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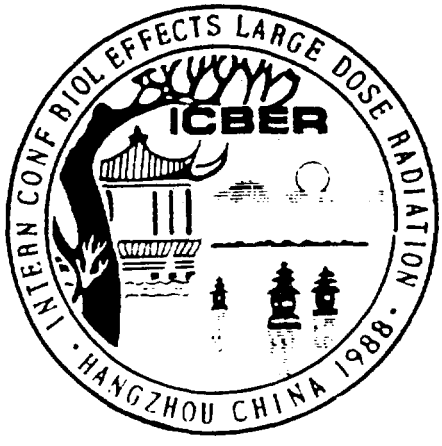

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ACUTE RADIATION SYNDROMES AND THEIR MANAGEMENT*

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ABSTRACT

Radiation syndromes produced by large doses of ionizing radiation are divided into three general groups depending on dose of radiation and time after exposure. The CNS syndrome requires many thousands of rad, appears in minutes to hours, and kills within hours to days. The GIS appears after doses of a few hundred to 2000 rad. It is characterized by nausea, vomiting, diarrhea, and disturbances of water and electrolyte metabolism. It has a high mortality in the first week after exposure. Survivors will then experience the BS as a result of marrow aplasia. Depending on dose, survival is possible with antibiotic and transfusion therapy. The relationship of granulocyte depression to mortality in dogs and human beings is illustrated. The role of depth dose pattern on mortality of radiation exposure is described and used as an indication of why air exposure doses may be misleading. The therapy of radiation injury is described based on antibiotics, transfusion therapy, and use of molecular regulators. The limited role of matched allogenic bone marrow transplants is discussed.

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INTRODUCTION

From perusal of the older literature and review of the Japanese experience at Hiroshima and Nagasaki (1), it appeared necessary to consider some broader aspects of radiation injury in general, such as the syndromes produced by radiation injury, the influence of depth dose of radiation, the unresolved question of lethality of radiation in man, the role of dose rate, and repair of injury during chronic exposure to radiation as in fallout fields decaying with the -1.2 law. Studies on pure radiation injury generally involve a single dose of x-ray or gamma rays at different dose rates, and it is rare to find sufficient data to evaluate the influence of depth dose patterns within the experimental subject. When one considers the numbers of animals used, the steepness of the sigmoidal radiation lethality curve between 10% and 90% mortality, the practice of studying animals exposed to single dose of radiation, one must consider the possibility that lethality differences observed may represent chance variation, not related to any therapy used. In a retrospective literature evaluation, these are questions that cannot be evaluated definitively. In respect to therapy, vast human clinical experience on use of antibiotics in management of trauma and thermal burns in man and formanagement of marrow aplasia produced by agents other than radiation, it can be categorically stated that antibiotics increase the survival rate of patients with extensive burns, trauma and individuals with temporary marrow hypoplasia. A crucial problem in radiation injury is whether the bone marrow will regenerate before the commensal or invading pathogenic bacteria develop resistance to the antibiotics available.

Radiation Lethality - The Classical Syndromes Produced by Uniform Whole-Body Irradiation:

The radiation syndromes produced by exposure to ionizing radiation are highly dependent on the energy of the radiation and hence to the depth dose patterns which will be considered later. Three, somewhat arbitrary and and overlapping syndromes are illustrated in Figure 12.

The Central Nervous System Syndrome

After large doses of several thousand rad, the Central Nervous System (CNS) syndrome is produced. Death may occur during exposure in some

laboratory animals that is preceded by hyper-excitability, ataxia, respiratory distress, and intermittent stupor. Doses capable of producing this syndrome are uniformly fatal. This syndrome has been observed in a few casualties described by Hubner et al. (2). If an occasional person were to survive the CNS syndrome, the individual has yet to experience the Gastrointestinal syndrome (GIS).

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The Gastrointestinal Syndrome

The GIS, when produced by doses in excess of 1500 rad, will be fatal within 3-9 days in laboratory animals and probably this also applies to human beings. The range in survival results from species and strain variations. It is named the GIS syndrome because of the marked nausea, vomiting, diarrhea, and denudation of the small bowel mucosa. The severe and persistent GIS is a uniformly fatal syndrome in most laboratory animals. It was observed in Japan and described by Oughtersen and Warren (1), and in some accidents by Hubner et al. (2). In dogs, Conard et al. (3), have prolonged life by intensive administration of intravenous fluids and plasma. It is of interest that animals surviving doses up to 1200 rad will regenerate the mucosa of the small intestine as described by Brecher et al. (4). The survivors of this syndrome have then to experience the sequelae of bone marrow depression, which has been termed the hemopoietic syndrome (HS) and was commonly observed in the Japanese exposed to nuclear radiation in Hiroshima and Nagasaki.

The Hemopoietic Syndrome

The HS is not necessarily fatal. It is a clinical picture that is seen in the lethal range for all mammals including man. The lethality levels reported represent the LD_{50} for the sequelae of bone marrow depression, namely, granulocytopenia with susceptibility to bacterial infection, thrombocytopenia with susceptibility to diffuse purpura and

anemia from suppression of red cell production and hemorrhage. Detailed descriptions of this syndrome in man and animals are described (1,2,5-13).

This picture of the three radiation syndromes, which overlap to a certain extent, is based primarily upon animal experimentation. Human experience (1,2,14-20) indicates that man corresponds reasonably closely to the general mammalian response. There are some differences in respect to the time of occurrence of signs and symptoms. The experience of the Japanese at Hiroshima and Nagasaki exposed to gamma radiation from a high-altitude nuclear device in which the fireball did not touch the ground are described in detail by Oughtersen and Warren (1). Hubner and Fry (2) have gathered together the total human experience in radiation injury and its management, with the exception of the Japanese atomic bomb casualties and the Marshallese fallout casualties.

Radiation Injury in the Japanese at Hiroshima and Nagasaki:

The CNS was not observed by the Japanese at Hiroshima or Nagasaki (1,15,24), nor would one have expected it to be observed since doses to produce the syndrome were well within the area of total destruction and no survival. The GIS, with deaths in the first week, are well documented clinically and pathologically as are deaths from the HS (1,15,18). In the case of man, the sequential sequence of deaths and depression of blood counts is different from that in animals. It takes longer for the HS to develop in man. For example, deaths from infection were most prevalent in the second to fourth weeks (maximum incidence during third week) and from hemorrhagic phenomena during the third to sixth weeks (maximum incidence in the fourth week). Deaths from radiation injury were occurring in the Japanese as late as the seventh week. This is in contrast to other animals, where deaths from the acute phase are uncommon later than the thirtieth day after exposure. The correlation of neutrophil counts with mortality, is shown in Figure 2. The data in Figure 2 are based on dogs that were exposed to a nuclear bomb in the Pacific proving ground. Comparable observations were made in the Japanese at Hiroshima and Nagasaki as are illustrated in Figures 3 and 4. In addition, it was shown that lowest leukocyte counts in the Japanese were observed in the fifth to the sixth week after exposures to the nuclear radiation (20). A comparable sequence in the depression of granulocytes was also seen in the Marshallese exposed to fallout radiation (5).

Probability of Survival following Exposure to Whole-Body Radiation:

The probability of survival can be related to symptomatology in man. The following analysis is based on the observations made on the Japanese in Hiroshima and Nagasaki (1). Individuals exposed in the lethal range (where some, but not all, die in the first several weeks after exposure) can be divided according to signs and symptoms, into groups having different prognosis. Thus, they may be divided into three groups in which survival is, respectively, improbable, possible and probable. This grouping was originally made by Cronkite (7). It is apparent that there is no sharp line of demarcation among the groups.

Survival Improbable: If vomiting occurs promptly or within a few hours and continues and is followed in rapid succession by prostration, diarrhea, anorexia, and fever, the prognosis is grave. Death will probably occur in 100% of these individuals within the first week. It is assumed that extensive administration of fluids and plasma may extend the life of these individuals so they may survive to develop the hemopoietic syndrome.

Survival Possible: Vomiting may occur, but will be of relatively short duration followed by a period of well-being. In this period of well-being, marked changes are taking place in the hemopoietic tissues. Lymphocytes are profoundly depressed within hours and remain so for months. The neutrophil count falls to low levels, the degree and time of maximum depression depending upon the dose as illustrated by et al. (20). Signs of bacterial infection may develop when the total neutrophil count falls below 500/µl. Platelet count may reach very levels after two weeks. Evidence of bleeding may occur within 2-4 This group represents a lethal dose range in the classical pharmacol sense. In the higher exposure groups of this category, the latent p lasts from 1-3 weeks with little clinical evidence of injuries other slight fatigue. At the termination of the latent period, the patien develop purpura, epilation, or cutaneous ulcerations, infections o or burns, diarrhea and/or melena. The mortality will be significant therapy, antibiotics and/or sulfonamides the survival time can be to be prolonged and if sufficient time is provided for bone marrow regeneration the survival rate will be increased substantially.

many soldiers had nausea and vomiting, recovered, felt well, returned to duty to later develop purpura, epilation, oral cutaneous lesions, and then died of infection. This is well-documented by Oughtersen and Warren (1). Despite the chaotic conditions that existed in Hiroshima, the data of Kikuchi and Yakisaka (19) indicates that there was more rapid decrease of granulocytes in individuals that could be assigned to the Survival Improbable and Survival Possible as compared to the Survival Probable group.

Survival Probable: This group consists of individuals who may or may not have had transient nausea and vomiting on the day of exposure. In this group, characterized by the Marshallese (6), there is no further evidence of effects of exposure except the hematologic changes that can be detected by serial studies of the blood with particular reference to granulocytes, lymphocytes and platelets. The lymphocytes may reach low levels early, within 48 hours, and show little evidence of recovery for many months after exposure. The granulocytes may show some depression during the second and third week. However, considerable variation is encountered. A late fall in the granulocytes during the 6th or 7th week after exposure may occur. Platelet counts reach the lowest levels at approxmately the 30th day at the time when maximum bleeding was observed in the Japanese who were exposed at Hiroshima and Nagasaki. The lowest platelet counts were also seen in the Marshallese exposed to fallout radiation around 30 days after exposure. In this group individuals with neutrophil counts below 1000/µl may be completely asymptomatic. Likewise, individuals with platelet counts of 75,000/µl or less may show no external signs of bleeding. Even though the defenses against infection are lowered by this sublethal dose of radiation, individuals with these severe degrees of hematologic depression may not develop infection. It is generally believed that premature administration of antibiotics prophylactically may jeopardize the probability of recovery in Survival Possible group by allowing bacteria to develop resistance to antibiotics.

Effects of a Single Dose of Gamma Radiation

Analysis of a Possible Human LD_{50}

In the first place, in all reality, the mortality response of man to radiation is not known with any degree of precision. One should think of the LD_{50} in the classic pharmacologic sense; that is, the mortality

response to radiation in the absence of treatment and other complicating factors. The LD_{50} will be increased by the use of antibiotics to control infections, by platelet transfusions to control bleeding, and the hemopoietic molecular regulators now available to stimulate an earlier recovery of hematopoiesis. In 1947 Newell (21) surveyed the opinion of radiologists of the 50% lethal dose of radiation in man. Their estimates varied considerably and the average was close to 450 rad, the commonly stated LD_{50}.

Many sources of data bear on the LD_{50} value for man and each has several shortcomings. These sources include radiation mortality data on large animals, the data from the Japanese exposed at Hiroshima and Nagasaki, the Marshallese data and data from patients given therapeutic total body radiation. The effects of geometry of exposure and energy of radiation on the mortality response is crucial (22-24). Bond and Robert (23) observed that the small animals appear to have a high LD_{50}, whereas large animals have a low LD_{50}. It would be logical from this to argue that man may have a low LD_{50}. In fact, one does not really know how to extrapolate from animals to man. In principle, at least, one might think that in Hiroshima and Nagasaki where many individuals were exposed, one would have a rather good idea of the radiation LD_{50} for man. This is not the case, however, because of the complicating factors of trauma, thermal injuries, poor nutrition, and, most importantly, the inability to correctly assign radiation doses to individuals that survived or died.

Cronkite and Bond (25) have approached the problem of LD_{50} in man by looking at the Marshallese response to 175 rad total body irradiation and the response of animals in general. Figure 5 illustrates an approach to estimating human LD_{50}. It is believed that the Marshallese were exposed to a near maximal sublethal dose of radiation. It would appear that 175 rad uniform total body irradiation would anchor the lower part of the dose-response curve. Certainly, in dogs and swine, if the dose of radiation were increased by 100 rad over that received by the Marshallese, one would be well into the lethal dose range. If one adds 50 rad to the estimated 175 rad that the Marshallese received, one has a probable low lethality, about 5-10%, of approximately 225 rad. If one uses the same slope as for dogs, the 90% mortality is about 500 rad. The midpoint be

10% and 90% is approximately 360 rad. Thus, one can make a first guess that the LD_{50} for manis in the vicinity of 360 rad midline in the absence of complicated thermal burns, trauma, or any effective therapy. This estimate is bolstered by the fact that patients given therapeutic total body irradiation have severe hematopoietic depression occurring at dose levels of about 200 rad.

Probable Effects of Therapy

On clinical grounds, one would think that the combined use of antibiotics, fresh whole blood and platelet transfusions when needed, would increase the survival rate. It has been clearly shown by Miller et al. (26) that antibiotics increase the survival rate of irradiated mice. Furth et al. (27) obtained no marked benefit from antibiotic and transfusion therapy in their studies. Subsequent studies by Sorenson et al. (28) and Perman et al. (29) have clearly shown that one can consistently reduce mortality from a near 100% fatal dose to about 10% mortality in dogs by the combined use of high dosage of successive antibiotics and whole blood transfusions supplemented by platelet-rich plasma when red cells are not needed. This enables one to shift the sigmoidal dose mortality curve of uncomplicated whole body radiation injury to a much steeper one shifting the LD_{50} from approximately 300 rad in the dog to a little over 400 rad. The 5% mortality is shifted from roughly 200 rad to about 400 rad resulting in a nearly vertical sigmoid mortality curve. After doses in excess of 500 rad little benefit is observed and with greater doses no animals survive, although the survival time is moderately increased. Thus, one can anticipate that antibiotics, blood transfusions and platelet transfusions would benefit human beings.

The relationship of mortality to depression in the granulocyte count in dogs and man further points up the important role of infection and value of antibiotics. In Figure 2 is shown the granulocyte count in dogs that were exposed to gamma radiation from a nuclear bomb and the correlation with percent mortality. The granulocyte curve at the far left is in dogs that were exposed to about 600 rad midline dose. Note that the blood counts declined and all animals were dead by the seventh day of exposure. At autopsy infection was clearly the major cause of death. In the next curve the mortality was also 100% with a slower decline in granulocyte count along with a longer survival time. At autopsy the major cause of

death was ascribed to infection and complicated by hemorrhage. The next curve shows a slower decline in the granulocyte count with a mortality of 80%. The animals at autopsy showed infection and hemorrhage as causes of death. The curve showing the least decline in the granulocyte count had a mortality of 10% with hemorrhage and infection the causes of death.

In Figures 3 and 4, the critical role of the granulocyte count in the Japanese as a determinant of mortality is illustrated. Figure 3 plots the mortality against the blood counts observed in the third, fourth, and fifth weeks. The lower the white count the higher the mortality. Figure 4 correlates the mortality at the end of nine weeks with the lowest white count observed. The most clearcut correlation of the importance of infection is in the work of Miller et al. (26), shown in Figure 6. In this figure, there is a clearcut correlation of mortality with the fraction of animals having positive blood and splenic bacterial cultures. Subsequent studies in Russia and the U.S. extend and confirm the role of infection. Lilmanian and Izvekova (30) have studied a whole series of antibiotics and their use in the treatment of radiation injury in mice, rats, and rabbits. They administered kanamycin, erythromycin, tetracycline, ampicillin, oxacillin, and oletetrine. The antibiotics were administered twice a day by mouth for a total of 20-25 days starting 24 hours after irradiation with a lethal dose of gamma rays. A combination of antibiotics was more effective than single antibiotics. The combination of kanamycin with tetracycline or erythromycin, or tetracycline with ampicillin was most effective. The antibiotic combinations changed a near 100% mortality, to more than 50% survival. Chernov et al. (31) and Trushina et al. (32) administered hexamine prior to exposure of dogs and monkeys followed by the administration of antibiotics. In the case of dogs, penicillin and streptomycin were used. The survivals increased from 11% to 69%. In their studies on monkeys, a combination of kanamycin, oletetrine, streptomycin and penicillin was used. There was an increase in survival from 20% to 50%.

The Effects of Geometry of Exposure and Radiation Injury on Depth-Dose Curves and Biological Effectiveness

The inadequacies of using an air dose of radiation for prognosis will be illustrated by showing the influence of exposure geometry and energy

depth-dose and biological effect. Figure 7 shows the influence of exposing a Masonite phantom to 2000 kVp x ray from a single direction than when the exposure is bilateral with half of the dose given to each side (33). The dose in the phantom was measured by Sievert ionization chambers and is expressed as percent of the surface dose. In the case of the unilateral exposure, the dose falls off as it is attenuated by inverse square and absorption so that the exit dose is about 45% of the entrance dose. Thus the bone marrow of large animals being exposed would have a progressively decreased dose as the beam is attenuated. However, with bilateral exposure there is very uniform deposition of energy throughout the tissue equivalent phantom. The biological consequences of the different dose pattern are great. It is of considerable importance to bear these differences in mind when evaluating therapy of radiation injury and trying to make an animal experimentation as comparable as possible to an assumed real-life human exposure.

Figure 8 shows a comparison of bilateral exposure to 4 Pi exposure (33). This situation is important when trying to evaluate the hazards of fallout irradiation with its wide range in energy and the radiation exposure approaching 4 Pi source. Since fallout radiation is delivered from a planar source, the usual narrow beam geometry is not applicable. In such a diffuse 360 degree field, the decrease of dose with depth in tissue is less pronounced than that resulting from a bilateral exposure to an x-ray beam because fallout from inverse square is in effect neutralized. For the same energy, the dose at the center of the body is approximately 50% higher than would result from a given air dose with narrow beam geometry. Figure 8 further illustrates the depth-dose curve from an experimental situation using spherically oriented cobalt-60 sources with a phantom placed at their center, compared with a conventional bilateral depth-dose curve obtained with a single Cobalt source (34). In the latter case, the air dose is usually measured at the point subsequently occupied by the center of the proximal surface of the patient or animal with respect to the source. For the field case, all surfaces are "proximal" in the sense that air dose measured anywhere in the space subsequently occupied by the individual is the same. It is this air dose which is measured by field instruments; it does not bear the same relationships as the surface dose and the depth dose as air dose measured in a "point source" beam in the

clinic or laboratory. It would appear under these circumstances and in most experimental conditions that the midline dose, rather than dose measured in air, would be the better common parameter in terms of which to predict biological effect. On this assumption, air dose value should be multiplied by approximately 1.5 in order to compare their effects to those of a given air dose from a "point source" beam geometry delivered bilaterally. Furthermore, the geometry of radiation from a fallout field is not identical either to the geometry of bilateral point sources or the spherically distributed sources since the plane source delivers a radiation largely at a grazing angle. However, the total field situation is better approximated by solid than by plane geometry.

Figure 9 shows depth-dose curves for different types of radiation to provide an idea of the difference in absorption of energy throughout a large animal body thus injury (in the lethal range) to the important target cell, the hematopoietic stem cell, which determines whether the bone marrow will regenerate. These depth-dose curves are determined in unit density material using small Sievert chambers implanted at 6 cm intervals in the phantoms. The doses are expressed as percent of the entrance air dose. Curve A represents the depth-dose curve from 250 kVp x ray. This is a commonly used energy of radiation in animal studies. Note, the surface dose is about 40% greater than the entrance air dose and this falls off very rapidly with depth in the tissue so that approximately in the midline corresponding to man it would be 60% of the entrance to the important target cell, the hemopoietic stem cell, which determines bone marrow regeneration. Since bone marrow was distributed throughout the body in the bones, the amount of energy deposited in the hemopoietic stem cell varies by a very large factor. The curve B shows a similar depth-dose curve for 2000 kVp x ray. Curve C is the initial bomb gamma radiation and curve D is cobalt-60 gamma radiation. It is evident that for the same air dose, injury to hematopoietic stem cells scattered throughout the bone marrow varies considerably and thus would be expected to result in different lethal dose curves.

The Effect of Different Radiation Depth-Dose Curves on Mortality in Mammals

Tullis et al. (35, 36) has studied this in the laboratory and in the atomic bomb field tests with swine as the target animals. This is illustrated in Figure 10, showing the sigmoid dose mortality curves for unilateral 2000 kVp x ray, bilateral 2000 kVp x ray, and the mortality from the highly energetic prompt gamma radiation from a fission bomb. The LD_{50} from unilateral 2000 kVp x ray is 500 rad in air. Bilateral 2000 kVp resulted in an LD_{50} of 400 rad in air. The initial bomb gamma radiation with LD_{50} was about 230 rad in air. These air doses can be converted to midline tissue doses based on comparative studies on depth-dose curves to 300, 220, and 184 rad. The differences are explained in part by lack of homogeneity in distribution of dose. In the case of the unilateral 2000 kVp x ray, tissues distal from the midline received much less than 300 rad and tissues proximal to the midline received more. In the case of bilateral 2000 kVp x ray, tissues proximal to and distal from the midline receive a greater absorbed dose. In the case of the prompt gamma radiation, tissues proximal to the midline receive a greater dose and those distal a lesser dose, and hence a higher and lower survival of hemopoietic stem cells on opposite sides of the midline.

As a result of the effect of energy and geometry of exposure, measured radiation doses in air are of relatively little use in predicting survival. For practical clinical management, it is the opinion of this author that one should be guided by the clinical and hematologic course and not by estimates of radiation doses in air or doses estimated by biological dosimetry.

Fallout Radiation Exposure of the Marshallese

The energy of a fallout field determines, in addition to the geometry of exposure, the depth-dose pattern. Figure 11 shows the energy spectrum of 4-day old fallout. The original source is the energy of inherent gamma emissions from the major components of the 4-day fallout. The solid black histogram is calculated distribution of energy taking into account Compton scattering. Thus the energy to which an individual is exposed varies from a few keV with little penetration to a peak at 1600 KEV. The effect of this energy distribution in the geometry of exposure on depth-dose curves is shown in Figure 12. The depth-dose curves of a fallout field and

gamma radiation are shown. The doses of radiation to the surface and the first few millimeters of the body were substantially higher than the midline dose of gamma radiation. The curves presented are a percent of the 3 cm dose of radiation. In addition, the clinical observations of the skin lesions forcefully demonstrated that the dose to the skin varied considerably between individuals and over the surface of any given individual because of the spotty nature of the radiation burns to the skin.

Another feature of fallout radiation is its decay. The fallout arrived about 4-5 hours after detonation. Figure 13 shows the accumulation of dose as a function of time after detonation. The dose rate decreased continuously as the fallout material decayed. The major portion of the dose was received at a higher dose rate. By the time that 90% of the dose had been received, the dose rate had fallen to less than 40% of initial value and thus is much different from any animal exposure condition in the literature. The influence of a dose rate falling by a 1.2 power function is not known.

Repair of Radiation Injury

This has been considered in some detail in a report of the NCRP (37). In the NCRP dissertation, it was stated that 150 rad over one week, 200 rad over one month, or 300 rad over four months is believed to be sublethal and that no medical care would be required. However, 250 rad over one week, 350 rad over one month, or 500 rad over four months is estimated to be in the 5% mortality range and that some medical care will be required. When 450 rad is received over one week, 600 rad or more over one month or longer, the mortality witnout therapy is estimated to be 50% or more and extensive medical care will be required. These are doses of rad in air and not midline tissue dose in rad.

Whether studies on mice are applicable to man is not known. In recent unpublished studies, we have investigated the influence of varying the time interval from 1-24 hours between 2.5 Gy, 250 kVp x ray to mice, for a total of 10 Gy. This is shown in Figure 14. At intervals of 1 and 2 hours, no mice survive 30 days. As the interval between the 2.5 Gy increments are increased, there is an apparent cyclic change in the fraction surviving. When the interval is 22 or 24 nours between the 2.5 Gy increment, 100% of the mice survive. Figure 15 snows the hematopoietic stem cell (CFU-S) pe

leg in normal mice and mice receiving a single dose of 100, 200, or 300 rad and the mice receiving 1000 rad in a single dose or 1000 rad in four 250 rad increments 24 hours apart. All 1000 rad animals died by the 11th day after irradiation and the survivors had a very low CFU-S content of about 1 per leg. Animals receiving a 250 rad dose at 24 hour intervals had an equal depression of their CFU-S, followed by an exponential recovery to near normal levels by 30 days after exposure.

Therapy of Whole Body Radiation Injury

Bacterial infection has long been established as the major cause of death in the irradiated animal in the LD_{50} range. The commensal organisms living primarily in the gastrointestinal tract are the usual organisms that kill the animal that is irradiated in the LD_{50} range (11, 26, 38-40). The use of antibiotics as an effective treatment was first shown by Miller et al. (41) with the administration of streptomycin in mice. In addition, germ-free animals have been studied (42, 43) and these animals live longer, dying from hemorrhage and anemia rather than infection in the absence of bacteria. The effectiveness of antibiotics falls off as one nears the 100% lethal dose level since bone marrow regeneration is delayed so long that bacteria develop resistance to the antibiotics being used before bone marrow regeneration ensues. Taketa (44) has intensively studied the roles of water-electrolytes and antibiotic therapy against the acute intestinal radiation death in the rat. In these studies it was clearly shown that microorganisms play a prominent role in the genesis of acute intestinal death in the rat, and this was modified by the use of antibiotics and intensive administration of water and electrolytes. It is a beneficial effect not limited to rodents. Dogs have been treated with success with antibiotics, fluid replacement, and blood transfusion. A dramatic improvement in mortality was obtained by Coulter et al. (45), Hammond (46), and Allen et al. (47). In the latter study, blood transfusions were combined with successive antibiotics. In view of the fact that commensal organisms of the intestine are frequently cultured from the blood of the fatally irradiated mouse, Webster (48) tested the effect of oral neomycin therapy upon the mortality from whole body x-irradiation of rats. Graded doses of radiation were used from 700 rad through 2500 rad. Neomycin treatment resulted in significant prolongation of the mean survival time of

irradiated animals at exposures between 500 and 1500 rad. After 1500 rad and 2500 rad there was a small, but consistent prolongation of the mean survival time. For exposures between 700 and 1100 rad, the 30-day lethality was consistently lower for the neomycin-treated rats. Sorenson et al. (28) and Perman et al. (29) discussed earlier have clearly established an effective treatment of fatally irradiated dogs utilizing successive antibiotics, fluids, platelet transfusions, and whole blood as needed. Shalnova (49) published an English-language review of all of the work done in Russia before 1975 on antibiotic therapy in radiation injury. The essence of the work is: 1) apply broad-spectrum antibiotics insuring suppression of microproliferation using a purposeful alternation of antibiotic cycles with different preparations; 2) use antibiotics to create bacterial static concentrations of antibiotics, not only in the blood and tissues but also in places of natural occurrence of microbes such as the gastrointestinal tract and respiratory tract; 3) utilize antibiotics as early as possible, and before infectious foci have developed.

The Management of Whole Body Radiation Injury With or Without Combined Burns and Wounds

As discussed earlier, estimates of the air-exposure dose are of little value for two reasons. First, one needs to know the depth-dose distribution and second, the dose estimates are generally inaccurate, bearing on the high side initially and then declining as further studies and analyses are made.

The first step is to determine the severity of the radiation injury on the basis of signs and symptoms. If there are no abnormal symptoms such as nausea, vomiting, or diarrhea, the dose of radiation is in all probability in the sublethal range. If there is severe nausea, vomiting, and diarrhea as discussed earlier, the individuals will fall into the severe gastrointestinal syndrome. If the early symptomatology subsides and there is a feeling of well-being with rapidly developing changes in the hematologic picture with developing lymphopenia, neutropenia, and thrombocytopenia, the individuals would fall into the hematopoietic syndrome. The following therapeutic regimen is proposed:

1. If the exposure involves contamination with radioactive materials, the individuals should be monitored for radioactivity and decontaminated as promptly as possible.

2. If exposed to neutrons, a whole body count should be made to estimate the amount of radionuclides produced.

3. Medical history, physical examination, and laboratory studies including a complete hematologic evaluation should be done as promptly as possible. Cytogenetic preparations of direct bone marrow and phytohemagglutinin stimulated peripheral blood lymphocytes should be set up for later analysis of biological dose estimate. As soon as possible, the lymphocytes should be obtained while still available, before lymphopenia sets in, for human lymphocyte (HLA) typing and storage for later mixed leukocyte cultures. The results of the tissue typing will be useful for matching of granulocyte, platelet transfusions and the identification of a possible bone marrow donor.

4. In the early stages, the first five days, fluid and electrolyte balance must be monitored closely and restored by the appropriate intravenous or oral solution.

5. Reverse isolation techniques to prevent ingress of pathogens to the irradiation individuals are generally believed to have been effective in preventing infections in patients undergoing treatment for leukemia and subsequent bone marrow transplantation. This would probably be a useful procedure in the event of a potentially fatal irradiation accident. If possible, the individual should be admitted to a modern laminar air-flow room with a complete regimen of skin sterilization, sterile diet, and non-absorbable antibiotics for sterilization of the gastrointestinal tract. If this is not feasible, measures should be initiated to prevent commensal and pathogenic infections. Reduction in the gastrointestinal flora is desirable, and this can be accomplished with oral, non-absorbable broad-spectrum antibiotics such as neomycin and antifungal agents such as nystatin.

6. Platelet transfusions, preferably fresh, should be given when the platelet count approaches 25,000 and repeated to maintain levels above this.

If the patient should become refractory to random donor platelets, the use of HLA-matched platelets from unrelated donors may become necessary. A family-member transfusion should not be administered until the possibility of bone marrow transplantation has been excluded because such transfusions might sensitize the patient to the antigens of a possible donor.

7. Granulocyte transfusions would be desirable to prevent infection in patients with a granulocyte count falling below 200/μl. Admittedly, these are not practical on any large scale.

8. Infection is the greatest threat to life. The onset of significant fever greater than 38°C should arouse strong suspicion of infection in the granulopenic patient. Fever with clinical signs of bacterial infection, or fever sustained more than 24 hours is an indication for initiating systemic antibacterial therapy even though cultures are negative. Since the most likely agent is an organism from normal bowel flora, initial therapy should include aminoglycoside and carbenicillin with additional antibiotics being added as indicated by bacterial culture sensitivities that are obtained. If cultures are negative or fever persists, therapy with a combination of trimephoperim and sulfanethoxazole or with amphotericin may be considered. After initiation of broad-spectrum antibiotic therapy, it should be continued until the granulocyte count rises above 500/μl, fever subsides, and evidence of infection disappears.

9. Washed packed red blood cells should be given as indicated to keep the hemoglobin above 8.5 g.

10. All blood products should be irradiated with 2000 rad before infusion into the patient in order to kill lymphocytes that might proliferate and impair the possibility of a bone marrow transplant.

11. Bone marrow transplantation will only rarely be indicated in an irradiation casualty because uncertainty about the magnitude of the radiation dose, inhomogeneity of the dose, and the requirement that the dose be within the limits of rescue of bone marrow transplantation, approximately 800-2000 rad. Below 800 rad immunity is not sufficiently suppressed and transplants are rejected. Above roughly 2000 rad there is no therapy. From the lymphocytes collected promptly, the casualty will have been HLA-typed and donors will have been identified. A genetically identical twin is the ideal donor. In one irradiation casualty exposed to approximately 600 rad showed a rapid hematopoietic recovery following transfusion of bone marrow from his twin. Although radiation dose was cited above as an indication for bone marrow transplantation, it is to be noted from the earlier discussion that doses and the depth-dose curves are not known with any degree of certainty and the doses used above were based on experimental conditions where radiation was delivered in a manner to assure uniform whole body distribution of absorbed energy.

Hematopoietic Molecular Regulators in the Management of the Bone Marrow Hypoplasia

In the last ten years several molecular regulators of hematopoiesis have been identified, purified, sequenced, and by recombinant DNA techniques are being produced in large amounts. These are interleukin-1 and 3, granulocyte- macrophage colony-stimulating factor, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and erythropoietin. Interleukin-1, a product primarily of activated monocyte or macrophages, stimulates T-cells, endothelial cells, and fibroblasts to produce granulocyte-macrophage colony- stimulating factor. The latter accelerates the production of granulocytes and macrophages in vitro and upon in vivo administration produces a granulocytosis with accelerated production of granulocytes. It also increases the effectiveness of the functional granulocytes in phagocytosis and bacterial killing. Granulocyte colony-stimulating factor accelerates in vitro the production of granulocytes in colonies and in vivo accelerates the production of granulocytes and improves the phagocytic and bacterial-killing capacities (50-55). IL-1 has been used as a radioprotector. When administered 20 hours prior to irradiation, IL-1 turns a near 100% lethal dose of radiation in the mouse to near 100% survival. When administered four hours before or 48 hours before, it is ineffective (50). GM-CSF and G-CSF have been administered to primates and shown to produce a sustained granulocytosis of 4-5 times the normal level as long as the materials are administered. It has been given to primates and mice in which the marrow has been suppressed by radiation or chemicals and the granulocyte counts are increased (51-54). Erythropoietin has been shown to be of major benefit in stimulating the production of red cells in individuals with severe anemia as a result of renal failure (55). It is assumed that these agents or combinations will be of potential benefit in the treatment of individuals with bone marrow suppression as a result of whole body irradiation. On the other hand, it is conceivable that forcing cells into mitosis before DNA is adequately repaired may fix genetic injury and result in either an early failure of the mitotic capacity of pluripotent stem cells or an earlier and increased incidence of leukemia. These are possibilities that need to be explored experimentally.

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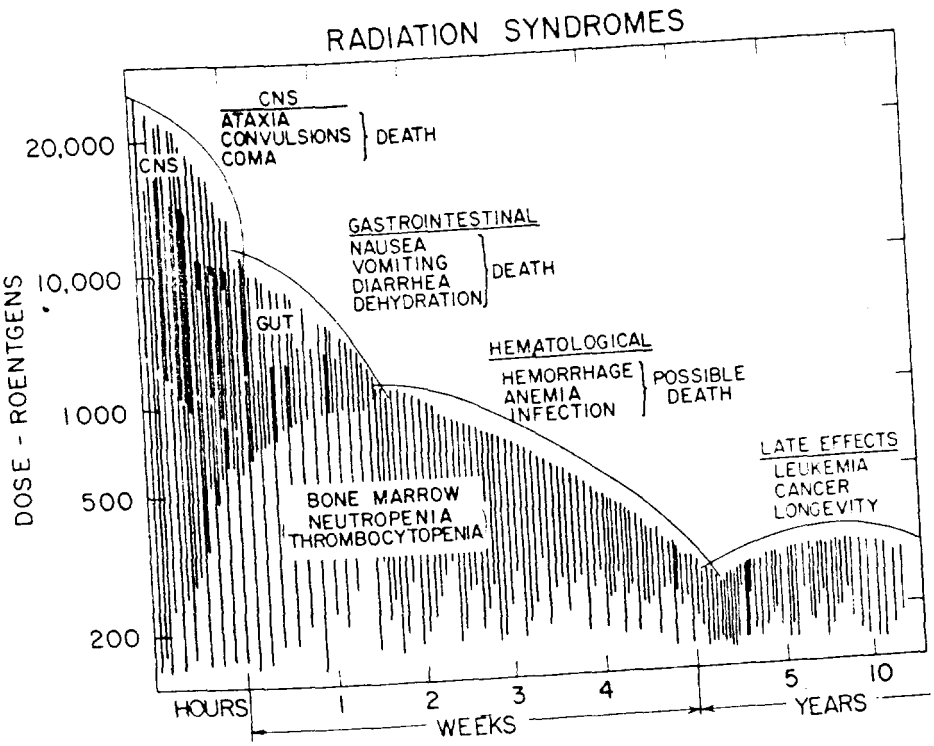

Figure 1. Schematic presentation of radiation syndromes produced by total body irradiation as a function of dose and time after irradiation

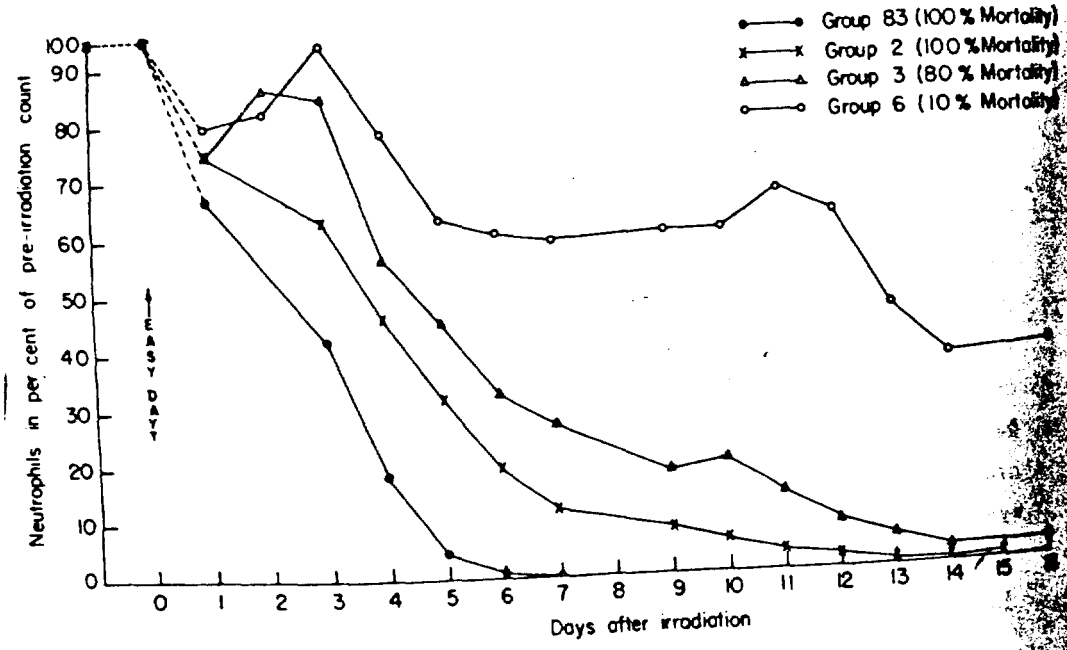

Figure 2. Sequential neutrophil counts in dogs exposed to nuclear bomb gamma radiation in relation to mortality.

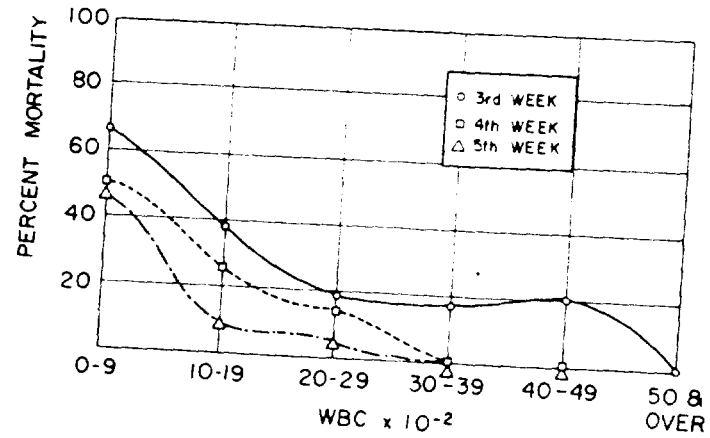

Figure 3. Mortality (died within 9 weeks) related to WBC level Hiroshima and Nagasaki

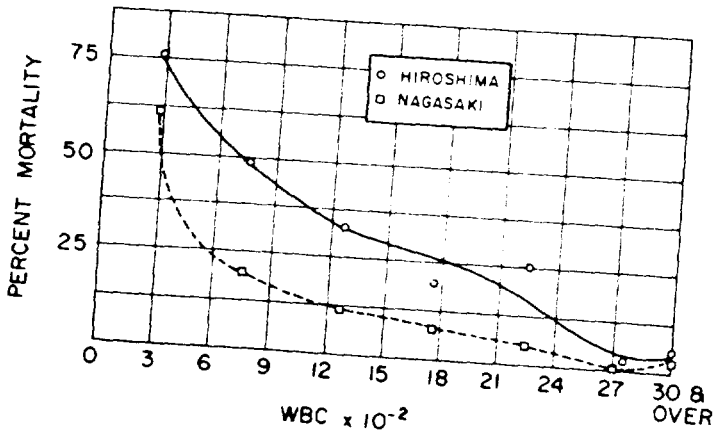

Figure 4. Mortality (died within 9 weeks) related to lowest WBC in first five weeks.

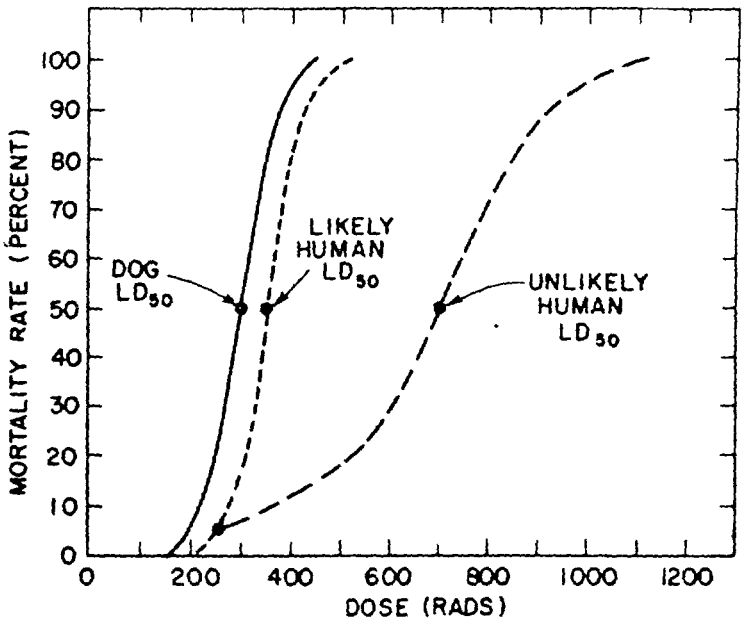

Figure 5. Schematic presentation of likely and unlikely radiation lethal dose curves for man from Cronkite and Bond (25).

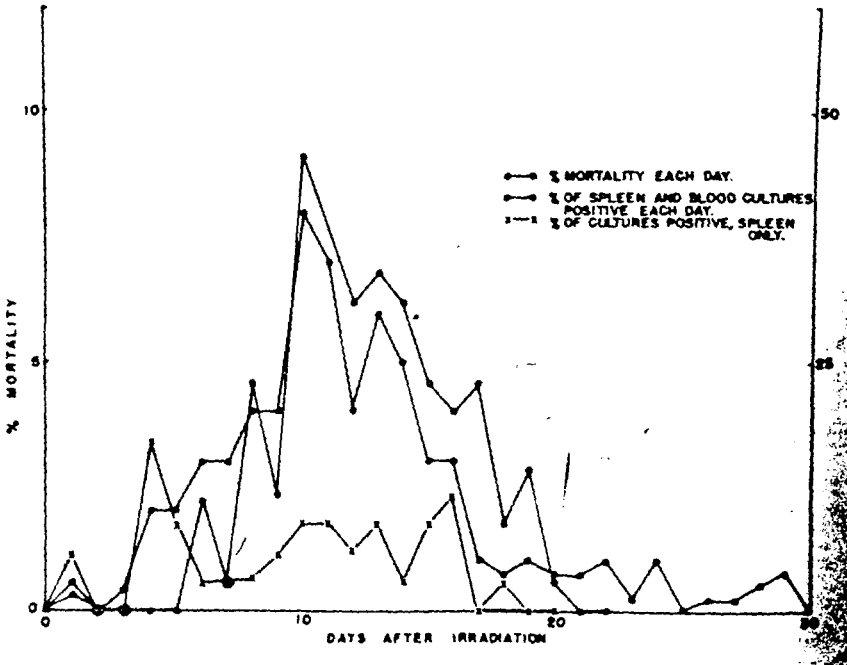

Figure 6. Frequency of deaths, positive blood and splenic cultures by days after irradiation with 450 r (200 KV X-ray). Mortality frequency based on 262 mice. Frequency of cultures based on 35 cultures performed daily. (Miller,C.P., Univ. Chicago, 1949, unpublished).

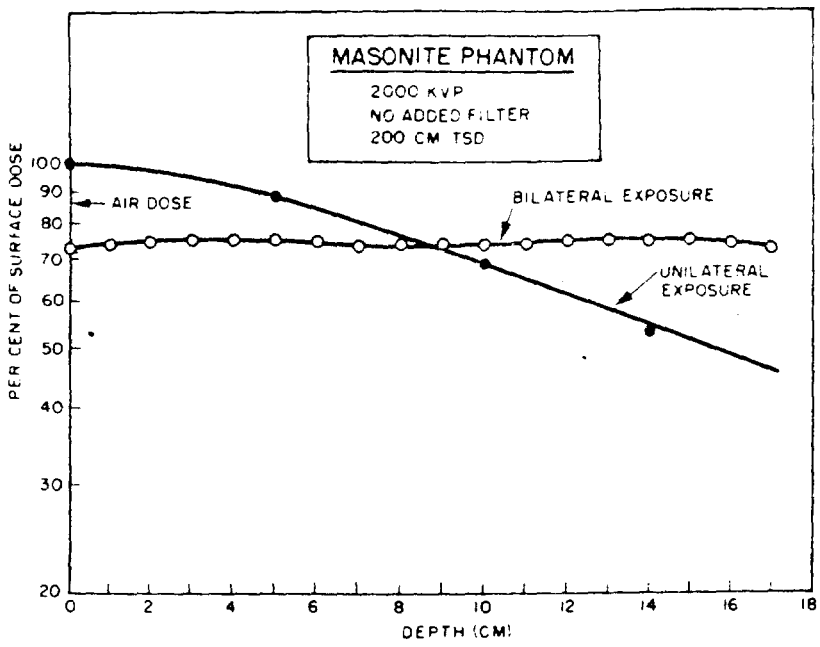

Figure 7. Depth-dose curves for 200 kVp x ray expressed as percent of surface dose for unilateral and bilateral radiation exposure from Bond et al. (34).

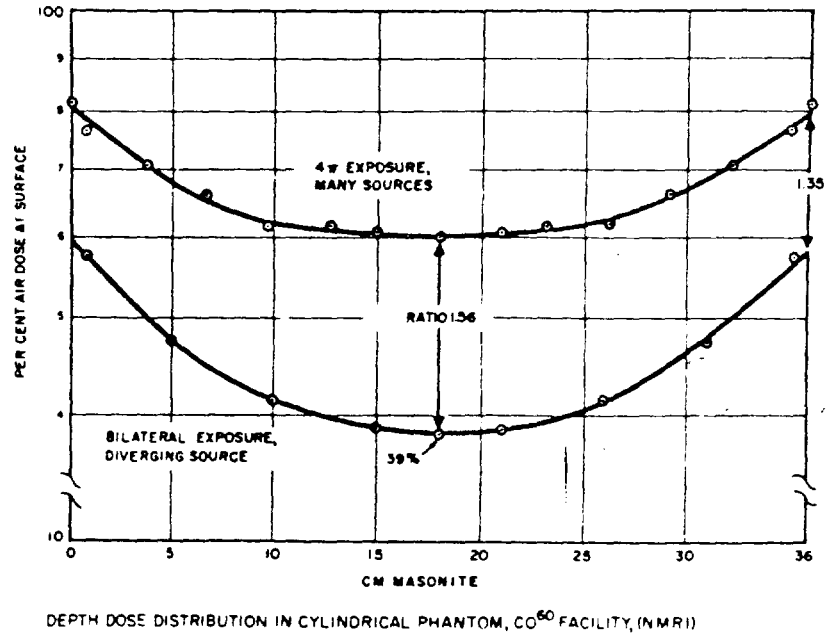

Figure 8. Comparison of depth-dose curves expressed as percent of air dose for bilateral and 4 Pi exposure from Bond et al. (34).

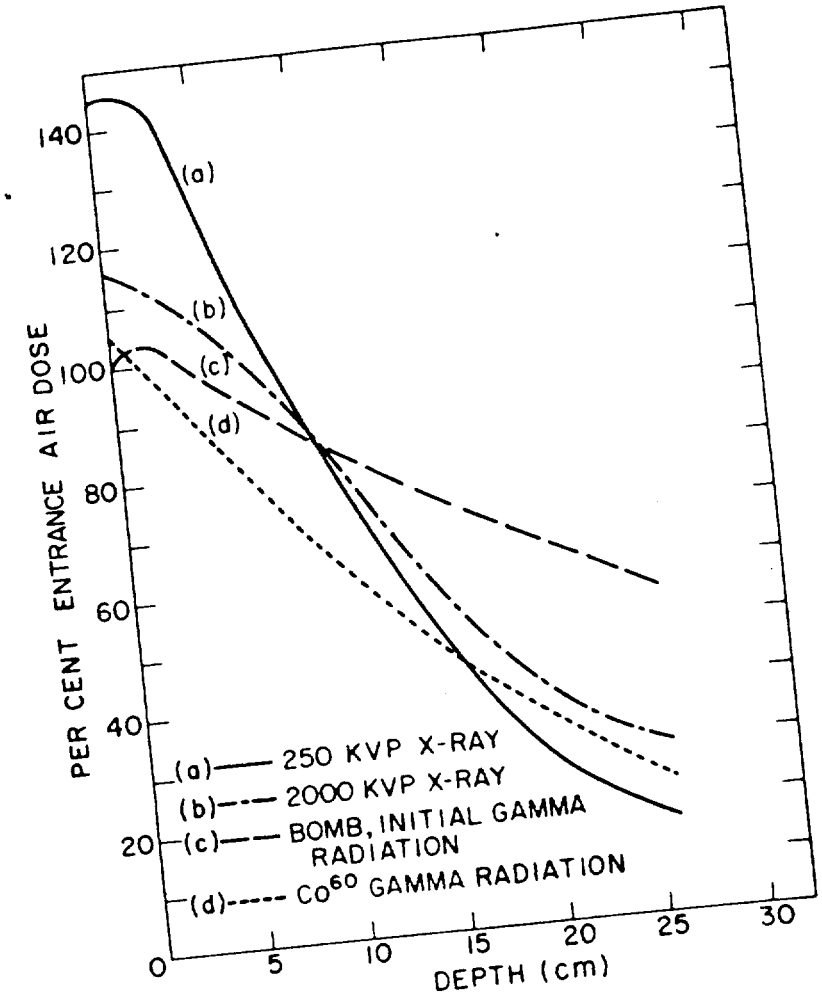

Figure 9. Comparison of depth-dose curves in Masonite phantom expressed as percent of entrance air dose for diverse sources of radiation from Bond et al. (34).

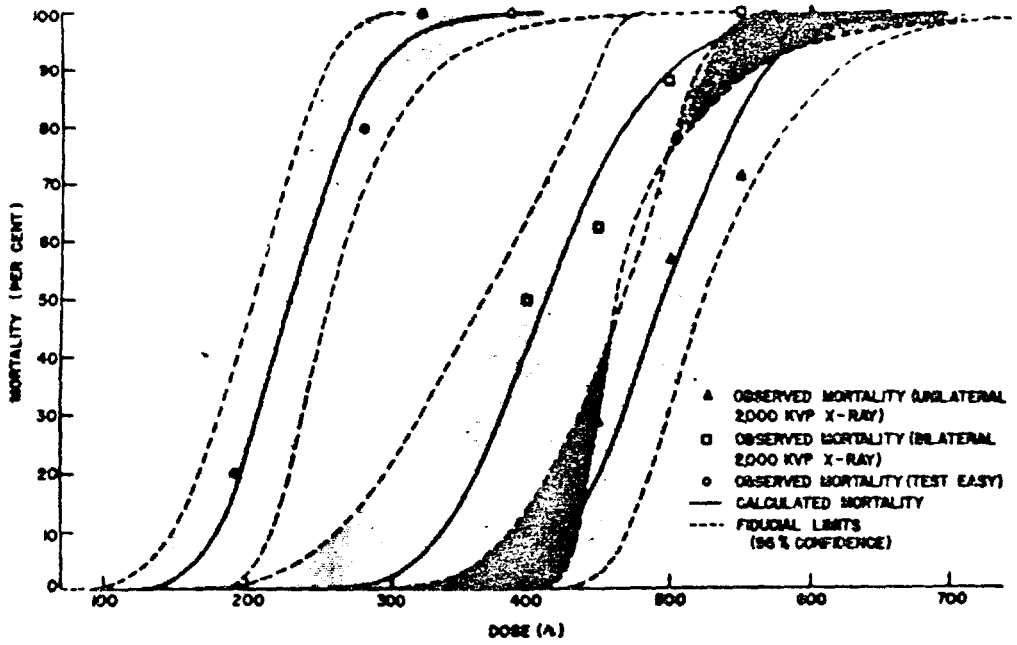

Figure 10. Radiation lethal dose curves for swine exposed to unilateral or bilateral 2000 kVp x ray and prompt atomic bomb gamma radiation.

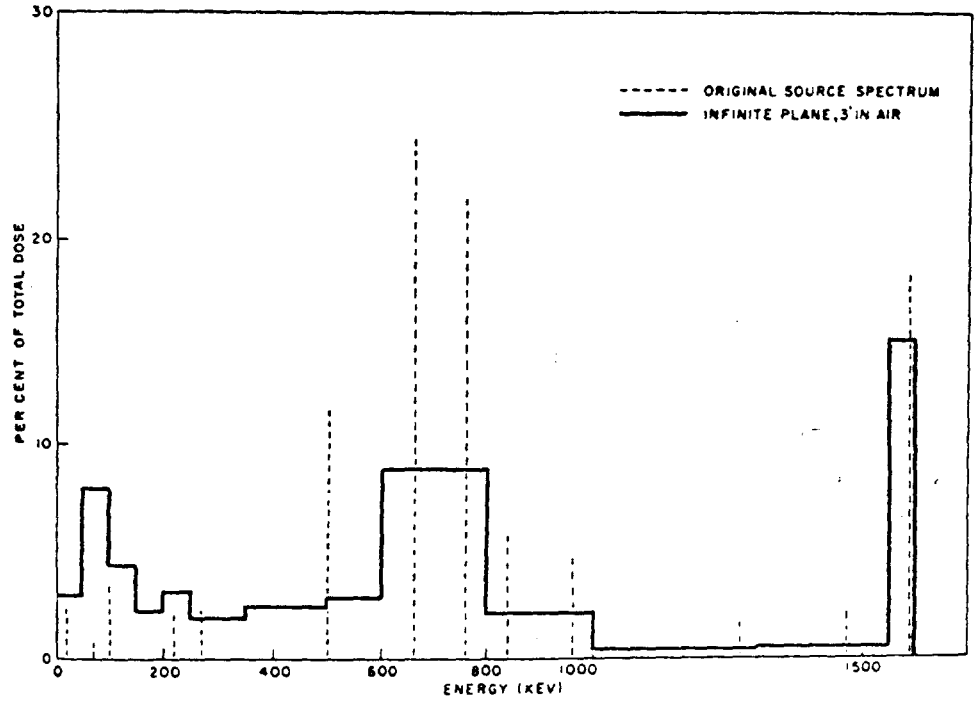

Figure 11. Inherent gamma emissions from fallout (mixed fission products) and the histogram of degraded energies produced by Compton scattering at level of infinite plane 3 feet in air above uniformly distributed fission products from Cronkite et al. (4).

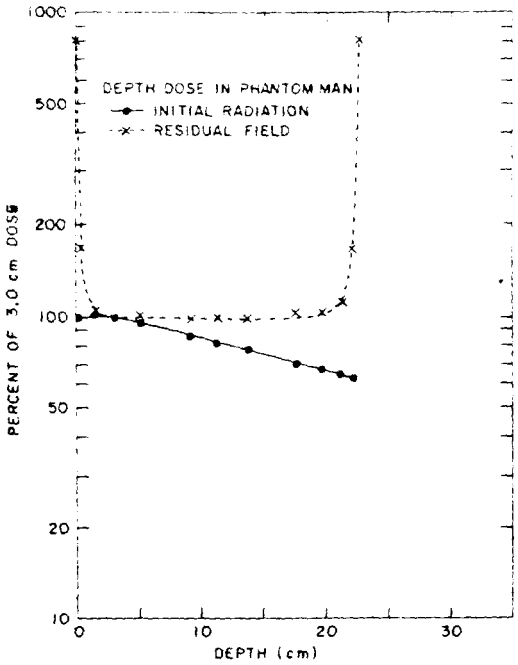

Figure 12. Depth-dose curves for fallout field and bomb gamma radiation. The dose is expressed as percent of the 3 cm dose because of the high beta component at the surface from Cronkite et al. (4).

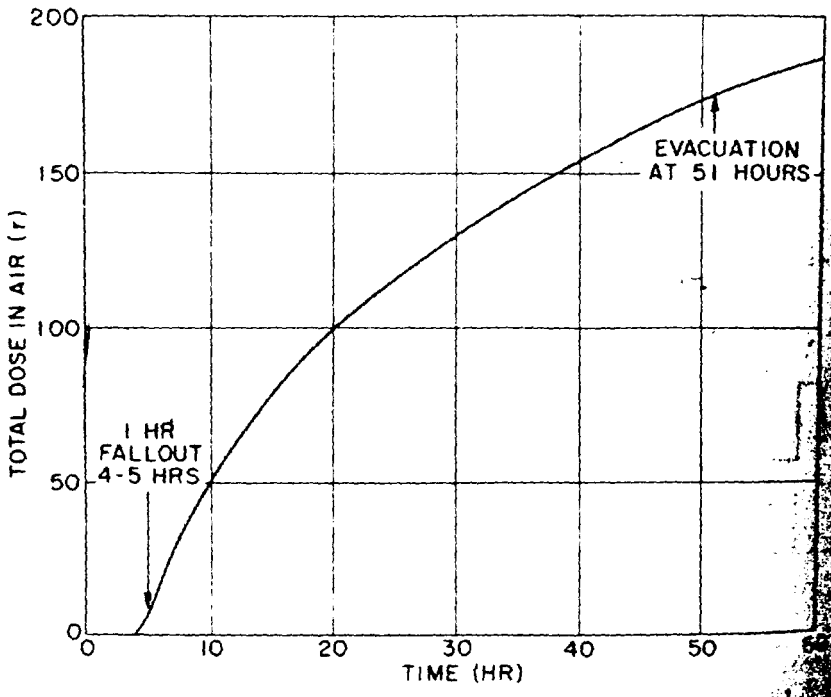

Figure 13. The accumulation of radiation dose in air as a function
after commencement of fallout on Rongelap from Cronkite

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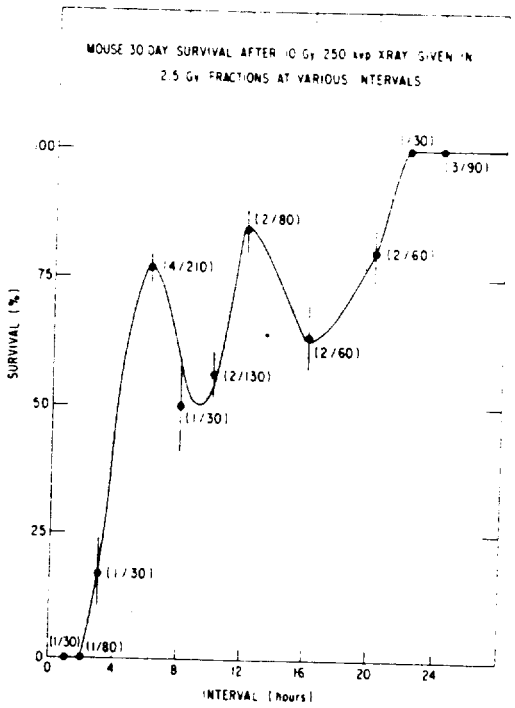
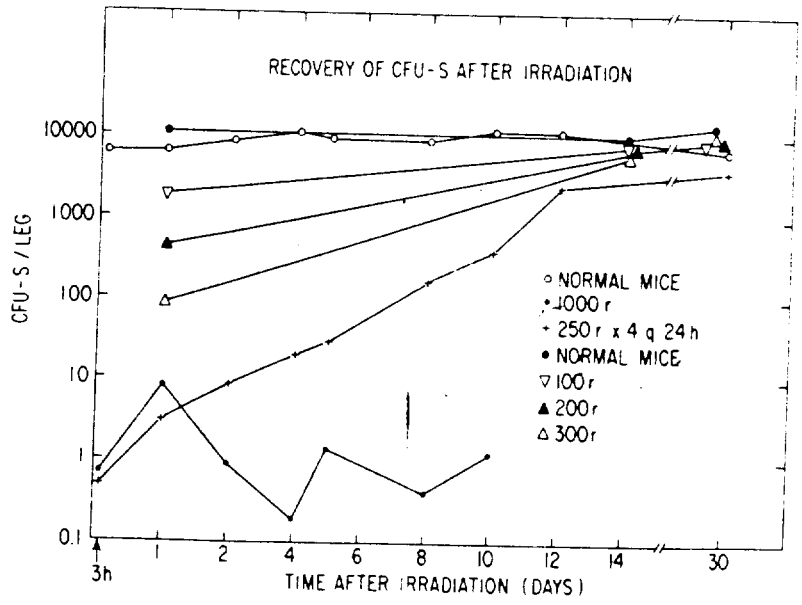


Figure 14. The percentage of mice surviving 30 days after exposure to 1000 rad given in increments of 250 rad at 1 to 24 hour intervals to illustrate repair of lethal injury.



15. The sequential changes in the 10-day CFU-S in control non-irradiated mice, mice exposed to 100,200,300 or 1000 rad in a single dose and mice exposed to 1000 rad given in increments of 2 5 rad at 24-hour intervals.