics are needed. Mammalian organs consist of three general types on the basis of cell production. First, there are those organs in which there is essentially no production of new cells from cessation of growth to death. Examples of this type are the brain, cardiac muscle, skeletal muscle and the collagenous tissues. Second, there is the class of organs in which there is the capa-

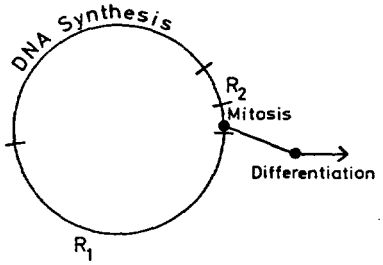

Fig. 4

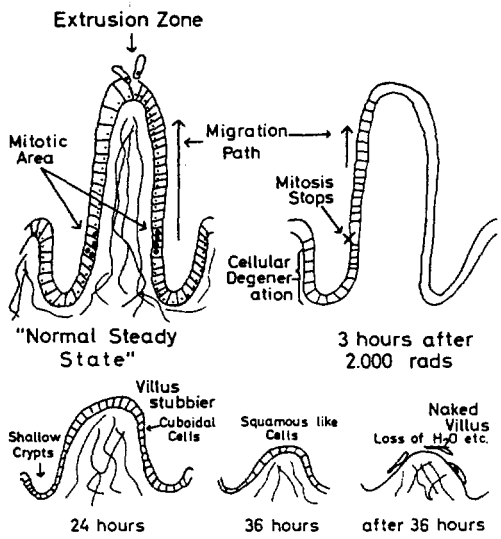

Fig. 5

Fig. 4. Schematic of cell generative cycle indicating the different time phases between successive mitoses which have radiobiological significance

Fig. 5. Schematic presentation of cell renewal in the small intestinal epithelium and the effects of 2000 rads of radiation upon proliferation of bowel epithelium leading to the gastrointestinal syndrome

bility of repair following injury, such as the liver, fibrous tissue, periosteum and blood vessels. Normally there is practically no cell turnover in these tissues, but upon injury the remaining tissues delete can burst into cell proliferation and repair the loss of cells or the separation of the tissues. Third, there are those tissues which are in a steady state of cell proliferation, in which the production rate equals the death rate of cells. Examples of these tissues are the epithelium of gastrointestinal tract, the skin, and the hemopoietic tissues. Cell proliferation is maintained in each of these cell lines by "the stem cell" which has the properties of self-replication and differentiation to exogenous influences that direct it down specific cellular lines. The cell cycle for a stem cell is illustrated in Fig. 4. The cell cycle consists of the following periods commencing after mitosis. First there is a rest period (R_1) prior to the commencement of DNA synthesis or chromosomal replication. During the rest period, of course, other metabolic processes may be very active. During DNA synthesis the chromosomes are replicated to preserve the genetic code. Also during this time there is a substantial amount of RNA synthesis. Upon the completion of the replication of chromosomes there is another rest period termed R_2 prior to mitosis. When cells divide they can be assumed to be possessed of equal genetic capabilities. However, random influences impinge upon the stem cell pool and on an average induce half of the

progeny to differentiate in order to maintain the steady state equilibrium of the stem cell pool and specific cell lines. One can measure the relative rate of cell proliferation by counting the number of mitotic figures, of cells that are in DNA synthesis, or by stopping mitosis at metaphase by stathokinetik agents such as colchicine, and observing the number of cells that accumulate in metaphase. For a more detailed description of the characteristics of cell renewal systems one is referred to BOND, FLIEDNER and ARCHAMBEAU (1965). The cell cycle is of particular importance in radiation effects, since the sensitivity of cells varies with the stage of the cell cycle. In general, cells are most sensitive to radiation during the mitotic, the late R_1 or early phases of DNA synthesis. In tissue culture after exposure to the same amount of radiation, 4 times the number of cells survive if exposed during late DNA synthesis, and most of the R_1 and R_2 periods as compared to exposure in synchronized cultures during the early DNA synthetic phases. Mitosis is also very sensitive, with about half as many cells surviving when exposed in mitosis as compared to late R_2 and early DNA synthesis. A simple cell renewal system for the gastrointestinal tract is illustrated in Fig. 5. Normally there is active proliferation of cells in the neck of the crypts of LIEBERKUHN. Cells migrate out the villus in an orderly fashion and are extruded at the tip. In the normal steady state it takes approximately 36 hours for cells to migrate to the tip of the villus.

Since the kinetics of cell proliferation in hemopoietic systems are described in considerable detail by BOND *et al.* (1965), only a pertinent summary will be presented herein.

a) Erythropoiesis

Stem cells are acted upon by erythropoietin to direct them down the erythropoietic pathway. The approximate generation time of erythropoietic precursors in the proliferating compartment is 24 hours in man. The total transit time from the stem cell to the reticulocyte is approximately 4 to 7 days. The mean life span of human red cells is 120 days. The steady state equilibrium is maintained by a feedback system that is sensitive to oxygen tension and perhaps the total mass of the red cells in the peripheral blood. Decreased oxygen tension increases the levels of erythropoietin which induces more stem cells down the erythropoietic pathway.

b) Granulocytopoiesis

Granulocytopoiesis is also reasonable well understood from the standpoint of the time involved in the flow of cells from the stem cell to the mature granulocyte in the peripheral blood (CRONKITE *et al.*, 1960; FLIEDNER *et al.*, 1965; CRONKITE and FLIEDNER, 1965). The factors that are responsible for the differentiation of stem cells into granulopoietic precursors are not known. The transit time for cells from the myeloblast to the first nondividing cell in man is about 6 days. The transit time through the maturing pool, that is from the metamyelocyte to the granulocyte, is 3 to 4 days. The total transit time from the stem cell to the mature granulocyte in the marrow is 9 to 10 days. Granulocytes disappear from the blood in a random fashion with a half-time of 6.6 hours (ATHENS *et al.*, 1961). The random process is terminated by a senescent process at 30 hours (FLIEDNER *et al.*, 1964).

c) Platelets

These are produced by the megakaryocytic system. The total transit time from the most immature megakaryocyte in the marrow to platelets in the peripheral blood has been described as lying between 4 and 10 days (man, CRONKITE *et al.*, 1961; rat, EBBE and STOHLMAN, 1965). The life span in the peripheral blood of man is of the order of 10 days (LEEKSMA *et al.*, 1956). Platelets are lost from the blood by a random process, and also have a finite life span that terminates the random loss.

d) Lymphopoietic tissues

The lymphocyte producing organs constitute a unique system. The lymphocytes may conveniently be divided into two classes on the basis of their size (SIPE *et al.*, 1966). The smaller class with volumes of 150 to 350 cubic microns is further sub-divided into two classes on the basis of life span. One is very short-lived and, at least in animal experiments, presumably is thymic in origin (EVERETT *et al.*, 1965). The other has a much longer life span, with some cells living in excess of a year (ROBINSON *et al.*, 1965). The larger lymphocytes have a relatively short life span measured in hours to a few days. A fraction of the small blood lymphocytes have a unique migration pathway from the blood through the postcapillary venules at the medullary cortical junction (GOWANS *et al.*, 1963).

These cells migrate through this venule into the substance of the lymph node, and then recycle out through the efferent lymph and into the blood. This recycling accounts for a very large fraction of the lymphocytic output of the lymphatic ducts. Since lymphocytes have these widely varying life spans and migration patterns but are not unique in respect to morphology, it is difficult to study the kinetics of these cells adequately and separately with available techniques.

e) Bone marrow

The bone marrow is the site of the formation of red cells, granulocytes and platelets. Normally in man all myelopoiesis takes place within the cavities of bones. Thus it is contained within rigid walls which do not permit volume changes. The hemopoietic bone marrow is composed principally of three cell renewal systems: erythropoietic, granulopoietic and thrombopoietic. The parameters of cell proliferation for these have been listed earlier. All three cell renewal systems are distributed throughout the extra-sinusoidal marrow spaces. Normally one never sees erythroblasts outside the marrow parenchyma. In addition, it is rare to see granulocytic cells more immature than the band in the peripheral circulation. It is possible that the mature granulocyte spends some of its life span outside the blood vessels. However, there is no clear-cut evidence for re-entry of ganulocytes into the blood vessels. There is no question that lymphocytes spend a substantial fraction of their life span outside the blood vessels as described under the recycling of lymphocytes earlier. The vascular structure of the bone marrow has been studied extensively. It is a closed system with a series of unique arteries and veins connected by a very fragile sinusoidal system which receives blood from the arterial capillaries and from which blood empties into the venous side (FLIEDNER *et al.*, 1956). It is believed that cells enter the blood stream through the sinusoidal endothelium.

3. General cytological and histological effects of radiation on tissue

Radiation can produce immediate cellular death, suppression of the motility of cells, suppression of reproduction of cells, the induction of anomalies of cellular division, a retardation of growth and, in the germ cells, mutations. Whether mutations occur also in somatic cells maintaining the cellular renewal systems is open to question. What is observed microscopically in mammalian tissues following exposure to radiation is a function of the time after irradiation, the dose of radiation, and the tissue involved. The sequence of microscopic effects in the so-called radiosensitive tissues (those tissues that are continually renewing themselves) is different from that observed in the radioresistant tissues (tissues, the cells of which are rarely replaced if at all from the time of birth, or after cessation of growth).

There is nothing specific about the observable microscopic effects of radiation. There is no special type of necrobiosis. The cells degenerate according to the manner of the particular cellular type or tissue. The picture associated with cellular death in histopathology has been described as coagulative necrosis, liquefactive necrosis, granular degeneration, and

cloudy parenchymatous degeneration. These phenomena are observed after irradiation. In a general sense, the more radioresistant types of tissues, for example, skeletal muscle, osseous, adipose, and glandular tissue, when exposed to sufficient amounts of radiation, undergo coagulative necrosis. It takes very large amounts of radiation to produce these changes. Although the cells themselves are still recognized, they undergo necrosis characterized by poor staining, disappearance of cellular detail, homogeneous appearing cytoplasm and disintegration of the nuclei. If the doses of radiation are sufficiently high, the necrosis will be visible in a matter of hours. The injured tissue may be absorbed very slowly following localized irradiation of radioresistant tissues. Following whole body irradiation with these large doses, survival time is very short, and there is not sufficient time for the whole sequence to unravel.

a) Central nervous system

Insight into the fact that there are a series of different modes of death following whole body irradiation arose from the fact that there are different survival times as a function of increasing dose of radiation. This is illustrated in Fig. 6. In the dose range of 200 to about 1000 R, the mean survival time varies somewhat but is in the vicinity of 10 to

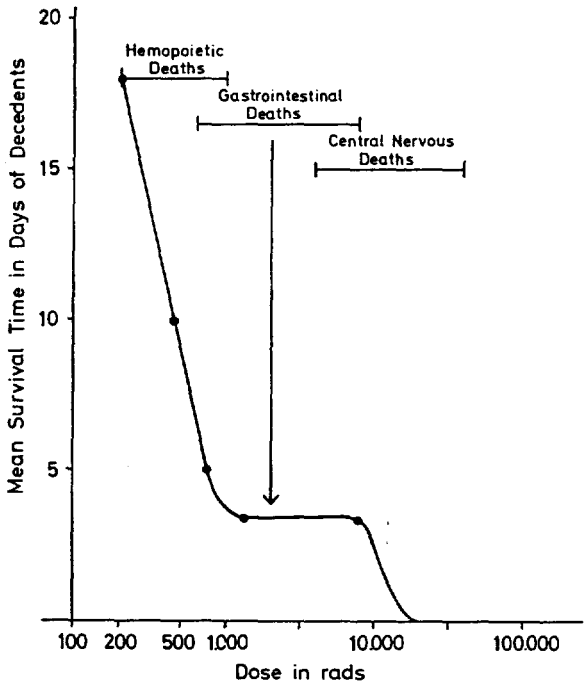

Fig. 6. Generalized curve for mean survival time of decedents as a function of the dose. Position of the curve varies with the species. Note overlapping in deaths from various modes and the plateau for gastrointestinal deaths

15 days depending upon the species. As the dose of radiation is increased over 1000 rad, a stable survival time of about 3 to 4 days is seen, which corresponds to the gastrointestinal syndrome to be described later. This plateau in survival time is constant to roughly 5—7000 R, with considerable variation between species. Again, the survival time commences to decrease, and with doses in excess of 10000 rad given in a short period of time, the survival time is of the order of 24 hours. As the dose is increased further, the survival time progressively becomes shorter, and animals die under the beam. The survival time

versus dose has been published for mice by CRONKITE (1951). As the survival time falls below 3 to 4 days, central nervous system symptomatology and severe injury of the central nervous system may be observed histologically. The central nervous system syndrome, when induced by whole body irradiation or irradiation of the head alone with uniform deposition of energy, is uniformly fatal in a short period of time. Only a brief summary will be presented. Details of the pathology and symptomatology are available from GERSTNER (1958), VAN CLEAVE (1962) and KRAYEVSKII (1965).

α) *The symptomatology of the CNS syndrome*

With extremely high doses of irradiation given at exceedingly high dose rates, respiratory difficulty commences, there may be a short period of agitation followed by marked apathy and death in a short period of time. When the radiation is given at slower dose rates, there may be a period of agitation followed by apathy, disorientation, disturbed equilibrium, ataxia, diarrhea, vomiting, opisthotonus, prostration, convulsions followed by coma and death. There is considerable variability in the sequence and the intensity of the various symptoms. In addition, there are also species differences. Part of the gastrointestinal symptomatology is due to irradiation of the gastrointestinal tract, but a portion is also due to direct injury of the head, since it can be produced by head irradiation alone.

Human symptomatology that has been observed will be described later.

β) *Histopathological changes in the central nervous system*

One of the characteristic phenomena is the perivascular and parenchymatous granulocytic infiltration of the meninges, chorioid plexuses and brain. These inflammatory infiltrations are composed predominantly of granulocytes and occur within a very few hours and later are replaced by mononuclear cells and later macrophages. If the survival is more than 4 to 5 hours, vasculitis is a constant finding. This consists of a perivascular granulocytic infiltration which involves all layers of the blood vessels, and may extend into the surrounding tissue. Veins and arteries of all sizes are equally involved. All parts of the cerebrum are involved. There are varying degrees of intensities, with the spinal cord and cerebellum apparently having less involvement. The intensity of the infiltration is biphasic, with peaks at 8 and 48 hours (VOGEL *et al.*, 1958). Edema becomes prominent. Hyperchromatic granule cells of the cerebellum and pyknosis of these cells are characteristic, dose-dependent finding following whole body and head irradiation. The hyperchromatism of these cells is uniform throughout the cerebellum of the monkey. Changes in these cells appear as early as two hours, and are maximal at 24 hours.

In a general sense, with doses less than 500 rads to the brain, very little is seen. Of course, in the late stages of the hemopoietic syndrome, when there is a severe depression in the platelets and a generalized purpura, hemorrhage may be seen in the meninges and the substance of the brain. With doses in excess of 1000 rads, one sees distinct effects upon the brain that increase with dose. There are considerable differences in species sensitivity. There is no generally agreed view as to the most sensitive cells in the brain. Some pathologists are inclined to consider the oligodendroglia as most sensitive. The permeability of the blood brain barrier is disturbed. Trypan blue injected intravenously stains the brain. In summary, then, diffuse edema of the brain may be seen with perivascular infiltration of leukocytes. The acute inflammatory response, the degeneration of neurons and local hemorrhage may result in prompt death of the animals. If they survive the first day or so, later liquefaction and necrosis of the white substance of the brain may become prominent. Since there is no cellular turnover in the nervous system, all effects are due either to the inflammatory response and edema, or direct injury and necrosis of neurons.

When the irradiation is inhomogeneous in its deposition within the brain, as occurred in the Lockport incident (HOWLAND *et al.*, 1961), there may be substantial nervous system symptomatology and direct physical evidence of cerebellar and cerebral injury, but prolonged survival, as will be described later in this chapter.

In marked contrast, apparently, to all of the other species, the burro develops severe nervous system symptomatology, and dies frequently from damage to the nervous system from doses of radiation below 1000 rads (THOMAS and BROWN, 1961). There is no explanation as yet why this mammalian species has such a sensitive nervous system.

b) Gastrointestinal system

In the sub-lethal range, less than 200 rads, there is a diminution in the mitotic index of the small bowel (WILLIAMS *et al.*, 1958) and a depression in the weight of the bowel that is dose-dependent (CONARD *et al.*, 1956). A slight amount of pyknosis and karyorrhexis in the crypts of LIEBERKUHN, and an occasional bizarre mitotic figure may be seen. Recovery takes place promptly. The mitotic index returns to normal in a matter of a few days, and there may be an actual overshoot in both the mitotic index and the weight of the bowel.

In the mid-lethal dose range for mammals, effects are similar to those with sub-lethal doses of radiation, except that the depression in the mitosis is greater, the duration of the depression in the mitotic index is longer, and the decrease in the weight of the bowel is greater. The return to a normal histologic appearance takes somewhat longer. There is also an overshoot in both the mitotic index and the weight upon recovery (QUASTLER, 1956).

In the mid-lethal dose range, there are certain changes that take place later in the bowel that bear no direct relationship to the early injury. There are sequelae of the generalized effects of depression of bone marrow function and the resulting pancytopenia. About 10—20 days after exposure, a tendency to bleed becomes prevalent, due to the marked thrombocytopenia. There may be numerous petechial hemorrhages scattered throughout the mucosa of the bowel. In some areas there may be more extensive hemorrhage that will dissect the mucosa of the bowel from the underlying muscularis, and may even act as a site of commencement of intussusception, a point that has considerable clinical importance. If the animal survives the general effects of the depression of bone marrow function, the gastrointestinal tract will completely recover. In both the sub-lethal and mid-lethal range there is relatively little that can be observed with regard to the histologic changes in the stomach and the colon. When the doses of radiation are increased to the "supra-lethal" range, there are considerable differences in species sensitivity, with the rat being more sensitive than most mammalian species. In the general vicinity of 1000 to 3000 rads, the effect on the gastrointestinal tract is quite striking. There is complete cessation of mitosis in the crypts of LIEBERKUHN. With doses up to 1600 rads this is temporary. However, if, as will be described later, animals are kept alive by appropriate therapy, regeneration will occur if the dose of radiation is not in excess of about 1600 rads. The cells in the crypts undergo typical pyknosis, karyorrhexis and bizarre large cells with peculiar nucleoli make their appearance. As the production of new cells diminishes and ceases completely, the cells on the villi continue to migrate out to the extrusion zone at the tip of the villus. Thus, as cells are lost from the extrusion zone, the total number of cells covering the villi decreases. As the cells continue to move out, mature and become extruded into the lumen of the bowel, the epithelium changes from columnar to cuboid to squamous. When the last few stretched out squamous appearing cells are sloughed off into the bowel, generally around the third to the fourth day in rodents, the bare villi are left exposed. The preceding are shown schematically in Fig. 5. At this time there is a serious loss of plasma into the bowel, and death occurs promptly within a few hours from this massive loss of fluid and electrolytes unless antishock therapy is instituted, particularly with plasma, fluids and electrolytes. Animals can be saved when the vascular beds collapse if death is prevented by heroic fluid therapy (CONARD *et al.*, 1956). A striking series of events have been shown to take place in the small bowel after approximately 1200 rads of gamma radiation. Therapy prevents death from the gut injury. Between the 4th and 6th days regeneration commences

(BRECHER *et al.*, 1958). Mixed between the bizarre abnormal cells are numerous hyperchromatic cells with much mitotic activity. The crypts are reconstituted, and cells again begin to migrate out on to the villi and reconstitute the normal appearance of the bowel by the tenth to the twelfth day after exposure. The sequence of the degenerative effects on the bowel is shown in Fig. 5. Whether the recovery is abortive as in the case of hemopoiesis is not established.

As recovery in the small bowel occurs, a similar sequence of degenerative events takes place in the stomach of treated dogs. as seen earlier in the small bowel. Through the sixth day the stomach mucosa appears normal. However, there then appears an obvious necrosis of the cells in the necks of the gastric glands followed by a desquamation of epithelium from the mucous surface of the stomach in a way comparable to that described before for the small intestinal tract. These observations demonstrate the essential role of time in addition to dose of radiation in any discussion of relative radiosensitivity. Even under conditions in which the dose to the gastrointestinal tract is identical in all parts, the sequence of events takes place much more rapidly in the small intestine than in the stomach. Thus, any estimate of radiosensitivity based on observation after a single dose of radiation, or only at a single time after exposure, may be misleading.

c) The effect on lymph nodes, thymus and spleen

The magnitude of effect on these organs is a function of dose and time after exposure. Changes in the splenic and thymic weight of mice have been used practically to assay mixed gamma and neutron radiation. After the initial usual shoulder on the curve showing the relationship between the ratio of the control spleens to the irradiated spleen, the log of the ratio of irradiated spleen and thymus to normal spleen and thymus is linearly related to the dose of radiation. This has been a most useful biological dosimeter. Shortly after exposure of lymphatic tissue to even very small amounts of radiation down to the order of 25—50 rads, one can see a moderate amount of pyknosis and karyorrhexis in the lymphocytes during the first few hours after exposure. The nuclear debris is rapidly phagocytosed and disposed of. Mitosis returns and the lymph nodes, after small amounts of radiation, are reconstituted. TROWELL (1946) has used the fraction of lymphocytes that are pyknotic as a dosimeter also. In the spleen and thymus one sees similar nuclear debris. After large doses of radiation, in the mid-lethal range, the destruction of the primary follicles of lymph nodes and spleen is quite striking and almost complete. Mitosis is essentially eradicated. By the third to the fifth day, at which time the maximum weight loss has taken place, the entire architecture of the lymph node is altered. The primary and secondary follicles have disappeared, the sinuses in the lymph nodes are distended with clear lymph, and there is an apparent increase in the number of plasma and stroma cells of the node due to the atrophy of the small lymphocytes normally present. As time goes on, there is a slow return to normal by an onset of mitosis and regeneration of the node. If the hemorrhagic phase of the whole body radiation syndrome commences, bleeding takes place peripherally in the tissues. The red cells are absorbed into the lymphatics and are in part phagocytosed by the reticulum cells of the sinuses as the bloody lymph flows past these phagocytic cells lining the sinuses. The lymph nodes become red very soon as a result of the concentration of red cells. At later time intervals the nodes become brown as the hemoglobin is destroyed.

In the thymus a similar sequence of events may be observed. The dense cortical portion of the thymus rapidly atrophies, and there may be reversal in the usual tinctorial appearance of the dense blue staining cortex and a lighter staining medulla. Upon regeneration the normal architecture returns. In the spleen the picture varies depending upon the species. In the mouse, and to a lesser extent the rat, the spleen normally has myelopoiesis in the red pulp in addition to lymphocyte production in the follicles and white pulp. One of the earliest observations is the inhibition of mitosis, followed by a depletion in erythropoiesis and myelopoiesis in the red pulp. Lastly, the megakaryocytes disappear by five to six days after

exposure in the mid-lethal range. During this period of time there is an atrophy of the Malpighian follicles, so that practically nothing but the stroma cells and the central arteriole is still visible. If the animal enters the hemorrhagic phase of the disease, there is a marked erythro-phagacytosis as bleeding takes place into the spleen. Macrophages are active in clearing up the hemorrhagic areas. The minimum weight of the spleen usually is seen around the fourth day after exposure.

d) Bone marrow

In the bone marrow one can see, shortly after irradiation, pyknosis in the erythropoietic precursors. Pyknosis in other bone marrow cell lines is extremely rare. Mitosis is reduced, as shown by FLIEDNER *et al.* (1959). The mitotic index of human beings exposed to a nuclear accident has been shown to be significantly depressed by the fourth day after exposure. The significant finding is the progressive disappearance of parenchyma with minimal evidence of cell destruction. In the rigid bony container this is compensated by dilatation of the fragile sinusoids. These later rupture and intramedullary hemorrhage becomes prominent (FLIEDNER *et al.*, 1955). With the exception of the hemorrhage, most of the late atrophy can be explained on the basis that the differentiated, proliferating pools of all cell lines continue to differentiate and are finally extruded into the blood. Since the stem cell pool has a D_0 of about 95 rads, doses in the lethal range (200—600 rads) severely deplete this pool, and hence the replenishment of differentiated cell lines is drastically impaired until the stem cell pool recovers its size and is receptive to differentiating influences.

The preceding descriptions of the various tissues are predicated on homogeneous absorption of energy throughout the body. If some areas have had significant shielding, so that more stem cells survive, there may be a very rapid regeneration of more heavily irradiated areas of the hemopoietic tissues by migration, proliferation and differentiation of stem cells from the less severely injured areas.

e) Blood vessels and connective tissues

Radiation affects the capillaries, veins and arteries. The doses necessary to produce visible effects are large, usually greater than 1500 rads. There is a swelling of capillary endothelium. Bizarre forms of cells may appear. Changes usually take many days to weeks to appear. There is degeneration of the smooth muscle and connective tissue coats of the blood vessels, particularly arterioles. Endarteriitis and obliteration of vessels may be obvious, as are calcareous deposits at very late times. The vascular changes interfere with circulation and produce all of the sequelae of impaired circulation. In the kidneys typical nephrosclerosis may develop. All vascular changes take doses in excess of the minimum lethal dose for mammals and require many weeks to develop. There is a very extensive literature on these changes by WARREN (1942).

4. Blood counts

Observations on the concentration of blood cells in the peripheral blood reflect the injury to the production of new cells, the effect upon the life span in the peripheral blood, and any incrased death rate of cells within the peripheral blood. In a general sense then, if all new production of cells is eliminated, the decrease in the peripheral blood, providing there is no shortened life span, will reflect the normal life span and mode of loss from the peripheral blood. For example, the general case can be stated as follows. If produciton ceases, there is no reservoir of mature cells outside the blood, and if the loss from the blood is a random process, then the cells will disappear from the peripheral blood exponentially with time simply as the normal half-life of the item in the blood. If there is no random loss of the cell, and the other conditions listed above apply, then the disappearance from

the peripheral blood will be a linear process. The relative radiation sensitivity of the stem cells has been determined by McCULLOCH *et al.* (1962). It has been shown that the D_0 is about 90 rads[1]. Accordingly, after doses in excess of 500 to 600 rads practically all new production from the stem cell level ceases until repletion of the stem cell compartment is complete and differentiation commences once again in each cell line. Actually at an LD_{50} it can be estimated from the dose effect curve that only about 1 of 500 stem cells would retain proliferative capabilities.

a) Effects upon erythrocytes

There is no significant effect upon erythrocytes in the peripheral blood until doses of many thousand rads are received. It has been shown in human beings by SCHIFFER *et al.* (1966) that human erythrocytes commence to have a shortened life span by the chromium labeling technique when doses in excess of 35 000 rads are received. After doses in the lethal dose range (200—600 rads) are received by dogs, there is a shortened life span only during the hemorrhagic phase, and cells are subjected to an additional injury by circulating through the lymphatic spaces and lymph nodes. The normal human erythrocytes have a life span of 120 days. Thus, after doses of radiation that completely eliminate new red cell production, there would be a decrease in the red cell mass of about 0.83 % per day. After doses of radiation in the mid-lethal dose range, as has been observed many times in human accidents, the reticulocytes decrease to very low values or may, temporarily, disappear. During this period of time there is a slow decrease in the red cell mass. If hemorrhage occurs, due to thrombocytopenia, the decrease is accelerated. The status of erythropoiesis can be easily evaluated practically by counting the reticulocytes in the peripheral blood. The preceding is the sequence after homogeneous or near homogeneous exposure. After inhomogeneous exposure the sequence is different as will be described in a later section.

b) Granulocytes

Granulocytes are lost from the peripheral blood by a random process with a half-time of 6.6 hours. However, there is a large reservoir of mature granulocytes in the bone marrow in addition to the non-dividing pool of maturing granulocytes from the metamyelocyte through the band level that will continue to mature and be ultimately extruded into the peripheral blood. From the observations listed earlier on granulocytopoiesis, it has been shown that the transit time through the maturation pool (metamyelocytes to granulocytes) is about four days. There is no evidence that the non-dividing, maturing cells are significantly injured by radiation in the lethal dose range. Thus, if the proliferating granulocytic pool of cells were to be eradicated, maturation and entrance into the peripheral blood would continue. It would therefore take about four days before the last metamyelocytes formed just before radiation would be transformed into segmented neutrophils. With no further production, then, the granulocytes should commence to decrease in the peripheral blood between the fourth and fifth days with a half-time of close to seven hours. This has been observed, as will be illustrated later in the description of human cases.

Actually, one observes generally an initial granulocytosis. This is assumed to represent a mobilization of the marginal leukocytes in the peripheral blood, and perhaps also some mobilization of the medullary reservoir. It clearly is not due to an accelerated production of new cells.

After lower doses of radiation an initial granulocytosis is generally observed, followed by a more leisurely decrease in the granulocyte level, attaining in animals minimal values around the tenth to the fifteenth day. Around this time there may be then a temporary rise in the granulocytes that has been termed "the abortive rise".

1 D_0 is that dose which reduces the fraction surviving by 37 % on the exponential part of the fraction surviving curve versus dose.

c) Platelets

In all mammalian species irrespective, apparently, of the dose of radiation, the platelets remain at normal level or perhaps increase moderately for four to five days after exposure. Thereafter the platelet counts diminish rapidly, and the depth to which they fall depends upon the dose of radiation. In all mammals, except man, the minimum platelet level is attained 8 to 10 days after exposure (CRONKITE and BRECHER, 1952). Below about the LD_{50} dose of radiation, the minimum level of platelets attained is dependent upon the dose of radiation (COHN and MILNE, 1956). Below 100 rads exposure there is a very minimal platelet depression. In human beings, after mid-lethal and lower doses of radiation, the minimal platelet levels are attained around 28 to 30 days after exposure (CRONKITE, BOND and DUNHAM, 1956). When reproduction of megakaryocytes is completely stopped, there is still an input of platelets into the blood for four to five days while the existing megakaryocytes continue to mature and produce platelets. Perhaps fewer platelets per megakaryocyte are produced (BOND, FLIEDNER and ARCHAMBEAU, 1965). As the megakaryocytes disappear from the bone marrow, there is then a disappearance of platelets from the peripheral blood, consistent with their life span and a random loss. It is not known at what level of exposure to radiation platelets are injured and disappear more rapidly.

5. Cytological effects of radiation on human bone marrow and peripheral blood

Pathologists have tended to say that study of the bone marrow and peripheral blood, except from the standpoint of changes in the concentration of cells and a relative hypoplasia, yields no useful information. In general, it is very useful to consider two types of morphologic injury that can be observed in the blood and the bone marrow. First are the phenomena seen in cells which are directly injured, and second are the abnormalities that occur as a result of abnormal mitoses. This has been studied extensively by FLIEDNER *et al.* (1961) in rats, and FLIEDNER *et al.* (1964) in accidentally irradiated human beings. In general, in the bone marrow the directly injured cells are for the most part red cell precursors. Direct injury is also very prevalent in the lymphocytic tissues. The effects seen are pyknosis, karyolysis and karyorrhexis. These phenomena are observed in cells before they have had a chance to enter mitosis after exposure to radiation. The mitotically connected cytologic abnormalities are observed later, after the irradiated cell has gone into or through mitosis. The directly injured cells are very rapidly removed from the bone marrow and other tissues, and this type of cell injury is not seen beyond the first few hours, or at most during the first day. Mitotically connected abnormalities reach their maximum incidence at approximately one day, but do no tdisappear from rat bone marrow until the third day and from human bone marrow until nine days or so. The characteristic types of abnormalities are chromatin dissociation with nuclear swelling, karyolysis, chromosome stickiness, chromosomal fragmentation, chromosomal bridges, tripolar or tretraploid mitosis, giant cells, binucleated cells, cytoplasmic chromatin clumps (karyomeres) and nuclear fragmentation. The preceding are illustrated by FLIEDNER *et al.* (1964).

In the peripheral blood abnormal myelocytic forms are seen, commencing about four days after exposure, and are present in the blood stream for about five to six days. The most prevalent is a giant neutrophil or metamyelocyte. In addition, one sees an occasional lymphocyte with a nuclear satellite. The latter may persist for very long periods of time (FLIEDNER *et al.*, 1964).

Although animal studies have been performed, it is unfortunate that a systematic study of cytological abnormalities in human bone marrow and blood at various time intervals after exposure has not been made. It may be very rewarding to study systematically the appearance of cells in the blood and bone marrow during the period of the abortive rise. It would be of particular interest to determine the DNA content prior to and during the abortive rise.

After all obvious injuries to cells in blood and marrow have disappeared, one can still detect injury by culturing marrow or blood, and detect mitotic abnormalities (BENDER and GOOCH, 1962).

VI. Physiopathological effects

As a result of the destruction of tissue, the interference of mitosis in the ordinary renewal of many tissues described earlier, and the absorption of the products of destruction of the tissue (purines, pyrimidines, vasoactive peptides etc.), a sequence of events is observed that is reasonably well established. The symptomatology varies in intensity with the dose of radiation and, in the case of partial body irradiation, the area of the body exposed. The description of the physiophatological effects can be divided into four parts: vital signs, symtomatology, increased susceptibility to infection and the results of hemopoietic depression. The following are discussed in much greater detail by ELLINGER.

1. The vital signs

The temperature remains constant following irradiation, except under two conditions. After massive doses of radiation, of the order of thousands of rads, there is general collapse and a rise and later fall in the body temperature. Also, after a few days, with doses in the mid-lethal range, there may be an increase in the temperature as a result of the development of infections. The pulse rate is variable, depending upon the dose of radiation and psychological factors. After the higher doses of radiation there is a tachycardia. The respiration is usually unchanged. After even moderate doses of radiation, there is a minor decrease in the blood pressure, presumably due to the release of histamine-like substances from the destruction of tissues. After massive doses of radiation, there is a precipitous fall of blood pressure. This may occur as a result of either irradiation of the abdomen alone or the head alone. The decrease in the blood pressure is precipitous, and a shock-like state develops which may be followed by death promptly unless heroic therapeutic measures of appropriate drug and fluid preplacement are instituted promptly. This is particularly well documented in the fatal radiation syndrome from an accidental nuclear excursion described by KARAS and STANBURY (1965). This patient received a neutron dose of approximately 2200 rads and a gamma ray dose of 6600 rads for a total of 8800 rads, which is probably 10 to 20 times the mean lethal dose for a man. Within minutes after exposure the patient complained of severe abdominal cramps, headache, he vomited and was incontinent of diarrheal stool. Initially his blood pressure was elevated, as was the temperature. Within 4 hours the blood pressure was falling and the pulse rate was rising. From then until death about 48 hours after exposure, blood pressure as maintained only by continuous intravenous infusion of Levarterenol and methylprednisolone. In addition to the hypotension there was also moderate disorientation and difficulty with speech.

2. Symptomatology

Symptomatology, observed is definitely a function of the dose of radiation. In all mammals studied, after very large doses of radiation in excess of 5—6000 rads, there are signs and symptoms referable to the central nervous system that develop within minutes or hours. This symptom complex following massive doses of radiation to either the head or the whole body has been termed "the central nervous system syndrome". To date it has always been 100 % fatal when due to homogeneous absorption of radiation in the brain. The level of radiation that it takes to produce this very acute nervous system death in human beings is not established. The symptomatology of the nervous system syndrome is described in more detail under this title. After lower doses of radiation, the symptomatology may be very variable. Changes in pulse rate are closely related to physiological effects. Headache, irritability, anorexia, nausea and vomiting are variable. In the

upper part of the lethal dose range these are quite prevalent. As the dose diminishes below the LD_{50}, the severity of all diminishes, and in the high sub-lethal range around 175—200 rads in human beings perhaps only a little nausea, transient vomiting and diarrhea will be observed.

3. Increased susceptibility to infection

This is a complex subject covered in detail by BOND, SILVERMAN and CRONKITE (1954) and summarized herein. One of the major causes of death is infection in all animals and in human beings. This was observed frequently after the nuclear bombing of Hiroshima and Nagasaki. The relationship of radiation injury to the various defenses against infection has been extensively studied. Defenses against infection can be divided into stationary and mobile forces. The stationary defenses are the surfaces of the body, the fixed phagocytic elements in the connective tissues, the connective tissues which react to local invasion, and the fixed macrophage elements in the various filters of the body (spleen, liver and lymph nodes). The mobile defenses are the circulating leukocytes and antibodies (natural and acquired) which can attack at the point of infection. Of great importance to the acquired antibody defenses is the ability to renew synthesis of specific antibodies on re-introduction of the antigen, or the so-called anamnestic response. Infection has been very well established as one of the lethal sequelae of whole body irradiation in the lethal and supra-lethal ranges, when the survival time is greater than 3 days (MILLER *et al.*, 1951). However, death occurs also in irradiated germ-free animals, even though the survival time was prolonged by a moderate amount. This fact and other data discussed later shows that infection is not the only cause of death in the lethal range. It has been possible to control infection in irradiated animals with appropriate antibiotics (MILLER *et al.*, 1951). If bacteria to which there is no known effective antibiotic invade, there is obviously no benefit. The bacteria that kill in irradiation injury frequently are the intestinal bacteria normally present. The normal physiology of intestinal bacteria is of interest. It is known that bacteria penetrate the normal intestinal wall, since one can culture orally introduced bacteria with distinctive color (S. marcescens) from mesenteric lymph nodes. In irradiated animals the organisms are able to pass through the mesenteric lymph nodes, and can be cultured from the spleen. The correlation of low granulocyte count with probability of death has been amply confirmed by many. However, the replacement of separated neutrophils in the dog (CRONKITE *et al.*, 1954, 1955) did not increase the survival rate, it only modified the histological picture. However the application of granulocyte transfusions in granulopenic human beings with leukemia has been definitely beneficial (FREIREICH *et al.*). In addition to the granulopenia, irradiated leukocytes develop an impairment in their ability to phagocytize bacteria after irradiation. This does not develop immediately, but after a period of days, coinciding in time with the abortive rise. Thus, it is not clear whether this is due directly to an effect of radiation on the granulocyte or to the fact that cells remaining with time are progressively older and may be cytologically abnormal. In addition, the migratory ability of leukocytes in in vitro systems is impaired at the same time as phagocytosis. The opsonic and phagocytic indices are depressed. The bactericidal power of the blood is clearly decreased after exposure to radiation. The reticulo-endothelial system (RES) immediately after radiation has an intact capability to phagocytize injected bacteria. However, the reticulo-endothelial system is not able to kill the phagocytized bacteria, and they may break out into the blood stream at a later date, producing overwhelming bacterial sepsis, unless there has been a recovery of granulocytopoiesis. The reasons for the inability of the reticulo-endothelial system to kill the ingested bacteria are not known. However, the time of re-establishment of the bacteremia more or less parallels the depression in granulocytes and implies that there may be an interaction between the number of circulating granulocytes and the power of the fixed macrophages in the reticulo-endothelial system to kill ingested bacteria. In addition to the general diminution in the bactericidal power of the serum from irradiated animals, there is apparently a bona fide diminution in

the properdin concentration of irradiated serum at the time when animals are most susceptible to infection. The experimental background for the preceding is reviewed (BOND *et al.*, 1954; BOND and CRONKITE, 1957). In summary then:

The increased susceptibility to infection in irradiated mammals is reasonably well understood. In most species, infection is a dominant cause of death in the lethal range. Obliteration of infection by means of the germ-free state does not eliminate death from other causes, primarily hemorrhagic phenomena. Protection by the mucosa of the normal bowel is relative, since bacteria can penetrate the normal bowel. The stationary defenses are altered. Changes in the morphological appearance and in the permeability of the connective tissues and skin following irradiation are known. The importance of these changes in defense against infection are not known. The ability of fixed reticuloendothelial cells to phagocytose bacteria appears to be relatively normal following whole body irradation, but the ability to retain and kill ingested bacteria appears to be impaired. Granulocytes are diminished in number, and evidence that they are functionally deficient is accumulating. New antibody production and in particular the secondary response for acquired antibody production are drastically inhibited. Lastly, the titer of natural antibodies (properdin) is reduced. Thus, there is little wonder that irradiated animals in the lethal range are exquisitely sensitive to the development of infection, even by the commensal organisms usually living in harmony on the surfaces of the body and within the gut.

4. Defects in hemostasis

Bleeding is a result of numerous facets, and the causes depend upon the dose of radiation and the time after exposure. After very high doses of radiation of many thousands of rads, there is apparently sufficient injury and disturbance to the capillary beds that result particularly in the gastrointestinal tract in stasis, apparent thrombosis and local bleeding of varying degrees. After very high levels of radiation, similarly one may also see capillary bleeding in cerebral blood vessels. After doses of radiation in the range of 200 to 1000 rads, a very definite tendency to bleed develops, providing that the animals live sufficiently long. Historically, the most critical observations on the pathogenesis of bleeding were made by FABRICIUS-MÖLLER, who correlated plateled levels with bleeding and noted that lead shielding of a leg during irradiation prevented later bleeding and the thrombopenia was much less marked. The French workers, in particular LACASSAGNE *et al.*, emphasized the probable importance of thrombocytopenia in the development of the bleeding tendency. ALLEN *et al.* claimed that heparinemia was a major cause of bleeding in addition to the thrombocytopenia in irradiated dogs, and that the thrombopenia actually sensitizes to heparin. Of the latter there is no doubt. Unfortunately, the concept of increased amounts of circulating heparin was readily accepted, probably because positive treatment by antiheparin agents, such as protamine or toluidine blue would neutralize the heparin and thus, in part at least, control the bleeding. Unfortunately, heparinemia has subsequently been proved not to be a cause of bleeding, and the anti-heparin agents of no value in treatment of radiation hemorrhage (JACKSON *et al.*, 1952). The defects in hemostasis that lead to bleeding are well documented. A progressive thrombopenia develops that is time- and dose-dependent. The thrombopenia leads to a quantitative deficiency in clot retraction, prothrombin utilization and capillary integrity. Lastly, at very low platelet levels with virtually no prothrombin conversion, the whole blood clotting time becomes remarkably prolonged. The bleeding tendency may take many forms, from merely a microscopic diapedesis of red cells into the connective tissue with absorption of the red cells into the lymphatics and their concentration in the filtering apparatus of lymph nodes. This very mild bleeding tendency may escalate to diffuse macroscopic purpura. When infectious processes become prominent, there may be ulcerations into small blood vessels with severe local bleeding that may result in exsanguination and death of the subject. Trauma and sepsis also increase the bleeding tendency.

The most direct evidence on the role of the platelet has been the proof that platelet transfusion will prevent bleeding or stop bleeding that has already commenced (CRONKITE *et al.*, 1954). It is of particular pertinence that the platelets must be viable and circulate in order to control the bleeding tendency. Lyophilized or frozen platelets are of no value in controlling the bleeding tendency (JACKSON *et al.*, 1957; FLIEDNER *et al.*, 1957). The platelet level at which bleeding may occur spontaneously has been studied by LAMERTON *et al.* in rats. At platelet levels above 40000 per cubic millimetre, bleeding and anemia did not occur. In human beings exposed to fall-out with platelets as low as 35000 per mm^3, bleeding was not observed except for menorrhagia (CRONKITE, BOND and DUNHAM, 1956). As mentioned earlier, there is a significant difference in the rate at which platelets fall in man and in other mammals.

VII. Radiation syndrome due to short-term exposure to penetrating radiation

The following condensed summary on syndromes is based on reports of human radiation injury (BRUCER; CRONKITE, BOND, DUNHAM, 1956; GERSKOVA and BAISOGOLOV; HASTERLIK and MARINELLI; HEMPELMANN *et al.*; HOWLAND *et al.*; INGRAM *et al.*; LE ROY; MATHÉ *et al.*; OUGHTERSEN and WARREN; PENDIC; ROSSI *et al.*; SHIPMAN *et al.*; KARAS and STANBURY). It is highly unlikely that one will see human radiation injury in which there is a very uniform deposition of energy throughout the entire body following criticality and laboratory accidents. However, exposure of human beings in fall-out fields will result in quite uniform deposition of energy throughout the body one cm below the surface. It is useful pedagogically to describe a hierarchy of death related to dose and time after exposure to radiation, in which there is a relatively uniform whole body, short-term high dose exposure. The relation of survival time to dose was considered earlier. Modes of death have been established by experimentation with reasonable degrees of homogeneity of exposure particularly in the smaller mammals. The studies are believed to be particularly pertinent because they implicate various organ systems. Furthermore, the same syndrome can be produced by regional exposure of the implicated organ systems. For example, after very high doses of radiation delivered either to the head or the whole body, a characteristic syndrome is observed that has been termed "the central nervous system syndrome" because of marked symptoms of brain dysfunction that are consistent with neurologic damage. When radiation is delivered to the abdomen alone or to the whole body in the range of roughly 700 to 3000 rads, a very characteristic symptomatology develops. The symptoms are related to the gastrointestinal tract, and thus have been termed "the gastrointestinal syndrome". In animals it is characterized by a stable survival time, particularly in mice and rats, of about 3 to 4 days. The survival time for other mammals varies somewhat but is also stable over a wide range of doses. After lower doses of radiation, in the range of 200 to 1000 rads, a mild, transient gastrointestinal syndrome occurs, and a typical hemopoietic syndrome develops, which is characterized by sequelae of pancytopenia due to aplasia of the bone marrow. In most mammals, the killing process of the hemopoietic syndrome is completed by 30 days. However, in contrast, in man the killing process is not completed until about 60 days after exposure. Even after apparent recovery, hidden radiation injury (somatic mutations?) may manifest itself later in the form of neoplasia, particularly leukemia, cataracts, shortened life span, etc.

1. The central nervous system syndrome

This syndrome has been very well described in monkeys by LANGHAM *et al.* in 1956. The full blown cerebral form seen in animals has not been observed in human beings.

It was not observed in Hiroshima or Nagasaki bacause persons who where close enough to the hypocenter to receive such high doses necessarily experienced lethal thermal burns or mechanical injuries as well, and thus were lost during the confusion of the first three post-attack days without examination and recording. However, nervous system symptoms were observed in a criticality accident at the Los Alamos scientific laboratory by SHIPMAN (1961) and by KARAS and STANBURY (1965). From animal observations, one can attempt to predict and describe for man the acute cerebral form of disease. Weakness, irritability, ataxia, disorientation, drowsiness, and listlessness, will develop rapidly and may be present immediately. This will proceed within a very short time to severe apathy, prostration and lethargy. There will be progressive loss of physical and mental activity. With very high doses, probably in excess of 8—10000 rads, there will probably be disorientation and unawareness of reality almost immediately. In addition, after exposure to these very high doses, a disturbance of the motor system can be anticipated. Seizures may occur either in the form of generalized muscle tremors or ataxic movements, with the likelihood of full-blown epileptoid convulsions of the grand-mal type. If individuals survive the convulsive phase, they will be prostrate, somnolent, and will expire within 2 to 3 days following exposure. Animal studies have shown clearly that progressive cerebral symptoms result from widespread inflammatory foci that begin to develop within one hour after irradiation. These non-bacterial, radiation-induced reactions simulate meningitis, encephalitis and vasculitis, and are soon associated with oedema of the brain.

2. The gastrointestinal syndrome

This syndrome can appropriately be divided into the non-fatal type that is observed in the mid-lethal and sub-lethal dose range. Here there is temporary anorexia, nausea, vomiting, and perhaps a little diarrhea. This subsides within a few hours to a day or so. In the mid-lethal range, gastrointestinal symptomatology may return during the period of time of marked infectious processes and hemorrhage. This phase in man occurs 4 to 6 weeks after exposure, and is primarily due to the ulceration and hemorrhage into the bowel rather than from the direct radiation injury to the mucosa of the gastrointestinal tract. This will be described in more detail under the hemopoietic syndrome. In the fatal form of gastrointestinal injury there are considerable differences in species sensitivity, with the rat being more sensitive, particularly in the younger ages, than other mammalian species. The histologic effects of high doses of radiation in the range of 1000 to 3000 rads has been described earlier. As discussed in an earlier part of the chapter, following doses of irradiation in excess of roughly 700 rads, the cells in the crypts undergo pyknosis, karyorrhexis, and mitosis ceases. With no new cell production the cells on the villi continue to migrate out to the extrusion zone and are lost at the tip of the villus. The total number of cells covering the villi decreases. Finally, there are many denuded, swollen, stubby villi from which a serious loss of plasma into the bowel commences. Although it is probably an over-simplification one tends to connect severe diarrhea, hemoconcentration and shock followed by death with the anatomical disturbances that are observed. This is clearly an over-simplification because it takes of the order of 2 to 3 days for the denudation to be significant, and with the higher doses of radiation there is a persistent vomiting and diarrhea apparently as result of autonomic disturbances having their origin within the emetic center of the brain and elsewhere in the nervous system. However, at least in dogs, when the dose of radiation does not exceed roughly 1500 rads, the bowel will recover histologically and symptoms subside when there is adequate plasma and fluid replacement to prevent the shock-like death from hemoconcentration and peripheral vascular collapse.

Clinically, the following sequence may be observed after doses in excess of 700 rad. Nausea occurs within a few minutes, and vomiting may be severe by 60 minutes after

exposure. The vomiting may increase in frequency, and diarrhea may become severe. The initial symptomatology after lower doses may subside. However, after very high doses, the signs and symptoms are persistent and continue until death. In the event that the initial symptomatology subsides, there may be a period of 1 to 3 days during which there is a sense of relative well-being, following which, around the third to the eight day a grave deterioration will occur. Severe nausea, vomiting and diarrhea again develop, and death occurs promptly as a result of a tremendous loss of plasma into the gastrointestinal tract. This severe gastrointestinal syndrome and its pathologic effects were described by HEMPELMANN *et al.* (1952) in a patient fatally irradiated at one of the nuclear accidents at the Los Alamos scientific laboratory. A very severe form of the gastrointestinal syndrome was described by KARAS and STANBURY (1965) after a critical excursion. A very mild, transient, non-fatal form of the gastrointestinal syndrome was observed in the Marshallese natives exposed to sub-lethal doses of radiation from fallout (CRONKITE, BOND and DUNHAM, 1956). In the preceding discussion on the pathogenesis and symptomatology observed, emphasis has been placed upon the local injury to the gastrointestinal tract. This is clearly an important facet, but not the only facet of the problem. As alluded to earlier, there is clearly a component mediated through the central nervous system, resulting in autonomic stimulation of motility in the gastrointestinal tract. In addition, it has been shown that ligation of the bile duct in the irradiated rat or cannulation and diversion of the bile prevents diarrhea (SULLIVAN, 1962). The role of bile in producing diarrhea has been related to an action of the bile salts on the irradiated bowel epithelium, since the diarrhea occurs at a time when there are marked histological disturbances of the gastrointestinal epithelium, and when depression of the absorptive function of the intestine is maximal. Ordinarily, bile salts are primarily absorbed in the distal ileum. Thus, bile salts increase in concentration in the colon. It is possible — though not proved — that the increased concentration of bile salts in the colon may produce the diarrhea. Another contributing fact that may have some clinical importance is that, in some animals at least, there is a substantial loss of sodium in the urine at least in the rat (JACKSON *et al.*, 1958).

Infection probably also plays a role, at least in some species of mammals, in the gastrointestinal syndrome. This is most clearly brought out in the studies that show it takes approximately 1.6 times as much radiation to produce the five day deaths in germ-free mice as it does in conventional animals (WILSON, 1963). In addition, antibiotics and bone marrow transplantation that delay or prevent infectious processes also favorably, decrease the mortability of the gastrointestinal syndrome. Although infection plays a role in the gastrointestinal syndrome and the resulting mortality in the dose range from roughly 600 to 1 200 rads after higher doses of radiation greater than 2000 rads antibiotics and bone marrow transplantation do not increase the survival rate. Death ensues from the combined neurological disturbance of the gastrointestinal tract and the severe injury to the mucosa that results in the severe diarrhea, loss of plasma, disturbances in electrolyte metabolism, vascular collapse and death.

3. Hemopoietic syndromes

The disturbances in hemopoiesis that lead to the clinical syndromes have been described earlier. In this section, the general phenomena which may be observed after exposure of human beings in the lethal dose range will be summarized. First, there may be some overlap with a transient disturbance due to influence on the nervous system and the gastrointestinal tract as described earlier. The basic cause of the hemopoietic syndromes is hypoplasia to aplasia of the bone marrow. The simplest forms are seen when there is uniform deposition of energy throughout the entire hemopoietic system. The time sequence will be significantly altered by partial body exposure or marked inhomogeneities. There are three facets to the hemopoietic syndrome. First to be observed are usually the infec-

tious aspects that generally come on earlier and may be seen as early as the seventh day after exposure. The reasons for the increased susceptibility to infection have been enumerated in an earlier section. The infections may be due to any bacteria. Generally, the infections result from invasion of the epithelial surfaces of the body by the commensal organisms that normally live on the surface of the body. Of course, any traumatic injury, thermal burn, or burns due to superficial ulceration of the skin from beta burns produced by fall-out material in contact with the skin provide portals of entry for bacteria. In addition, hemorrhagic areas in the bowel may result in superficial ulceration and hence further portals of entry for bacteria. The infectious processes will be much more severe and develop more rapidly wth overwhelming sepsis and prompt death if true pathogens invade. In addition, sites of chronic infection in the urinary tract or latent tuberculous lesions may be reactivated. The granulocyte depression is primarily responsible for the increased susceptibility to infection. This occurs earlier than the thrombopenia which is responsible primarily for hemorrhage. One may therefore see fatal infection before significant hemorrhagic manifestations develop.

In man, as described earlier, hemorrhage is due primarily to thrombocytopenia. After doses up to the mid-lethal dose range it takes approximately 30 days for the platelets to reach the minimum levels. Until the platelets fall below roughly 25000 per mm^3, no bleeding is observed. The bleeding has been manifested in some individuals as only a mild cutaneous purpura. Sometimes it is manifested as a very severe epistaxis. There may be severe bleeding into the lungs that causes death. Bleeding may also be prominent around the larynx and result in respiratory obstruction. Another severe complication of bleeding may be the induction of intussusception of the bowel by hematomata with the concomitant acute abdominal episode that necessitates abdominal exploration under very hazardous conditions. Fatal hemorrhages may also take place from bacterial ulcerations of the bowel, and result in exsanguination. In addition, one may rarely have a fatal cerebral or myocardial hemorrhage. In man, hemorrhagic manifestations are rarely seen prior to the fourth week, and subsided by the end of the sixth to the seventh week in the Japanese.

Anemia may also be a major problem. This develops much more slowly for reasons described earlier. With complete cessation of blood production one will have a decrease in the red cell mass of 0.83 % per day. When hemorrhage occurs, two factors contribute to the acceleration of the development of the anemia.

First is the overt loss of blood from the body, and second is the shortened life span of red cells that recycle from the tissues throught the lymphatics. In the presence of severe bacterial infection, there may also be a severe hemolytic component.

4. Clinical evaluation of human beings exposed to radiation

There has been a strong desire on the part of physicians considering human radiation injury to depend upon estimates of radiation exposure for evaluation of the severity of the injury. One of the major objectives of this entire chapter is to demonstrate that, although precise estimates of radiation dose and — more important — the distribution of dose within the body are important from the standpoint of later statistical evaluation of radiation hazards, dose per se is not really essential for the management of radiation injury. Accordingly, from a practical standpoint, many years ago a practical clinical classification of radiation injury was proposed by CRONKITE (1951). Initially this classification was proposed as a means of assisting in the management of mass radiation casualties in the event of nuclear warfare. It is still useful from a clinical standpoint. This classification consists of three general categories: survival improbable, survival possible, and survival probable. More recently FLIEDNER (1964) has analysed all available hematologic data that has been collected on human radiation exposures, and presented the hematologic picture for the above three categories.

a) Survival improbable

Individuals in the survival improbable group will experience prompt-intractable nausea, vomiting and diarrhea. Unless, as discussed earlier, there is drastic fluid and plasma replacement to compensate for the loss of fluid into the gastrointestinal tract, these individuals will die within a matter of a few days. Even with fluid replacement, they will yet experience sequelae of bone marrow aplasia and pancytopenia, and probably have 100 % mortality at a later date. The blood pictures for individuals in this category are scanty. In Fig. 7 the sequence in the granulocytes, lymphocytes and platelets is plotted. Note that there was a striking initial granulocytosis present in two of the three cases shown, sometime between the first and the third day. All of the patients had very low granulocyte counts by the fifth day after exposure. Unfortunately, it was impossible to

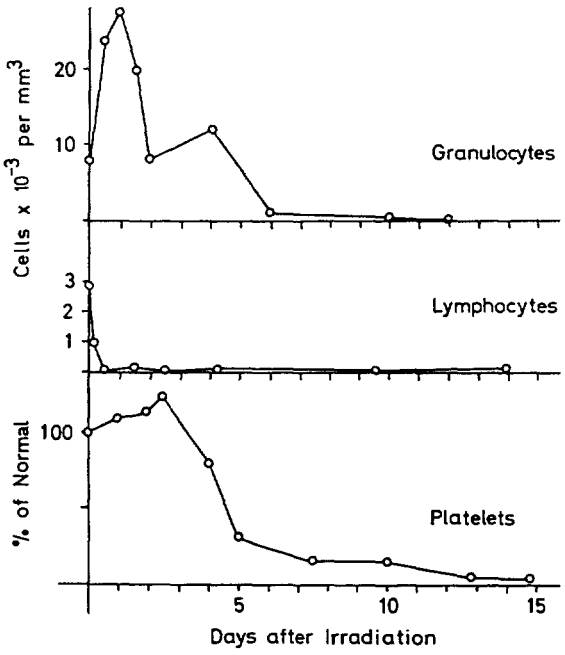

Fig. 7. Granulocyte, lymphocyte and platelet counts in survival improbable category. Curves idealized from FLIEDNER (1964)

get blood counts in the Hiroshima casualties prior to the fifth day after exposure. However, in individuals dying in the first two weeks, the leukocyte counts between the fifth and the twelfth days were below 500 per mm^3 (JACOBS *et al.*). The lymphocytes in these three cases had dropped to very low levels within hours after exposure. In one case, lymphocytes disappeared by 6 hours. Platelet counts were also very low by the eighth to the tenth day after exposure in the individuals in whom they were studied. Thus, with sufficiently high doses platelets diminish in human beings apparently as rapidly as they do in the other mammals. The cases which die within the first 3—4 days after irradiation have usually severe gastrointestinal symptomatology which is presumably due to a combination of central nervous system and gut injury. The relative importance of each varies with time after exposure. In the first few hours the gastrointestinal symptomatology is more likely central in origin and at later intervals the result of direct injury to the gut becomes more prominent. In addition, the most severe have been complicated by severe radiation injury to the cutaneous tissues. It is of interest in the patient presented by KARAS and STANBURY (1965) dying 49 hours after exposure, that lymphocytes had dis-

appeared from the blood by 15 hours after exposure. During the period from exposure to death, the granulocyte count continually climbed until it reached almost 50000,39 hours after exposure and 10 hours before death. This patient had severe gastrointestinal symptomatology until death. The patients observed by HEMPELMANN *et al.* (1957) and OUGHTERSEN and WARREN dying 7—16 days after exposure also had severe gut symptoms. At autopsy histopathologic examination of the bowel indicated a loss of the duodenal epithelium and complete erosion of the epithelium of ileum and jejunum. In the ulcerated portion of the jejunum, bacteria reportedly had invaded the intestinal wall. Thus, it appears, with the scanty information that is available, that the gastrointestinal syndrome reported in man may be accentuated by the granulocytic insufficiency and infection. Thus, prompt and continuous nausea, vomiting and diarrhea followed by virtual disappearance of neutrophils within 5 to 6 days, and a steady decline of platelets to low values by the 8th to the 10th day, are very poor prognostic signs. Survival in these cases must be considered improbable with all types of available therapy at the present time.

b) Survival possible

In general, the survival possible group will consist of individuals in whom the nausea and vomiting is relatively brief, subsiding within a period of 1 to 2 days, and followed by a period of well-being. These individuals will later suffer primarily from the hemopoietic syndrome. These are the patients who have a spontaneous statistical chance of survival that has been described by the classic sigmoid dose mortality curve. From data discussed earlier on the probable lethal dose for human beings, it has been postulated in the absence of therapy that the most likely human LD_{50} is in the vicinity of 360 rads. Patients in the survival possible group, after the subsidence of the initial symptoms, will show a typical series of changes developing in the peripheral blood, and ultimate granulocytopenia, thrombocytopenia and persistent lymphopenia. The patients on whom the blood picture in this category are based represent individuals who probably were exposed to relatively uniform whole body radiation in the range of 200 to 450 rads. There were marked variations in the circumstances of the exposure, the dose rate, radiation quality and energy, and a certain degree of additional complications were present. Despite these differences, a rather uniform hematological picture was observed. In Fig. 8, the probable sequence of leukocytes, lymphocytes and platelets is shown for this group. The graphs are redrawn, showing roughly the average response of the 17 individuals that FLIEDNER (1964) analysed in more detail. There is an initial granulocytosis occuring in most individuals within the first 2 to 4 days after exposure. Thereafter, there is a sharp decline which, if extrapolated, would reach zero values by 8 to 10 days. However, this decline is terminated by either a rebound or a plateau. The rebound or plateau lasts about 10 to 12 days. The preceding rise or plateau has been termed "the abortive rise". Around the 22nd day a final leukopenia commences. The granulocytes continue to decrease downwards, attaining the minimum values after about 34 days. A slow recovery in the granulocyte count commences after about the 36th day. However, in some patients this is a very slow process. In contrast, to the granulocyte count, the lymphocytes show a much less variable course. It is of interest and importance to note that the lymphocytes do not reach zero levels in any of the cases as in the category "survival improbable". Within 3 to 4 days the lymphocytes reach their minimum and remain at this level for at least 5 weeks. Thereafter the lymphocyte counts slowly recover, but may not reach normal values for weeks or many months.

In contrast to the patients in the "survival" improbable group, there is a much slower diminution in the platelet counts. The minimal values are not attained until about 28 to 39 days after exposure. Actually, there is a period during the first few days after exposure in which there is only a slight decrease or a constant platelet level. A thrombocytosis, as has been observed in animals, has not as yet been observed in the human beings. Actually, the sharp drop in platelet count does not commence until about 20 days. After the nadir

is reached around the 30th day, a slow recovery commences with many weeks to return to normal.

Although extensive studies of the bone marrow have not been performed on human beings exposed in the survival possible category, it is believed that a useful procedure in this dose range is the serial determination of the mitotic index of the bone marrow. In normal individuals, the mitotic index of normal human bone marrow between the hours of 10.00 a.m. and 1.00 p.m. is approximately 9 per 100 cells (FLIEDNER *et al.*, 1959). In the casualties that occurred following exposure in the criticalty accident at Oak Ridge, the mitotic index was studied and found to be significantly decreased in the exposure of 50 to 200 rads. By the 4th day after exposure, in the more heavily exposed individuals,

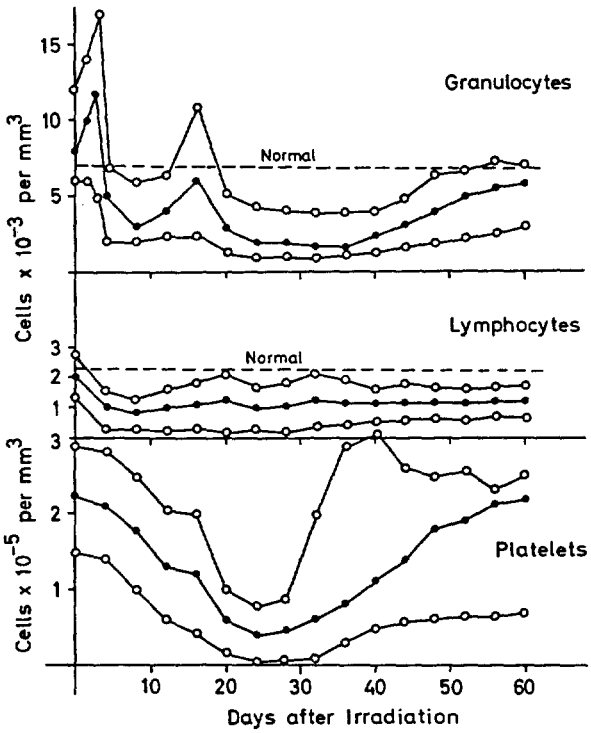

Fig. 8. Granulocyte, lymphocyte and platelet counts in patients in survival possible category. Open circle represent upper and lower limits of observed data and the solid points the mid trend. Curves idealized from FLIEDNER (1964)

the mitotic index reached almost zero. Furthermore, there was an apparent dose dependency in the depression. Thus, it is believed that the bone marrow aspirations performed promptly after an assumed exposure and at daily intervals for a period of one week would be most useful in detecting exposure to radiation in the 50 to 300 rads range. In addition to straightforward enumeration of the mitotic figures, qualitative changes are also evident. These changes consist of binucleated cells, mitotic bridges, fragments, stickiness and clumping of the chromosomes which can be quantitated. If a complete aplasia of the marrow has recurred, then examination of the marrow should be able to detect beginning regeneration, which is a most favorable prognostic sign.

A typical case of radiation injury in the survival possible category is summarized form OUGHTERSON and WARREN. A 25-year-old soldier was about 0.6 miles from the hypocenter in Hiroshima. He complained of malaise on the first day, but recovered. Between days 4 and 8 he worked on a drill field and marched 9.3 miles. Epilation began on day 8. On day 22, petechiae appeared. He was admitted to a hospital on day 26, with a sharp tempera-

ture rise on day 27, reaching 40.3° C on day 28, with subsequent gradual lysis. The petechiae began to clear on day 34, and the patient was discharged on day 59. Many other Japanese soldiers had malaise, nausea and vomiting on the first day of exposure. They recovered from the initial symptomatology, did hard physical work for 2 to 3 weeks and then developed purpura and severe infections. The mortality in this group was high.

c) Survival probable

This group consists of individuals who have had either no initial symptoms or mild or fleeting ones, disappearing within a few hours. Unless these individuals have sequelae of marrow depression, these patients will show no further subjective effects of irradiation, and obviously constitute no therapeutic problem. However, it is clear from many animal experimental studies that individuals in this category will be more susceptible to pathogenic organisms if present. Typical blood picture seen in this category is illustrated in Fig. 9. The granulocytes show an initial decrease during the first 8 days after exposure.

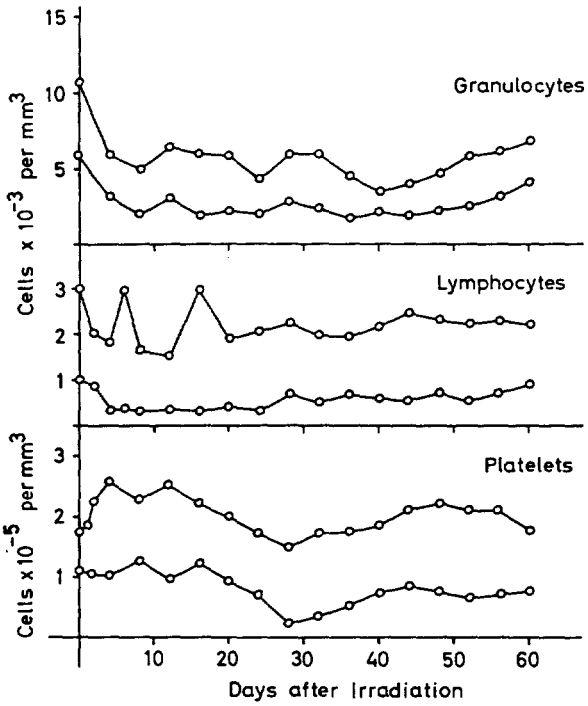

Fig. 9. Granulocyte, lymphocyte and platelet counts in survival probable category. Open circles represent highest and lowest values observed

However, they do not drop below 2000 per mm^3. Thereafter, the declin elevels off and approaches a late minimum after about 40 uays. During the first two weeks there is practically no change on the platelet counts. Thereafter, the platelet counts commence to fall and reach the minimal values around 28 days after exposure. Thereafter, there is a recovery in the platelet count which takes a matter of months.

The lymphocyte counts show a marked initial drop after exposure, the minimal values being attained within 2 to 3 days, with considerable variation from patient to patient. The depression remains constant for several weeks.

In general it has often been stated that the blood count has relatively little prognostic value. In respect to the lymphocyte, this is probably true, since doses up to about 300 rads produce almost a maximal depression in the lymphocytes, and further increase in

dose, unless it is extremely high, do not depress this level further. However, the neutrophil count is extremely useful from a prognostic standpoint, as has been demonstrated in dogs, where there is a clear-cut difference in the rate of depression of the granulocyte count at 100 %, 80 %, and 10 % mortality respectively (CRONKITE and BRECHER, 1955). From the animal observations and the human observations summarized before, it can be seen that on clinical and laboratory grounds one can fairly well categorize patients into the relative degrees of radiation injury. This is clearly the first step in the management of radiation injury.

The preceding casualty sorting and general considerations about prognosis are relevant to therapy. In reality, one is confronted with the treatment of a patient who presents basically the same problems as the management of any other patient with pancytopenia. However, the irradiated patient presents the additional challenge that the aplastic state of the bone marrow may be reversible. Thus, if the patient can be carried through the critical period, he may recover, in contrast to the many cases of idiopathic or drug-induced bone marrow aplasia that are rarely reversible.

5. Influence of inhomogeneities of dose of radiation and partial body exposure

The first human radiation casualties from a criticality accident were characterized by marked inhomogeneities of the absorbed dose (HEMPELMANN *et al.*, 1952). In some of the individuals, many thousands of rads were received by the hands with almost total destruction of the epithelium. The superficial skin over the abdomen and the face also received tremendous amounts of radiation, with the absorbed dose grading off towards the back and down to the legs that had some shielding. Very severe gastrointestinal injury was observed in two of the individuals. In the fatal cases, there was severe injury to the gastrointestinal tract, and marked necrosis of the skin of the hands and the face, with prominent oedema and erythema of the side of the body facing the criticality event. In addition, there was severe hemopoietic depression.

In the last criticality accident at Los Alamos scientific laboratory (SHIPMAN *et al.*), the dose to the head and the thorax was measured in thousands of roentgens. Immediately after exposure, the individual was disorientated, amnestic, and shortly thereafter went into collapse and was prevented from immediate death by extensive fluid and electrolyte replacement. He died within a short period of time, and at autopsy there was serious injury to the myocardium in addition to the central nervous system.

In the Lockport incident, a group of individuals had removed the lead shield from a Klystron tube that was not functioning properly. The device was emitting unfiltered 200 kV X-rays. The details of this incident are described by HOWLAND *et al.* (1961) and INGRAM *et al.* The dose distribution to the head of one individual showed marked inhomogeneities in the absorbed dose through the head. The initial neurologic symptoms were minimal, but later severe neurologic symptoms developed, demonstrating that neurologic injury per se is not necessarily fatal unless the absorbed dose is uniform throughout the head and greater than the minimum necessary to produce the neurologic syndrome. In the Lockport accident, vomiting was present initially and subsided in 4 patients out of 7 within the first day. Nausea was present in 5 of the patients and subsided more gradually, only after one week in the most seriously injured man. Headache was a serious problem in the Lockport incident. The type of pain experienced in the most heavily irradiated casualties, whose doses to the head were estimated to be about 1500 rads, was that of a deep pain located in the center of the head, unlike any headache experienced before. This is probably due to the relatively high inhomogeneous dose to the brain. In the more severe cases, small petechial showers and a few vesicular oral lesions were observed during the 4th week. The marked inhomogeneity and the component of the soft X-rays may have contributed to capillary injury in the Lockport cases. A clinical and hematologic

course of the more severe Lockport patients that received of the order of 1500 rads to the head and 300 rads to the trunk difiered significantly from syndromes described earlier. The symptomatology appeared to come in waves for weeks and months after exposure. These late reactions were preceded in one patient by transient erythema during the first 7 days, between days 13 and 19, and between days 24 and 29. However, on day 38, this patient became febrile, somnolent, and mentally depressed, with conjunctivitis, photophobia, and pain on movements of eyes. On day 44 another febrile attack was observed, with a new wave of somnolence and a moderate ataxia. With this, transient paresthesias of the right arm and left hand were present, and mild reflex changes were also noted. These neurological signs continued over a period of 12 days, the somnolence for 8 to 10 days. The neurological picture was compatible with diffuse involvement of the central nervous system. The Lockport cases are particularly confusing because of the sustained depression in the blood counts and the failure of the striking recovery around the 30th day in platelets observed in other human whole body injury. The reticulocytes showed a tendency to rise continually in both of the more severly exposed Lockport patients. This has not been observed in more uniform whole body exposure. The reasons for the discrepancies in the blood changes between more or less uniform whole body exposure and the X-irradiation to the trunk with a higher exposure of the head are not clear. From animal experiments in which partial body shielding produces a speedier recovery, one would expect inhomogeneous exposure such as in the Lockport incident to see more rapid recovery. Why erythropoiesis continued with a striking increase in the reticulocyte count from the very beginning with a continuous failure for a prolonged period of time in granulocytopoiesis and thrombocytopoiesis, is obscure. Clearly, much more information is needed on the influence of inhomogeneous exposure of human beings.

a) Partial body exposure

There is little direct information on human beings except from radiotherapy. There is considerable information on partial body exposure on animals, part of which will be summarized. Irradiation of the abdomen only produces gastrointestinal symptomatology. However, there are differences in survival time when the whole body is irradiated as compared to irradiation of the abdomen only, the exteriorized bowel or only a portion of the bowel. There is an extension of 2 to 3 days in survival time when only a portion of the abdomen or its contents are irradiated (BOND *et al.*, 1950; SULLIVAN *et al.*, 1959). In addition, there is also apparently a delay in the denudation of the epithelium of the irradiated bowel when only the abdomen or a portion of the bowel is irradiated. The longer survival time when the abdomen or the exteriorized bowel is irradiated is in part explained on the basis that a portion of the bowel is shielded, and thus fluid and electrolytes are better maintained. The increasing survival time with exposure of smaller segments of bowel is consistent with this concept. Selective irradiation of the oropharynx in the mouth has led to a syndrome described by QUASTLER *et al.* as "oral death".

Another source of information on the influence of partial body irradiation is derived from the aftermaths of excessive therapeutic radiation. This has been summarized by CRONKITE (1966). The following is a condensation of the preceding reference. Large single doses in excess of 2000 rads or larger doses given over a longer period of time to the kidney will produce a radiation nephritis. Within a period of 6 to 13 months, or shorter in children, changes in renal function are observed. Chemical and cytological findings of nephritis are what one would expect. Hypertension and its sequelae follow.

Myopathy is produced by irradiation in single doses of around 1600 rads. Fractionation of the irradiation necessitates larger amounts of radiation. 5000 rads delivered over a 6 to 9 week period has resulted in severe inflammatory processes within muscles. Endarteriitis obliterans and the subsequent necrosis of muscle and connective tissue are characteristic.

Pneumonitis can be produced by single doses of roughly 2000 rads. The clinical symptoms are dyspnea, cough, pain and an increased temperature probably related to pneumonia. The clinical and pathologic severity is correlated with the volume and area of the lungs exposed.

Impaired bone growth and osteonecrosis. This has long been recognized as a concomitant of heavy reontgen therapy over growing bones in children. With fractionated doses it is due primarily to progressive vascular obliteration. Bone necrosis inevitably follows in due course. The bones of growing children are a particular problem. In the Marshallese only 175 rads to the whole body resultet in impaired skeletal growth in some of the children (CONARD *et al.*, 1963).

6. Therapy of the acute radiation syndromes

Therapy of all diseases is based on proved clinical principles that apply to the treatment of signs and symptoms that are present in the course of the disorder. As mentioned earlier, the diagnosis of radiation injury and its clinical management are not dependent upon an accurate knowledge of the radiation doses received. As a matter of fact, it may be simpler to manage radiation injury without any initial knowledge of dosimetry, since all initial estimates so far have been greatly in excess of the ultimate established dose. This tendency for the physicist to over-estimate initially is understandable, but may be very disturbing to the physician responsible and the patient if he happens to know it (and he almost certainly will).

In general sense, then, one is confronted with the following problems. First, there is symptomatic relief of the central nervous system and gastrointestinal symptoms. Second, there may be severe pain and discomfort due to intestinal cramps. Third, there may be anxiety and a depression. Fourth, there are problems concerning fluid and electrolyte replacement and the maintenance of reasonable blood pressure and pulse. Fifth, there is the question of direct therapy or prevention of infectious complications, thrombopenic purpura and anemia. These general problems may occur to varying degrees in any of the major divisions of the radiation syndrome.

In respect to the central nervous system syndrome produced by very large amounts of radiation, there is little that one can do other than give sedation to control symptoms. In the case of the gastrointestinal syndrome, the intestinal hypermobility and vomiting that comes on early is probably related more to the nervous system than direct injury of the gastrointestinal tract. In all probability this can be controlled to a large extent by dithenhydramine in 100 mg doses given intramuscularly. Probably the most efficacious agent for pain and irritability is morphine in 12 mg subcutaneous doses. Since, as pointed out earlier, there is probably a synergism between the injury to the gastrointestinal tract and a rapidly developing granulocytopenia producing local infection of the bowel, one should consider the desirability of sterilization of the intestinal tract with Neomycin in 1 g doses every 4 hours orally. In the very severe cases of radiation injury, intravenous methylprednisolone and levarterenol may be of some help in maintaining an adequate blood pressure. In desperate cases of hypotension, one may try metaraminol and hypertensinogen.

However, it is highly probable that if the condition is so severe in the first few hours after irradiation that the preceding type of therapy is needed for the combination of neurological and gastrointestinal symptomatology, no therapy will increase the probability of survival. However, it is mandatory to keep the patient comfortable and treat each symptom complex irrespective of the prognosis. The management of the hemopoietic syndrome involves prevention of infection, treatment of infection when it occurs, prevention of bleeding and its control if it occurs, and prevention of anemia by appropriate transfusion, and considering the possibility of marrow transplantation to restore hemopoietic function.

a) Definite therapeutic outline and guiding principles

α) The cardinal therapeutic principle is to do nothing without a clear-cur clinical indication. Except for the severe forms of radiation injury as discussed earlier, there is no urgency. However, if there is a question of neutron exposure, a sample of blood for determination of the activation of sodium must be obtained immediately. From the latter, an estimate of the thermal neutron dose can be made. Whole body counter measurement of induced radioactive sodium is better.

β) A history and physical examination is particularly pertinent, and must be detailed with special reference to detecting the possibility of prior chronic infections of any type. It is highly desirable to obtain immediately any earlier hospital records of the patient.

γ) Inform responsible medical, administrative, health physics and legal authorities promptly. In dealing with radiation accidents, one obviously is primarily concerned immediately with the welfare of the patient, but because of the great public interest in the problem one cannot avoid inquiries from the press and diverse curiously interested people and agencies.

δ) Hospitalize the individuals as rapidly as reasonable until the degree of exposure has been ascertained.

ε) Follow closely the peripheral granulocyte, lymphocyte, platelet counts and hematocrits. Blood counts should be performed at daily intervals for one week and thereafter 3 times a week for at least 4 weeks. Then, the interval for blood study should be determined on the basis of the prior sequence. A bone marrow aspiration is essential as soon as possible after exposure, and at 1, 2 and 4 days after irradiation. Thereafter, a marrow aspiration should be performed 1 to 2 times a week, in order to observe for the possibility of spontaneous regeneration. With these studies and the general clinical appearance, one can determine the survival category in which an individual should be placed by the 4th or 5th day, utilizing the principles described earlier in this chapter.

ζ) Weigh daily and record fluid intake and output with intermittent electrolyte studies on the blood.

η) Institute the highest quality of nursing care. Particular attention should be paid to oral and skin hygiene. Portals of entry for bacteria are frequently the oral mucosa, abrasions of the skin, or around the anogenital area. Strict asepsis is mandatory with all procedures involving a cutaneous puncture.

ϑ) If it is believed that the short-term exposure has been in excess of 200 rads, or if the patients conform to the survival possible group, reverse isolation should be instituted promptly in order to prevent to introduction of pathogens into the patient's environment. Perform throat and nasal cultures on the staff. Staphylococcal carriers should not be permitted to participate in the care of irradiated individuals.

ι) In addition to the regular recording of vital signs, blood pressure and pulse should be watched carefully in the event that there are serious gastrointestinal symptoms. In particular, pay attention to the fluid and electrolyte balance, and correct as necessary with the appropriate solutions or plasma.

$\varkappa$) If signs of infection develop, such as a sudden spike in fever, or the development of ulcerations when the leukocyte count is below 1500 per mm^3, give antibiotics in large doses. Antibiotics are rarely indicated prophylactically. It is recommended that antibiotic doses be 3 times those that are ordinarily used. If the temperature is not controlled with the antibiotic employed, switch to another antibiotic. If the temperature rises again, switch to still another antibiotic. Of course, the choice of antibiotic will be determined in part by the bacterial cultures, but do not wait for the sensitivities to be determined, since the introduction of true pathogens may result in rapid, progressive overwhelming infection in the pancytopenic state. With commensal organisms, the infections do not progress as rapidly, but it takes time to get bacterial cultural confirmation of the infecting organism.

Use oral antifungal antibiotics when giving broad spectrum antibiotics. Sulfonamides have been used with success in pancyteopenias from other causes, and should always be given due consideration.

λ) Watch the platelet count carefully and observe the patient for signs of bleeding. Watch for the presence of hematuria, cutaneous petechiae or retinal bleeding. If there is any indication of bleeding give platelets in a single, whole blood transfusion until the hematocrit is at a reasonable level. Blood must be fresh (less than 4 hours old). When the hematocrit is elevated to satisfactory levels. give freshly separated platelets in a single transfusion in amounts equivalent to those found in approximately one third of the blood volume of the patient. Follow the patient closely, and retransfuse as indicated by the clinical picture. Generally speaking, platelet transfusions will not be necessary at more frequent intervals than 3 to 5 days. It is not necessary to maintain a normal platelet count. The probability of bleeding, with platelets in excess of 40000, is very rare indeed. In fact, bleeding is rarely observed until platelets fall below 25000 per mm^3.

μ) In summary, when indicated, push antibiotic therapy vigorously to control infection and platelet transfusion to stop bleeding. Above all, try to prevent serious infection by reserve isolation and prevent gastrointestinal bleeding by bed rest and careful attention to the bowels, since fatal hemorrhage has been initial by straining at stool in the pancytopenic state. Combined antibiotic and transfusion therapy has significantly increased the survival rate of dogs exposed up to an $LD_{95\text{-}100}$ dose of radiation by SORENSEN *et al.* (1960). At supralethal doses this regimen has been of no avail. One can anticipate that a similar regimen would be equally as effective in man exposed to biologically comparable doses of radiation. Many individuals have now survived after even fairly high doses of radiation without any therapy. Thus, unless signs of hemorrhage of infection, or extreme depression of peripheral blood counts appear, no treatment is needed. In the Marshallese exposed to high sub-lethal doses of radiation, in whom an epidemic of upper respiratory infections developed, practically no therapy was indicated or needed. In the 5 individuals exposed to neutron and gamma radiation in the industrial Y-12 accident at Oak Ridge, therapy, was limited to treatment of infection in a single individual who responded well. In these individuals, peripheral blood count depression was severe and in the Oak Ridge accident some loss of hair and some evidence of bleeding were also noted.

The use of antibiotics prophylactically has been recommended by others. However, it is felt that this is definitely contraindicated, for this may result in unnecessary development of resistant bacteria within the irradiated individual prior to the onset of infection, thus shortening the period of time over which the antibiotics may sustain life, and thereby also shortening the period of time during which spontaneous regeneration in the bone marrow may take place. However, with the overwhelming doses with a very severe gastrointestinal syndrome, consideration to the use of non-absorbable antibiotics to sterilize the intestine and prevent local infection accentuating the gastrointestinal syndrome should be given. Perhaps it is of academic interest, since individuals exposed to such doses of radiation probably have no statistical chance of survival any way.

If the dose of radiation is high, in excess of 500 rads, or if the individuals are deteriorating with a very rapid decline in the granulocyte and the platelet counts, one of course must consider the possibility of attempting homologous bone marrow transplantation. The selection of patients for homotransplantation of bone marrow is very difficult. Certainly, if the dose of radiation has been proved without doubt to be definitely in excess of 600 rads (probability of spontaneous survival nil) one should consider homologous transplantation of bone marrow. However, one cannot be very enthusiastic about the probability of a successful homologous bone marrow transplantation for two significant reasons. First, in animals the dose of radiation must be very high in order to suppress immunity sufficiently for the foreign tissue to settle out and grow, and second, the number of cells required to protect animals is so large that a comparable amount could only be obtained from a single

human donor by multiple aspiration which necessitates general anesthesia. However, situations may well arise in which one must give serious consideration to attempting transplantation of marrow. The biological background of marrow transplantation has been presented by Loutit and Micklem (1966).

The situation may be summarized somewhat as follows. Homologous bone marrow contains cells which have the capability of repopulating bone marrow and restoring immunological competence by donor cells. The former is desired and the latter is to be avoided. The establishment of immunological competence by donor cells permits these cells to launch a graft versus host disease (secondary disease or allogenic disease). The foreign, immunologically competent cells attack kidneys liver, lymph nodes, skin, and intestinal tract, producing severe symptomatology and death in a large fraction of treated animals. This has been shown by Mathé *et al.* to be formidable problem also in man. Following any attempted homotransplantation in man, one desires a temporary take of the hemopoietic tissue to save a life. It is hoped that this will be followed by a slow recovery of the host's immunologically competent system, which would then reject the transplanted bone marrow. In parallel with this, one wishes the host's bone marrow to recover. This has been apparently observed from time to time in experimental animals by chance alone. It is not clear as to how one can deliberately attain the desired result in man. For certain possible situations one should give serious thought to the preservation of bone marrow for autologous transfusion. It has been established by Alpen *et al.* and Thomas *et al.* that autologous transfusions significantly increase the survival rate of fatally irradiated dogs. Kurnick *et al.* have evidence that suggests preserved autologous marrow is of value in human beings with marrow depressed from extensive chemotherapy. Since marrow can be preserved satisfactorily one should consider the possible conditions where one might have greater probabilities of severe radiation injury and consider the desirability of preparing and preserving one's own marrow for possible future use. However, in this case one is confronted with the problem of submitting the individual to a small but definite hazard to life by general anesthesia in obtaining enough of his own marrow to the small but definite possibility of being involved in an accident at a later time and then needing the preserved marrow.

The entire problem is when and how to transplant bone marrow and obtain the desired results described above, or, in the event that a permanent take of the marrow is needed, to suppress secondary disease. There is no doubt that if one gets a permanent take of the transplanted marrow, the individuals would have died had the marrow not been transplanted. Now the question is how to suppress the secondary disease. These complicated problems do not have satisfactory answers at the present time, and one is referred to the World Health Organisation monograph on "Diagnosis and Treatment of Acute Radiation Injury" and "La Greffe des Cellules Hématopoiétiques Allogénique" for more details.

7. Prophylactic therapy

No-one will disagree that in any operation where hazard is involved, every possible precaution must be taken at the planning stage. Work with radiation is no exception, and the remarkable rarity of accidents in modern radiation work is a tribute to the planners in the nuclear energy industry of all countries. Much of the credit is due to the health physicists.

The first and necessary function of the health physicist is to advise and help his colleagues in other scientific and engineering disciplines to design, test and operate their various installations with safety. Clearly, the first time an assembly is operated is the most hazardous time. However, experience has clearly indicated that the hazards also continue because of natural capability of humans to err. Even in the case of often repeated successful operations, accidents do occur. This was demonstrated clearly in the Oak Ridge accident at Los Alamos accidents. Acoordingly, one of the most important functions in prevention

of accidents is the continuing enthusiastic vigilance of the health physicist and his colleagues. This clearly is an unpleasant police function, and one to which industrial psychologists should well give significant attention. There is no substitute for planning adequate protective measures and continuing enthusiastic vigilance on the part of those who must continually observe potentially hazardous operations to see that they remain safe in functioning.

The question of chemical protection against radiation has been intensively studied, both for a basic understanding of the mechanism of action of radiation, and with the hope that some practical prophylactic measure might be developed that could protect individuals operating in a radiation area. In fact, it has been shown that there are many agents which will increase resistance of animals to radiation by about a factor of 2. The two most effective procedures are the induction of severe hypoxia, and the administration of high concentrations of certain sulfhydro compounds. The former clearly is too hazardous in itself, and the second also has serious pharmacological effects, that prevents, at the present time, practical use of these agents. Of course, basic studies are continuing in this important field, but it is regrettable that nothing as yet of a practical nature has arisen that can be administered prior to exposure and will protect individuals against radiation.

VIII. Beta exposure of the skin from fall-out

This general problem has been covered in great detail by CONARD *et al.* The problem will only be summarized briefly here in. Generally it was considered that beta radiation from fission products would not constitute any hazard to human beings. However, in 1954 the importance of this hazard became apparent when widespread radiation lesions of the skin developed in a large group of people accidentally exposed to fall-out radiation in Marshall Islands following the experimental detonation of a large nuclear device. In addition to exposure of some 239 Marshallese people and 28 Americans, there were 23 Japanese fishermen exposed on the fishing boat. Up to this time some beta burns had been observed on the backs of animals near the atomic energy testing site. In addition, exposure of the hands of several individuals who had carelessly handled fission products, samples from a detonation, resulted in the development of severe lesions.

The lesions of the skin induced by fall-out are primarily due to the beta radiation from the fission products adhering to the particular fall-out material, and are therefore referred to as beta burns. Actually, in the fall-out accident, the radioactive material fell out of the sky, resembling small snow flakes. In this instance, the fall-out material consisted of calcium oxide from the incineration of the calcium carbonate of the coral islands. However, the chemical and physical make-up of fall-out will vary according to the type of terrain or soil over which the detonation occurs. All fall-out is particulate in nature, but the size and other characteristics of the particles will depend on the physical and chemical properties of the soil. The calcium oxide of the fall-out material in this accident partly dissolved in the perspiration of the skin and brought the adsorbed radioactive particles in very close contact.

The beta emitters of the fall-out material have a wide range of energies from a few kV to a few MeV. The depth of penetration is limited by the most energetic component. When in direct contact with the skin 50% of the most energetic component will be absorbed within 1000 microns. Thus injury will be relatively superficial. However, severe burns necessitating skin grafting have been produced by accidental contamination of hands by fission products (KNOWLTON *et al.*).

During the first 24—48 hours after the fall-out descended on the Marshallese there was a varying degree of itching, burning and tingling of the skin along with lacrymation. How much of this was due to or accentuated by the calcium oxide and its caustic action on moist skin is not known. These symptoms subsided and for a period of about 2 weeks there were no symptoms or signs referable to the skin. At this time small highly pigmented

macules appeared accompanied by intense itching and burning. These lesions were located on the exposed skin and were most commonly seen on the neck, face, cubital fossa, and feet. These coalesced into larger plaques and finally superficial desquamation of the epidermis occured. In a few instances there was severe edema, pain, and deeper ulceration on the dorsum of the feet and in one patient the back of the ears. All lesions ultimately healed. The ones in which there was deeper ulceration left residual scars and de-pigmented areas.

In addition to the skin lesions there were varying degrees of epilation. All hair regrew with normal color and texture. Treatment was limited to local antibiotic ointments and cleanliness when ulceration appeared.

The people who had beta burns have been carefully observed. To date, 16 years after the accident, no cases of cutaneous cancer have developed. Scars are present. Biopsies have shown mild typical late radiation effects in blood vessels and connective tissue however no trophic ulcers have developed. Perhaps radiation injury of the epithelium is an insufficient injury to produce epitheliomata and the secondary trophic disturbances due to ulceration and its sequelae are required to produce radiation induced cancer of the skin.

IX. Recovery from radiation injury and influence of prior whole body exposure on response to later exposure

In general the first order model for exponential recovery from radiation injury formulated by Blair in 1950 has been widely accepted and used to estimate hazards and residual injury at various times after prior exposure. The experimental basis for this model is the extensive study of the behaviour of mice previously exposed to radiation of various doses and later challenged to determine changes in the LD_{50}. As a result of accumulation of data on radiation effects on mammals in general and the accidental exposure of human beings to fall-out considerable doubt was thrown on the validity of the general application of the exponential recovery concept. Alpen (1966) began some years ago to systematically study the mortality and hematological response of a wide spectrum of mammals (mice to swine) after the first and subsequent exposures to radiation. First the LD_{50} for mammals falls into two categories one for small mammals (rat, mouse, hamster, and rabbit) with an LD_{50} of 889—941 rads and one for large mammals (dog, burro, goat, sheep and swine) with an LD_{50} of 251—376 rads. The monkey is midway between and the guinea pig has an LD_{50} of 255 rads rather than the 900 rads one might expect in a small animal.

The hematological responses in the early phases are relatively similar with some differences in the rapidity of the development of the reduced counts. There are striking differences in the recovery patterns which depend upon the species and not the dose of radiation.

When all species were studied for radiation recovery following the administration of $^2/_3$ of the LD_{50} it was found that only the mouse gave an exponential recovery following exposure. Even with the mouse there are significant deviations during the first few hours following the conditioning dose. The recovery patterns for the mammals are quoted from Alpen:

a) "a temporary delay in the commencement of the decrease in radiosensitivity termed the recovery plateau"

b) "a two component decrease in radiosensitivity made up of an early fast phase and a later slower phase"

c) "a recrudescence of radiosensitivity such that the animal is more radiosensitive following a period of early recovery"

d) "a period of radioresistance of 'over recovery' of varying duration and character".

None of the animals had all four of the characteristics listed above. Each species has its own unique pattern. The response pattern of man of course is not known but there is no cogent reason to believe that man is different from all other mammalian species. Accordingly these general principles should be incorporated into one's thinking when trying to evaluate repetitive whole body exposure of human beings.

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