CHAPTER III
Biological Effects Of Ionizing Radiation

A. General Considerations

During the past 20 years much has been learned regarding the fundamental mechanisms of radiation damage of living organisms. Ionization produced in the living cell disrupts molecular and cellular processes. The disruptive processes are numerous and include enzyme inhibition, production of gene mutations and chromosome aberrations, breakage of molecular bonds and modification of DNA synthesis. Subsequent to exposure, repair processes intervene at all levels of biological organization. At the cellular level, for example, a number of subsequent divisions may occur, and some damaged cells may die while others may undergo repair. The cells composing the various tissues of an animal have different division rates, ranging all the way from a few hours for some epidermal cells to essentially no divison in the case of cells composing the adult nervous system. This leads to the general conclusion that acute or early radiation effects are usually a function of damage in those tissues composed of rapidly dividing cells. Chronic or delayed effects may be a manifestation of the accumulation of irreparable damage in all tissues. A number of theories have been proposed to explain both radiation induced irreparable injury, as well as natural aging. A prominent theory concerns the accumulation of somatic mutations as an explanation of the natural aging process and for the accelerated aging or life shortening observed in irradiated animals.[63-66] Although the accumulation of fundamental knowledge helps us understand how radiation damage may be produced, it is not sufficient at the present time to provide criteria on which to evaluate radiation risk in a complex living organism. In this case, it is necessary to rely largely on data obtained from observations of the effects of conventional radiation exposure on experimental animals and on man exposed accidentally or for medical purposes.

Radiation effects may be divided into two general categories: (1) somatic effects, and (2) genetic effects. Somatic effects are those manifested directly by the recipient of the radiation, in contrast to genetic effects which do not show up directly in the irradiated organism but rather in its progeny. Somatic effects (or more explicitly, their signs and manifestations) may be divided further into (1) early, and (2) late or delayed.

A clear appreciation of the difference between early and late somatic effects is extremely important in considering the radiation problems of space operations. Early effects are those producing signs and symptoms of radiation damage within minutes to 30 to 60 days subsequent to exposure. Manifestations of early effects occur only after relatively high doses (above about 50 rads) delivered at relatively high dose rates (several rads/hr) and increase in severity with increasing dose.

It is these early radiation effects that could produce death or decreased performance capability of a flight crew and thereby result in catastrophy or failure of the mission or both.

Late or delayed effects are those manifesting themselves only after many months or many years, and they appear to be probabilistic functions of the total accumulated dose. Such effects will have no bearing on performance capability of the crew and no influence on mission outcome except for very long duration missions. They are important, however, in considering the general life-time well-being of flight personnel and the actuarial risk of space flight as a career.

Early and late somatic effects, as observed in experimental animals and man exposed to the conventional radiations available on earth, are discussed in the following sections. It must be recognized that many factors inherent in the space radiation environment will tend to modify the quantitative dose-response relationships proposed.

B. Early Somatic Effects

Early effects or their evoked signs and symptoms · are occasionally referred to as acute or prompt and include, among other things, early lethality; destruction of the bone marrow; damage or destruction of the gastrointestinal tract and associated diarrhea, nausea, vomiting, and gastrointestinal hemorrhage; behavioral changes and central nervous system dysfunction; reddening, sloughing, and ulceration of the skin; loss of hair; and damage or destruction of the germinal epithelium resulting in drop in sperm count and sterility. Such responses are highly dose rate-dependent below a few rads per minute, and the critical doses required to produce early signs of radiation damage at these intermediate dose rates are not known specifically. In general, the higher the dose (and dose rate in the intermediate range), the more pronounced the effects and (beyond certain critical latent periods) the earlier the time of onset.

Since unimpaired human performance is essential for mission success, the latent period between radiation exposure and appearance of signs and symptoms will influence the probability of mission success in the event of an emergency exposure. It is important, therefore, to recognize that some signs of early effect appear much sooner than others. Those signs which appear within minutes to hours after exposure include the prodromal reaction (nausea, vomiting, diarrhea, fatigue), skin erythema, and (at very large doses) acute central nervous system (CNS) dysfunction. Manifestations that appear later than several hours, but still within 30 to 60 days after an exposure, may include death, hematopoietic depression or destruction, and

associated phenomena (interstitial hemorrhage, infection, fever), destruction of gastrointestinal mucosa, skin desquamation, epilation, and sterility.

In contrast to late or delayed effects, signs of early effects appear as threshold phenomena (i.e., the total dose must reach some critical level before signs and symptoms of radiation damage become evident). For the most part, if signs do not appear within 60 days after exposure, the threshold dose for manifestation of early effects has not been exceeded. The dose absorbed under these circumstances then adds some increment of injury to the total of the delayed effects.

1. EARLY LETHALITY

All doses of radiation, from very large ones to infinitely small ones, may be considered lethal in that such doses are assumed to increase the probability of death. However, based on time after exposure, two separate divisions of radiation lethality are apparent. Early lethality is arbitrarily chosen as death within 30 to 60 days where a particular death can be ascribed to a specific radiation dose. The second division includes all deaths occurring beyond 60 days after an exposure regardless of whether signs of radiation damage did or did not occur during the 60-day period. In the latter case, the dose contributes to the actuarial life shortening risk of the exposed individual in the sense of a delayed effect.

A quantitative dose-response relationship for early lethality (death within 60 days) in man is not known. Of most critical interest is the relationship over the range of hematopoietic death (destruction of the bone marrow), which is about 200 to about 1000 rads. Grahn[67] and Supron[68], among others, have proposed hypothetical curves representing the probability of death in man as a function of hard X- or gamma-ray dose. Such curves are usually derived by presuming an LD^{60}_{50} dose (that dose which will produce death of 50 per cent of a population sample within 60 days) on the basis of animal experimentation and available human observations and assuming a Gaussian distribution of death versus dose about the LD_{50} value. Opinions as to the LD_{50} of penetrating electromagnetic radiation for man range from about 250 to 700 rads. Cronkite and Bond[69] considered the LD_{50} for man through analogy with the hematological observations of the Marshallese exposed to nuclear fallout in 1954 and the general response of all mammals to acute lethal doses of highly penetrating rays. They concluded that the near maximal sublethal dose for man was in the vicinity of 200 rads and that the LD_{50} might be about 360. Harris[70] derived an LD_{50} from the Japanese atomic bomb casualties on the basis of calculated dose as a function of distance from point of detonation and postulated an LD_{50} of 700 rads ± 25 per cent. This value is not generally accepted because of the possibility of absolute errors in dose estimates. He was able to derive a relative dose-lethality relationship, however, which should be less dependent on absolute errors in dose calculation. Three renowned committees have published opinions as to the LD_{50}

for man. The United Nations Scientific Committee on Effects of Atomic Radiation[71] reported their best estimate of the acute LD_{50} for man was 300 to 500 rads. The National Academy of Sciences-National Research Council Committee on Biological Effects of Atomic Radiation[72] estimated 400 to 600 rads, and the National Committee on Radiation Protection and Measurements[73] chose an LD_{50} of 450 rads. Figure III-1 shows the probability of death as a function of acute radiation dose derived merely by normalizing the relative dose-mortality distribution reported in the Japanese atomic bomb casualties through the extremes of the LD_{50} estimates reported by the United Nations and NAS-NRC committees. Although this figure is almost entirely hypothetical, it represents the best judgment of the outstanding authorities on the biological effects of radiation. The heavily shaded area representing the region of overlap of the opinions of the two committees may be used to narrow the spread when applying the relationship to a selected age group of 25 to 44 years. It may be of some significance that the spontaneous death rate in this age group from all causes other than suicide and accident is 0.127 per cent (127 deaths/100,000) per year.[74] The estimated 60-day death rate in this age group would be 0.02 per cent. When the probability function in Figure III-1 is extrapolated to zero radiation dose, the 60-day probability of death (excluding accidents and suicide) from radiation exposure is greater than the estimated spontaneous death rate by only a factor of approximately 2.

According to Figure III-1 the LD_{50} dose of acutely delivered (over 24 hours or less) whole-body penetra-
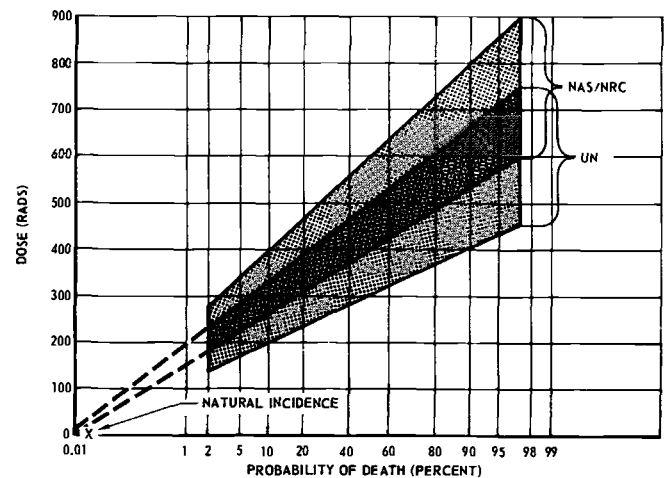

Figure III-1. Probability of early lethality in man as a function of acute whole-body dose of highly penetrating electromagnetic radiation.

ting electro-magnetic radiation for healthy adults lies in the range of 400 to 500 rads and that the probability of death (within 60 days) from a dose of 200 rads may be of the order of 1 to 3 per cent. On the same basis, a 95 per cent probability of death may result from a radiation dose of 575 to 700 rads.

Animal experiments show that early death from a-cute effects is not produced to any significant extent

by X- or gamma-ray doses below about 200 rads. Above 200 rads, mean survival time and the mode whereby lethality is produced are dependent on the magnitude of the dose.[75,76]

The relationship between survival time and whole-body exposures of mice, rats, and monkeys for doses between 400 and 40,000 rads is shown in Figure III-2.
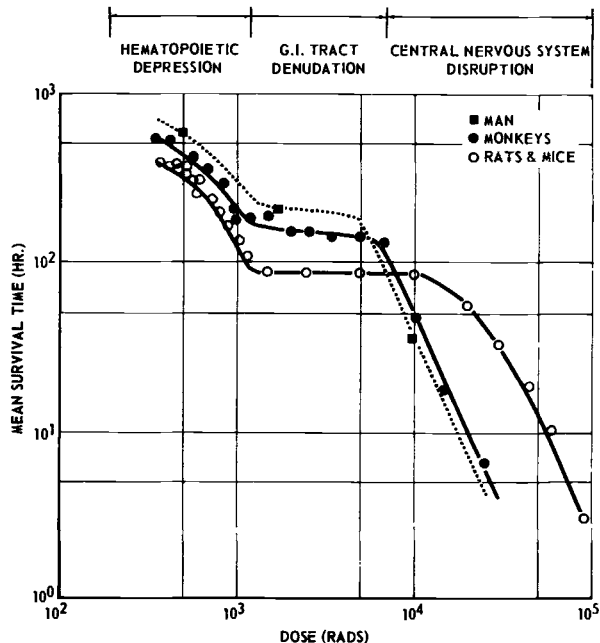

Figure III-2. Relationship between acute whole-body dose of penetrating electromagnetic radiation and median survival time of mice, rats, monkeys, and presumably of man.

Not all animals that received doses of less than 700 to 800 rads died within 30 to 60 days, which was considered the limit of early lethality. The mean survival times given are for those animals dying within this period. The data points represent averages for several animals. When applied to an individual animal, the uncertainty in survival time may be as much as a factor of 3. The primary purpose of showing these data is not to predict survival time but rather to point out the various modes of death as an adjunct to the understanding of acute radiation lethality and its dose dependence. Figure III-2 shows three distinct regions. The first region covers the dosage range of from about 400 to 1200 rads, over which survival time decreases exponentially with increasing dose. This region is frequently referred to as the region of hematopoietic death because bone marrow depression (and complete destruction at the higher doses) is the most prominent characteristic of the radiation syndrome, both clinically and pathologically.

Designation of this range as the region of hematopoietic death is not intended to imply that damage to other tissues does not contribute to death. Even in this region, nausea, vomiting, and diarrhea (signs of gastrointestinal dysfunction) are prominent signs that increase with increasing radiation dose. Bacteremia contributes heavily to lethality which may be associated both with hematopoietic destruction and gastrointestinal damage. The increasing contribution

of gastrointestinal damage to death is undoubtedly in part responsible for the exponential decrease in mean survival time with increasing dose over this range.

Throughout the dosage range of about 1200 to about 5000 to 10,000 rads, there is a plateau in the mean survival curve. This plateau is commonly referred to as the region of gastrointestinal death. Again, the designation is based on the most prominent pathological and clinical characteristics of the syndrome. Pathologically, there is a progressive loss of gastrointestinal mucosa secondary to arrested mitosis of the basal cells of the epithelium. Gastrointestinal tract damage may progress to the stage of interstitial hemorrhage, bloody diarrhea, bacteremia, and extensive ulceration (especially in the stomach and lower bowel). In this dosage range, bone marrow is completely destroyed and other tissues severely damaged; it seems, however, that damage to the gastrointestinal tract is the limiting factor of survival.

Above 5000 to 10,000 rads (depending on species), mean survival time again begins to decrease with increasing dose, and death is accompanied by progressively increasing signs of central nervous system involvement. Thus, this region of the survival curve is referred to as the region of central nervous system death. Incapacitation occurs relatively rapidly to almost immediately (depending upon the dose), from which there may be partial recovery followed by lapse into coma and death in a few hours. Frequently periods of coma are interrupted by fits of violent activity, terminating in attacks of clonic and tonic convulsions.[75] The dotted curve in Figure III-2 shows a very tenuous guess as to man's survival response to increasing doses of acute penetrating radiation. The Los Alamos Scientific Laboratory has experienced three fatal criticality accidents,[77,78] one in the dosage range of each of the regions of death. The respective doses were about 600, 1700, and 10,000 rads (in the latter case, largely to the head and upper two-thirds of the torso). The curve was drawn merely by assuming man's response would parallel qualitatively that of monkeys and that the three survival times were quantitatively representative of the three regions of death. Obviously, the curve has no real validity but the guess is probably as good as anyone can make on the basis of present knowledge.

2. EARLY SUBLETHAL EFFECTS

Acute radiation exposures which do not result in early lethality either because of the size of the dose, quality of the radiation, or exposure conditions (e.g., partial-body exposure) produce signs of early radiation effects. The severity and time of occurrence of such effects may determine the time and degree of functional decrement of a space crew. The probabilities of mission success of a manned space system are, in turn, influenced by these factors. If the probability of extensive performance decrement is high, its duration long, and the time to onset short, the probability of

mission success is diminished accordingly.

Early sublethal effects differ considerably in their influence on human performance capability for a given degree of severity. The hematopoietic effects, prodromal symptoms, and certain skin effects such as erythema and necrosis will influence human performance extensively as a function of the degree of severity. On the other hand, such effects as those of epilation, loss of fertility, and changes in emotional state or certain sensory functions should have little or no direct influence on performance. The severity of their effects may be great but, because no debilitation or malaise is experienced, performance will not be directly affected.

Sublethal early effects are discussed in what may be their relative order of potential importance in manned space operations.

a. Initial or Prodromal Reaction (Radiation Sickness)

Radiation sickness is a general term used to designate the combination of signs and symptoms (loss of appetite, listlessness, apathy, nausea, vomiting, fatigue, etc.) observed shortly after acute radiation exposure. More explicitly, these early manifestations may be referred to as the initial or prodromal reaction.

Unfortunately, the initial reaction is one of the most difficult of the early responses to evaluate quantitatively in relation to radiation dose, and yet it may be potentially the earliest and one of the most likely factors to produce a decrement in human performance capability. Individual susceptibility, which cannot be predetermined, is a prime factor in determining the dose at which the prodromal reaction may appear, as well as its severity and duration. Individual susceptibility undoubtedly is influenced by psychological or nervous condition and may be influenced by body size and general state of health.[79] In addition to individual susceptibility and dose, other factors influencing initiation, severity, and duration of the reaction involve areas and organs or regions of the body exposed.

Gerstner[80] reviewed the subject of man's reaction to short-term radiation and found that, despite the variables involved, the prodromal reaction follows a rather definite pattern. Figure III-3 shows his conception of the expected dose-severity-time pattern (as evidenced by nausea and vomiting) evoked in a population group exposed to acute doses of penetrating radiation expressed in rad units. Although the dose-incidence-time relationships are conjectural in many details, the figure depicts several well established characteristics of the syndrome. After a short asymptomatic latent period, there begins a growing feeling of fatigue, which may be accompanied by mental depression and emotional disturbance. Almost simultaneously, gastrointentinal distress develops which may progress to nausea, retching, and vomiting, reaching a maximum in severity in about 4 to 6 hours after exposure. After reaching a maximum, the condition begins to improve rapidly. The degree of upset and length of the recovery period are dependent on the dose and the individual sensitivity of the subject. In

moderately severe cases, fatigue and episodes of nausea and vomiting may persist into the second day. On the third day most of the symptoms disappear, the expected sequence of disappearance being vomiting first, followed in order by nausea, fatigue, and finally anorexia.

If a short-term dose of radiation is high enough to evoke the reaction at all, there is better than a 90 per cent probability that signs and symptoms will appear between 1 and 5 hours post exposure. If the dose is of sufficient magnitude to elicit the response, the time of onset and time of maximum severity will show relatively little dependence on dose or on the surface area or volume of the body exposed.

Before attempting to discuss any possibility of a dose-probability relationship, it is necessary to consider the influence of mass, area, and region of the body exposed. Total-body exposure is perhaps little more effective than exposure of certain specific regions or areas composing relatively small fractions of the total body mass. When applied to various regions, equal doses elicit reactions which are identical in kind but different in degree of severity; hence, ease with which the distress is evoked depends on the topographic area exposed. This is of considerable potential significance to the space radiation problem, where exposure will certainly be nonuniform both with respect to body area exposed and depth-dose distribution. There is wide divergence of opinion as to the mechanism whereby irradiation of a localized region or area can produce a generalized sickness. Court Brown and Mahler[81] suggest the production of a diffusible toxic factor. Wallace[82] has suggested direct effects on the gastrointestinal tract and other organs in the radiation field, and Jenkinson and Brown[83] postulate local and generalized increase in capillary perme-
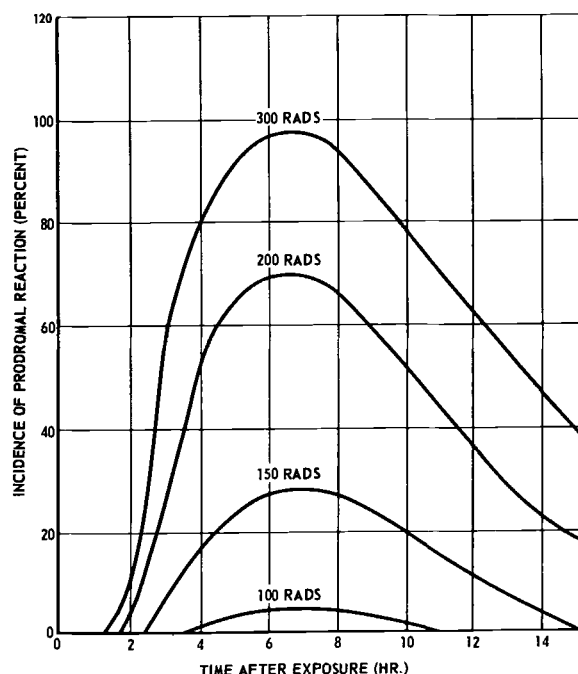

Figure III-3. Time-course and severity of prodromal symptoms in man in relation to acute radiation dose. (Modified from Gerstner.[80])

ability (confirmed by others[54]) and thereby a relationship between sickness and the vascularity or size of the capillary bed in the tissues exposed. Others propose choline poisoning[85] and histamine release.[86-88]

Although there is little agreement on the mechanism of production of radiation sickness, there is general agreement on relative sensitivity of gross body areas. It seems generally agreed that the trunk is the critical region and that sensitivity over the trunk is greater in the epigastric region and drops off toward the head, as well as toward the thighs.[89-91] Groedel and Lossen[92] reported that the same dose that induces the prodromal reaction in 50 per cent of patients when applied to the abdomen causes a 33 per cent response when applied to the thorax, 25 per cent when applied to the head and neck, and no effect when applied to the extremities.

What is needed for space applications is a quantitative relationship between the radiation dose and the probability of significant prodromal reaction. One approach to this problem is to employ the mean integral dose as the measure of absorbed radiation. Court Brown and collaborators[79,81,93] have studied the relationship between integral dose and time of onset of the initial reaction, which is to some degree an indicator of severity, since usually the earlier the time of onset the greater the distress.

In 25 patients irradiated along the spine and over the sacroiliac region, Court Brown and Abbatt[79] found no correlation between the integral dose in megagram roentgens (220 to 250 KVP X-rays) and time of onset (and inferred severity) of symptoms. The same lack of correlation was true among 15 subjects receiving radiation to the pelvis. For both anatomical regions, there was a strong correlation with surface or midline dose, with the pelvic region being much less sensitive than the spinal area. In both situations, there was also a strong correlation with body size, the larger the body size and surface area the less severe the reaction. They concluded that integral dose alone cannot be correlated with the severity of radiation sickness and that expression of dose should be qualified by the level of dose

received in specified organs and tissues of known sensitivity.

At present any attempt to establish a dose-probability relationship for incidence of the prodromal reaction will be largely hypothetical and based on a few semiquantitative observations and opinions. Deductions from observations of the Japanese atomic bomb casualties, victims of nuclear accidents, and the experiences of the medical profession with therapeutic radiation have led to the opinion that essentially 100 per cent of all people receiving whole-body exposure equivalent to 300 r of penetrating radiation will experience acute radiation sickness.[94,95] These same sources led to the opinion that a very few subjects (perhaps 1 to 5 per cent) receiving exposures of 100 r may show mild prodromal response. Miller, Fletcher, and Gerstner[96] observed nausea and vomiting in 17 of 30 patients (57 per cent) who received a whole-body exposure dose of 200 r of 250 KVP X-rays. Eighty per cent showed signs of the initial reaction. Seven out of 12 patients receiving exposures of from 125 to 175 r showed signs of initial reaction also. Twenty out of 21 spondylitis cases (97 per cent) who received exposure doses of between 200 and 400 r (average 275 r) of X-rays to the sacroiliac joints and the spine showed a prodromal reaction, and 57 per cent experienced vomiting.[93] The area exposed was about 600 cm² and represented about 10 per cent of the surface area of the trunk. Had the entire area of the trunk been irradiated (as in whole-body exposure), incidence of vomiting probably would have been somewhat higher.

The general opinions expressed in numerous therapeutic radiology reports led to the impression that exposure doses of from 150 to 200 r over regions of the trunk or abdomen will elicit a prodromal reaction in about 50 per cent of exposed patients.

On the basis of the foregoing discussion, one may hazard the intuitive guess shown in Figure III-4 as to the probability of an individual showing prodromal symptoms during the first few hours following acute exposure. In making such a guess, it was assumed that whole-body exposure and exposure over a substantial
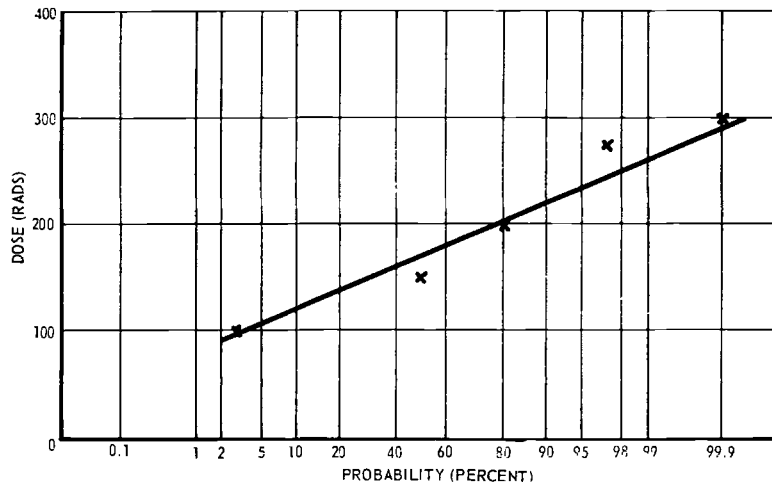

Figure III-4. Conjectural dose-response probability relationship for prodromal response to acute radiation exposure.
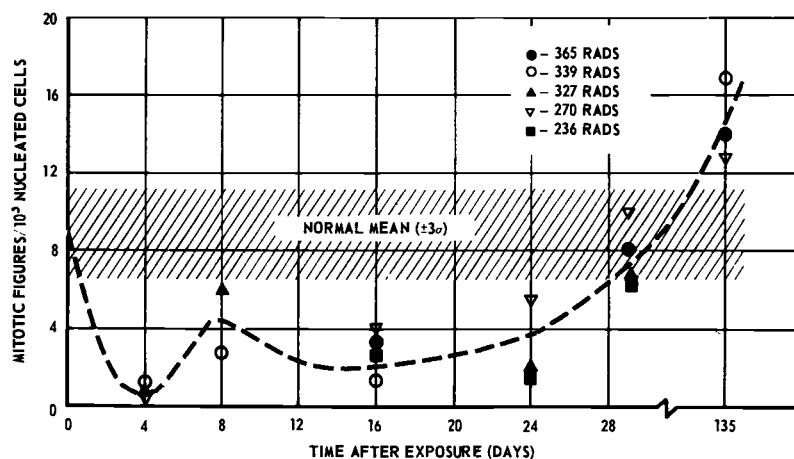
Figure III-5. Time-course of the bone marrow mitotic index of the more heavily exposed Oak Ridge accident cases.[110]

area of the trunk or abdomen are essentially the same. It was assumed also that 99.9 per cent of all subjects exposed to 300 r will show acute radiation sickness and that this is compatible with the general expression that essentially 100 per cent of all so exposed will become sick. Furthermore, it was assumed that the exposure doses expressed in roentgens could be converted directly to tissue dose on the basis of 1 r = 1 rad. Any reference to Figure III-4 should take into consideration the tenuous and hypothetical nature of these assumptions and the inadequacy of pertinent data.

b. Hematopoietic Depression

The hematological effects of acute whole-body radiation exposure have been studied extensively. Observations of effects in man have been made on the Japanese atomic bomb victims,[97,98] the Marshallese natives exposed to nuclear fallout,[99,100] reactor and criticality accident cases,[77,78,100-105] therapeutically irradiated cancer patients,[96] and patients exposed for other medical reasons.[106-109]

Acute whole-body doses greater than 50 to 100 rads may produce detectable changes in the cellular elements of the peripheral blood. The response seen in the circulating blood is a manifestation of bone marrow aplasia due to marrow cell destruction and mitotic inhibition. The effect of acute radiation exposure on the proliferative activity of the bone marrow of the Oak Ridge Y-12 criticality accident cases[102] was demonstrated by Fliedner et al.[102,110] through serial determinations of the mitotic index. The average mitotic index (which is the fraction of nucleated cells in mitosis at any given time) of normal adult bone marrow was found to be 8.97/1000. Figure III-5 shows the mitotic index for the most heavily exposed accident victims (236 to 365 rads) as a function of time after exposure. At these doses, there definitely was a significant drop in the mitotic index by the 4th day after exposure. Thereafter, there was possibly an abortive rise around the 8th day and a second minimum on about the 15th day. At 29 days, the mitotic index was still below

but within 3 standard deviations of the mean. At 130 days after exposure, the mitotic index had risen to more than 3 standard deviations above the mean. These observations show conclusively a direct effect of acute radiation exposure on the proliferative activity of human bone marrow.

Radiation depression of hematopoietic function has been studied largely via observations on the circulating blood rather than direct observations of the marrow. A slow progressive drop in the red blood cell count, hematocrit, and hemoglobin values occurs following total-body doses in excess of 100 to 200 rads, reaching a minimum in about 30 to 40 days after exposure. A return to normal may occur in about 60 days. Doses in the vicinity of 400 rads or greater may be required to produce a 50 per cent drop in erythrocytic values.

Thrombocyte (platelet) levels in the circulating blood drop also as a result of radiation exposure. They tend to remain rather stationary or show an initial rise during the first 8 to 10 days. Beyond the 10th day, the platelets drop progressively to a minimum between 20 and 30 days after exposure. A return to normal or above normal values occurs between the 40th and 50th days. As with some of the other elements of the peripheral blood, there is a tendency for the platelet values to return to normal or above normal levels much more rapidly with high doses (about 250 to 300 rads) than with lower doses. Data do not seem adequate to justify an attempt to establish a dose-time-thrombocyte response relationship. Within broad limits, however, the higher the dose the lower the thrombocyte count. With doses of about 300 rads, the count may drop from a normal level of 2.5 x 10^5 per mm^3 to a minimum of about 15 per cent of normal.

The white cell elements of the peripheral blood are among the most sensitive indications of acute radiation exposure. Figures III-6 and III-7 show idealized curves for the time-course of mean total leucocyte and lymphocyte counts, respectively, in relation to dose. Although idealized drastically, the solid portion of each curve is by no means hypothetical, having been derived from the human data reported in Refs. 77, 78, 96, 99, 102-106. Although the general pattern is the same,

the time-course of white cell response following acute radiation exposure seems to be somewhat different for criticality accidents and for uniform whole-body radiation given for medical purposes. In the former case, the changes do not seem to occur quite as rapidly nor are they as drastic for supposedly equivalent doses. Figures III-6 and III-7 include some data from both
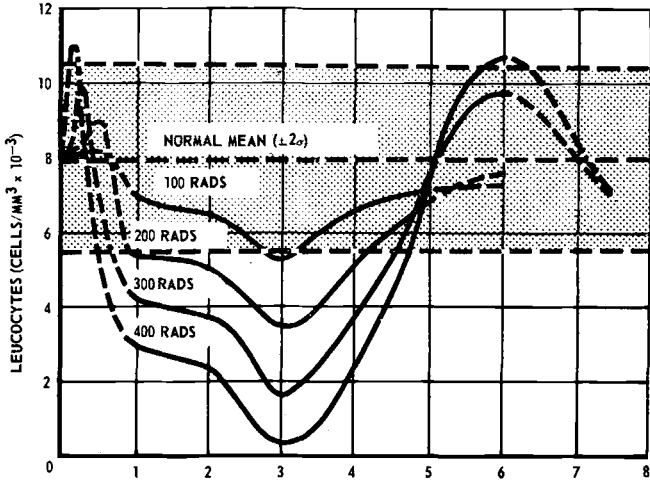

Figure III-6. Idealized time-course of mean total leucocyte count in relation to radiation dose. (Derived from pooled accident and medical exposure data.)

types of exposure. Possible explanations for these observed differences may be greater nonuniformity of dose distribution, quality and nature of the radiation, the usually higher dose rates accompanying the accidental exposures, and the difference in health of the individuals involved.

The figures were derived from individuals for which adequate data were available, and a weekly average cell count was calculated. A scatter diagram of cell count versus dose was made for each week (1 through 7) and the best fit line determined by the method of least squares. The least squares fits were then normalized to the normal adult population mean cell count at zero dose. The cell counts as a function of time for doses of 100, 200, 300, and 400 rads were then read from the normalized weekly graphs and plotted. The technique could not be applied beyond 5 weeks for doses below 200 to 250 rads and beyond 7 weeks for higher doses. Obviously, the curves represent only crude averages, but they do portray generally the time-course of cell counts as a function of radiation dose. However, it is to be noted that the minimum cell counts
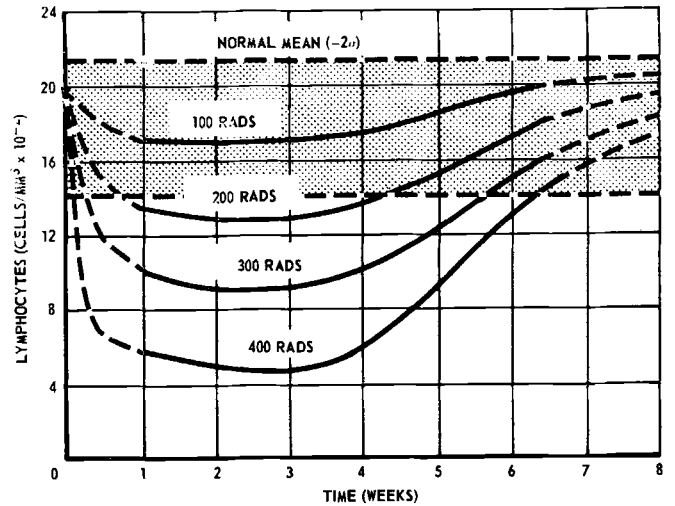

Figure III-7. Idealized time-course of the mean lymphocyte count in relation to radiation dose. (Derived from pooled accident and medical exposure data.)

have been shifted from approximately 4 weeks to 3 weeks after exposure, where the fourth week minimum is the usual one shown for accident cases.

Following radiation exposure, the leucocyte count may actually increase (especially at higher doses) during the first 1 to 3 days, after which it drops to a first
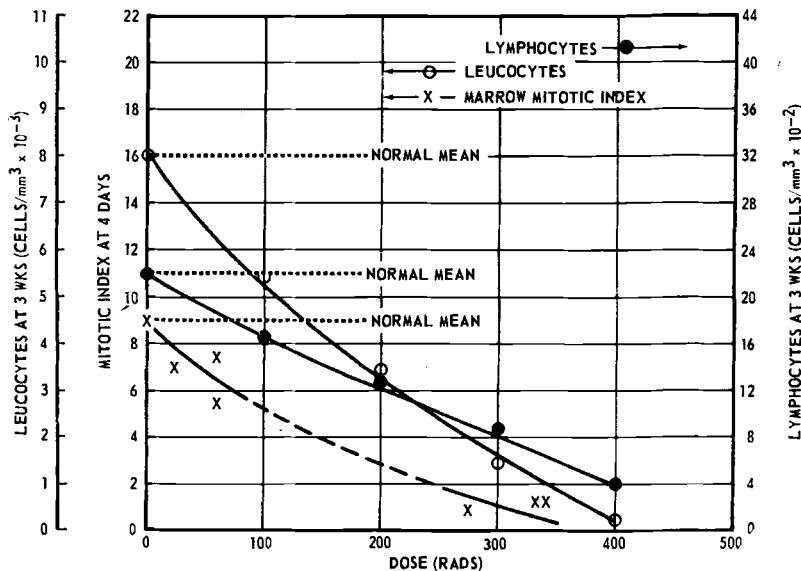

Figure III-8. Dose-response relationships for mean leucocyte and lymphocyte counts and for bone marrow mitotic index.

minimum on about the 5th to 7th day. It then levels off (or may tend to increase) until about the 14th to 16th day, after which it drops to an even lower minimum at about 3 to 4 weeks. The second minimum is terminated with a rapid recovery which seems more pronounced with doses in excess of 250 to 300 rads. With the higher doses, the leucocyte count may actually reach levels considerably above normal by the end of the 6th week, after which it may drop below normal again, suggesting an undulating course of recovery. With doses below about 250 rads, the leucocyte count appears to rise less rapidly and may remain in the low normal range for many weeks or even months after exposure.

The lymphocyte count is dose-dependent and starts dropping almost immediately after radiation exposure, reaching a minimum in about 3 to 5 days and essentially remains at that level until it is well into the 4th week. During the 4th week, recovery begins and normal values are approached in about 6 to 9 weeks, depending on the dose.

The information given in the two previous figures may be used to develop a general dose-response relationship for the total leucocyte and lymphocyte counts following acute radiation. Figure III-8 shows the 3- to 4-week minimum leucocyte and lymphocyte values read from Figures III-6 and III-7 plotted against dose. The 4-day minimum mitotic index of the bone marrow of the Oak Ridge accident cases as reported by Fliedner et al.[110] is shown also. These relationships have little value when applied to an exposed individual. The inherent day-to-day and individual fluctuations in cell counts (as indicated by the standard deviations of the normal means given in the three previous figures) preclude their use as a biological dosimeter or a precise indicator of the degree of radiation damage. While the relationship between hematopoietic depression and radiation status of the individual as it may relate to performance capability cannot be evaluated, maintenance of a normal or near-normal blood picture may be essential to the general well-being of a flight crew. Furthermore, the relatively low threshold and the uncertain repair process for hematopoietic damage make such manifestations of concern especially with regard to the possibilities of progressive hematopoietic deterioration as a result of a series of randomly repeated acute and semi-acute exposures superimposed on a continuous low-level ambient background.

Despite their limitations, radiation-induced changes in the various elements of the blood are believed to have considerable prognostic value.[111] The lymphocyte count is valuable as an early criterion of radiation injury. If there are 1200 or more lymphocytes per mm³ at 48 hours after exposure, it is unlikely that the individual has received a fatal dose. Counts in the vicinity of 300 lymphocytes per mm³ indicate serious exposure that could terminate in fatality. The total white and granulocyte counts may be of value in following the progress of a radiation exposure case, as well as signifying in a general way the degree of seriousness of the exposure.

c. **Early Skin Effects**

Early signs of radiation effects on the skin may occur with sublethal doses when exposure is localized or is from radiation of low penetrability. The skin, being the outermost organ of the body, absorbs all of the soft components of the radiation. For this reason, early effects on the skin may be particularly significant to manned space operations. This is especially true for those operations outside the protective shielding of the spacecraft, resulting in exposure of the skin to the softer components of the Van Allen belt radiations or to lower energy solar flare protons. The high energy alpha particle component observed in some solar flares may be significant in considering skin exposure.

The first sign of radiation damage to the skin is the development of erythema (resembling sunburn), which increases in sharpness with increasing dose. After sufficiently high doses, a series of specific reactions are observed to follow each other, often overlapping to some extent in their occurrence. In chronologic order, they are erythema (which may disappear and reappear periodically), epilation, bleb formation, sloughing of skin layers, and finally repair and pigmentation.[112] Although of lesser physiologic importance, epilation is one of the most dramatic early signs of radiation damage of the skin. A dose of as little as 200 rads of soft radiation may produce temporary loss of hair, the scalp and beard being the most sensitive. Epilation begins in 13 to 17 days after exposure and, depending on the dose and quality of the radiation, may progress to complete baldness. Regrowth of hair may be virtually complete in 3 to 6 months unless the dose was in excess of about 2000 rads, which may result in permanent epilation.

The majority of observations of early skin effects are for low and intermediate energy X-ray exposures measured in air, and in most cases it is possible only to convert crudely from exposure dose in r to tissue dose in rads at the depth of interest. Duffy, Anderson, and Voke[113] and MacComb and Quimby[114,115] used a minimal skin reaction threshold to study rate of recovery of human skin from acute radiation exposure. The standard threshold exposure dose was defined as that quantity of radiation which, when delivered in one exposure, produced in 80 per cent of subjects a very slight erythema[113] or delayed pigmentation.[114,115] The standard threshold exposure dose of 200 KVP X-rays (0.5 mm copper filtration, 50 cm target-skin distance, dose rate 40 to 60 r/min) was 525 r when delivered to a 70-cm² area[115] of the forearm. A compromised attempt to convert air dose to skin dose[116] suggests a threshold for very slight erythema of about 650 to 700 rads under the conditions specified. Using the same quality of radiation, essentially the same exposure conditions (except for area of 4 cm²), and an erythema meter to measure intensity of reaction, Reisner[117] found the threshold exposure dose for a very sharp erythema was 1000 r (about 1050 rads). Jolles and Mitchell[118] reported the single exposure "tolerance" dose of filtered 180 KVP X-Rays (HVL 1.25 mm copper, FSD 40 cm,

TABLE III-1. EFFECT OF BETA RAYS ON THE SKIN OF THE PIG AS A FUNCTION OF ENERGY AND INTENSITY OF RADIATION

Isotope	Max. Energy (Mev)	Ave. Energy (Mev)	Ave. Half Value in Tissue (μ)	Threshold of Recognizable Transdermal Injury		Threshold of Atrophy and Chronic Inflammatory Changes	
				Surface Dose (rads)	Dose at 90 μ (rads)	Surface Dose (rads)	Dose at 90 μ (rads)
S^{35}	0.17	0.05	40	2×10^4	1.2×10^3	$> 4 \times 10^5$	....
Co^{60}	0.31	0.09	86	4×10^3	1.6×10^3	$5\text{-}6 \times 10^3$	$2\text{-}2.4 \times 10^3$
Cs^{137}	0.52	0.23	170	2×10^3	1.7×10^3	$2.5\text{-}3 \times 10^3$	$2.1\text{-}2.5 \times 10^3$
Y^{91}	1.60	0.62	610	1.5×10^3	1.2×10^3	$\cdot\ 2.5\text{-}3 \times 10^3$	$2\text{-}2.5 \times 10^3$
Sr^{90}	0.54	0.20	170⎱	1.5×10^3	1.4×10^3	$2\text{-}2.5 \times 10^3$	$1.8\text{-}2.3 \times 10^3$
Y^{90}	2.24	0.93	870⎰				
Average dose at 90 μ depth					1.4×10^3		$2\text{-}2.4 \times 10^3$

exposure area 100 cm²) for production of moist desquamation (which could be healed with routine dressings within 4 weeks) as 1540 r. This would correspond to a tissue dose of about 2000 rads.

Wirth and Raper[119] estimated the first-degree reaction (mild erythema) threshold dose of P^{32} beta rays (average energy 0.6 Mev) at 635 rads and the second-degree (slight vesicance) threshold at about 1200 rads. Robbins et al.[120] reported observations on 6 men with accidental skin burns (over relatively large areas) produced by scattered electrons from a 1.2-Mev electrostatic generator and estimated the dose-producing second-to-third degree reactions at 1000 to 2000 rads. The observations of Moritz and Henriques[121] on effects of beta particles from S^{35}, Co^{60}, C^{137}, Y^{91}, and Sr^{90}/Y^{90} on the skin of pigs (anatomically and functionally quite similar to human skin) are summarized in Table III-1 and are particularly applicable to a consideration of the influence of radiation quality and intensity on skin effect.

The degree of effect in the skin quite naturally is dependent on the depth-dose distribution in relation to the critical cells and structures composing the organ. Radiations which do not penetrate the thickness of the cornified layer of the skin (about 70 μ) would have no effect regardless of the magnitude of the exposure dose. More energetic radiations penetrating through the epidermis (thickness about 80 to 100 μ) would result in epidermal necrosis. Deeper penetration into the dermis would result in progressively severe effects, including damage to the dermal capillaries[84] and other structures, culminating in transdermal necrosis, sloughing, and ulceration completely through the skin layer.

The data shown in Table III-1 suggest that the threshold dose (at 0.1 mm, the depth of the basal layers of the epidermis) of recognizable early transdermal injury to the skin is about 1200 to 1700 rads and the threshold for early atrophy and chronic inflammatory changes is about 1800 to 2500 rads, while the dose at the surface is strictly a function of the penetrating quality of the beta particles.

These observations of dose-effect relationships for high-energy beta rays are generally compatible with those observed for 180 to 200 KVP X-rays and suggest threshold tissue doses (at a depth of ~0.1 mm) of about 650 to 700, 1050, and 2000 rads for very slight erythema, very sharp erythema, and moist desquama-

tion, respectively, for radiations of this quality delivered in a single acute dose. The dose-effect relationship, however, is known to vary with radiation quality, exposure protraction or fractionation, and possibly with area.[118] The time-intensity-dose dependency of early skin effects is discussed later.

d. Fertility and Sterility

Although the sterilizing effect of acute radiation exposure will have no bearing on space mission success or failure, it is considered important to discuss the dose-effect relationship as a part of the over-all space radiation problem because of the possibility of individual concern. Doses as low as 25 rads to the testicles, either locally or as whole-body exposure, will produce a detectable decrease in sperm count. About 150 rads may induce brief sub-fertility, and about 250 rads may produce temporary sterility for 1 to 2 years.[122] Figure III-9 demonstrates the course of temporary radiation sterility via serial sperm counts and testicular biopsies in a 34-year-old man following an accidental nuclear
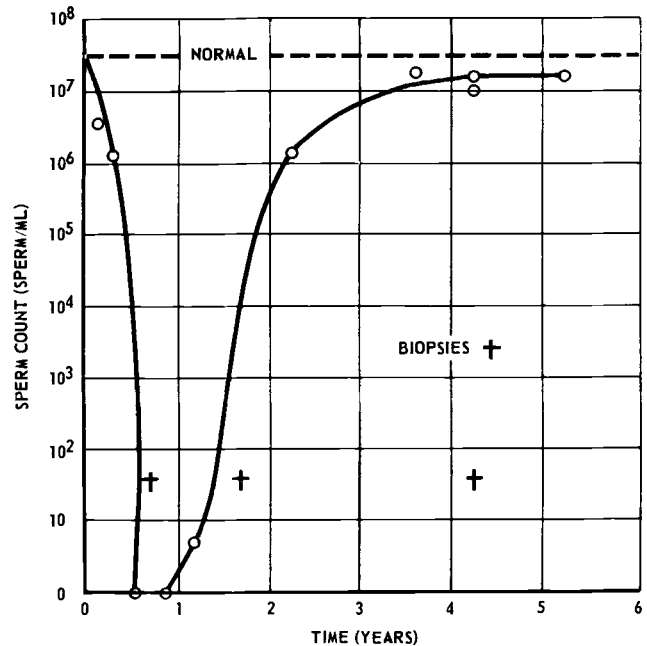

Figure III-9. Course of radiation sterility in man (as evidenced by sperm counts) following acute exposure to about 400 rad equivalents of 80 kv X-rays.[123]

criticality excursion in which the total-body exposure was equivalent to about 400 rads of 80-kev X-rays.[123] Within 6 months after exposure, the sperm count had dropped to zero and microscopic examination of a testicular biopsy taken at 8 months showed complete aspermia and widespread cellular destruction. Eighteen months after the accident, a testicular biopsy showed widespread repair and spermatogenesis recurring in many of the testicular tubules. Four years after the accident, the sperm count reached a maximum of approximately 1.7 x 10⁷/ml. Although this value is not within average normal range, the patient has since fathered two normal healthy children. Doses in excess of 500 to 600 rads to the testicles would probably be required to produce permanent sterility.[122]

e. Neural and Behavioral Effects

For some time it has been believed that the nervous system was quite radioresistant, since massive doses were required to produce early gross structural and functional changes. As mentioned earlier under discussion of median survival time, doses of 5000 rads and greater were required to evoke central nervous system death and bring about signs of gross neurological dysfunction. Data on monkeys indicate a threshold dose of between 1700 and 2000 rads for destruction of the rod cells of the retina, and doses in excess of 10,000 rads were required to destroy cone cells. The latency period for microscopic appearance of damage in the retinal tissue was about 5 hours.[124]

Carefully planned observations[125] in humans of radiation effects on learning and retention showed no decrement in performance with radiation doses in the sublethal range (15 to 200 rads), although there was a statistically significant decrease in the quadratic component of the 10-day complex coordination learning curve as the radiation dose increased. The implication of this observation to operational problems is uncertain and, since the patients were diseased, whether it is a true radiation effect is debatable. Systematic studies in monkeys following single and divided radiation exposures in the lethal and (in some cases) supralethal range have been carried out in which the observations included learning and retention of discrimination habits, habit generalization, manipulation of environmental objects, delayed response, attentiveness to environmental cues, solution of puzzles, locomotion, and free cage behavior. Results of most of these investigations (summarized and referenced in a review by Payne[125]) suggest no seemingly important loss of performance capability except that which can be associated with the general debilitation induced by the radiation. There is evidence, however, that large but sublethal acute radiation doses to the head produce damage which causes delayed changes in general intellectual performance.

Recent evidence indicates that the assumed radioresistance of neural tissue may not be entirely valid insofar as subtle bioelectrical, psychological, and behavioral changes are concerned. Specific alterations in spontaneous and evoked brain electrical activity have been demonstrated in cats receiving doses as low as 200 rads. Soviet investigators have reported electroencephalographic (EEG) disturbances and changes in conditioned behavioral response of animals with integrated doses as small as 5 rads and in a few cases with less than 1 rad. There has been considerable reluctance among Western scientists to accept these results because of their many deficiencies in experimental design and because plausible alternative explanations are available. Conditioning studies by Western scientists have demonstrated that stimuli associated with irradiation induce aversive behavior in animals. These avoidance responses thus developed are distinctive behavioral effects and suggest that the dependent variables used in previous studies may not have been sufficiently sensitive to detect behavioral changes. Doses of less than 25 rads produce significant decrease in conditioned saccharine water consumption in rats during a post radiation period. The behavioral, psychological, pathological, and other aspects of the response of the nervous system to ionizing radiations are reviewed and referenced in excellent reports of two recent symposia.[126,127]

The implications of low dose psychological and behavioral responses for manned space flight operations are not clear at the present time. Undoubtedly they should be considered in the future when more definitive observations are available and long duration manned missions are approaching reality.

C. Late or Delayed Somatic Effects

Late or delayed manifestations of somatic radiation damage are those which do not appear until after a latent period of months, years, or the remaining life span of the individual. These effects are nonspecific in that they cannot be correlated to any particular radiation exposure. The lack of correlation between a particular dose and the ultimate manifestations of effect arises, in part, from the relatively long latent period before the appearance of injury and, in part, to the fact that the effects from continuous and/or multiple exposures are additive but not necessarily in a one-to-one ratio in their final expression.

The late effects (or manifestations) of primary concern are general life shortening, increased probability of leukemia and other neoplastic diseases, greater probability of opacities or cataracts of the ocular lens, and permanent impairment of the skin. These effects are the same qualitatively, regardless of the nature of the radiation and whether exposure is continuous, intermittent, or from a single acute dose. Although modified quantitatively by a variety of factors (dose rate or protraction, depth-dose distribution, portion and region of the body irradiated, nature and quality of the radiation, etc.), delayed effects are nonthreshold phenomena and impose on an exposed individual an actuarial risk in proportion to the integral dose. In this case, the associated actuarial risks provide both the necessity and basis for exposure limits for long duration missions and space flight careers.

Dose-effect relationships for late effects in man are even more uncertain than for early effects. Information from animal experimentation, medical uses of radiation, and the Japanese atomic bomb survivors provides some insight into such relationships. A recent paper on late radiation effects in man as related to space flight has been published by Grahn.[128]

1. GENERAL LIFE SHORTENING

Numerous experiments have shown that a statistical sample of an animal population exposed to significant doses of radiation has a shorter average life span than does an unirradiated sample of the same population and that the degree of life shortening is a function of the accumulated dose. There is little reason to doubt and some reason to believe that radiation exposure would have the same effect on man. Life shortening cannot be attributed to any one specific cause. The irradiated sample seems to die sooner as a result of an increase in age-specific death rate over that of the unexposed controls. Quantitative evaluation of a dose-response relationship is complicated by the fact that the response is dose-rate dependent. Figure III-10 (adapted from Grahn[128]) shows a general relationship between accumulated dose and reduction of life expectancy in the mouse and represents the limiting conditions between single acute exposures at high dose rates and continuous exposure over the life-time of the animal. These curves indicate that the life shortening effect in the mouse varies from about 0.5 to 2 per cent of the mean life expectancy for a dose of 100 rads, de-depending on whether exposure is acute or continuous. Intermittent acute exposures superimposed on a continuous low-level background, as may be expected in space missions, would be somewhere in between these limiting conditions, depending on the magnitude, frequency, and spacing of the acute incidents. If the total exposure during a mission or a career happens to be reasonably protracted and does not exceed 50 to 100
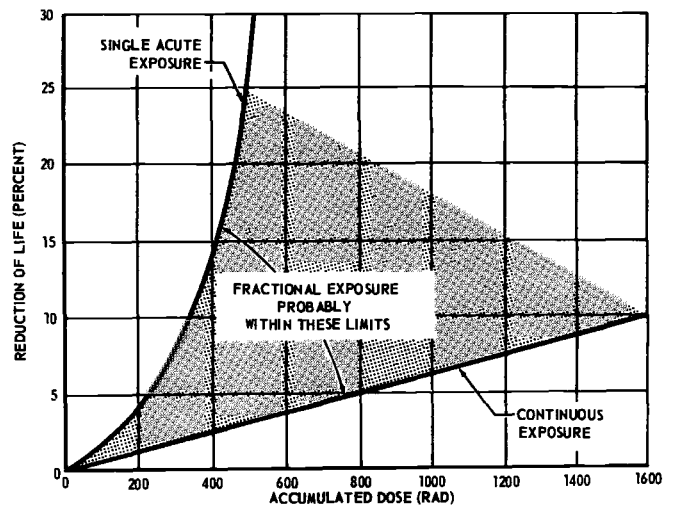

Figure III-10. Idealized general relationship between accumulated dose of penetrating electromagnetic radiation and life expectancy of the mouse.[128]

rads, the life shortening effect might be expected to coincide essentially with the lower curve. If exposure consists of acute incidents of this magnitude, the actuarial risk may be expected to shift in the direction of the upper limit indicated in the graph. Adequate data are not available to establish a quantitative dose-effect relationship for man. There is reason to feel, however, that various species may not vary greatly in life shortening effect when it is expressed as a percentage of the normal life expectancy. On the basis of this assumption, Grahn[128] has proposed that the actuarial life shortening effect of continuous radiation exposure in man can be represented by the expression,

$$Y = A\,e^{-1.05D},$$

where Y is the predicted life expectancy beyond age 20, A is the mean life expectancy beyond that age with no exposure, and D is the dose rate in rads/day. This expression is shown graphically in Figure III-11, assuming A to be 50 years, which might be expected to
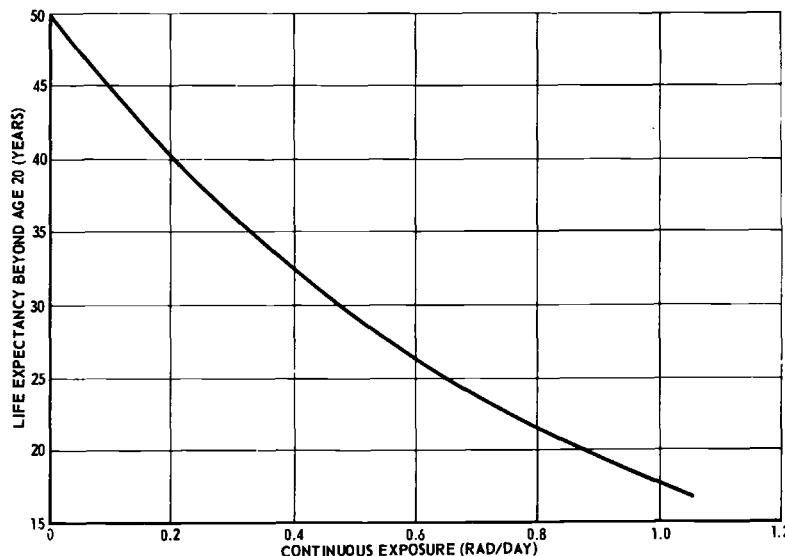

Figure III-11. Postulated effect of continuous radiation exposure on actuarial life expectancy of man.[128]

coincide more closely with the life expectancy beyond age 20 of a selected population than the 45 years assumed by Grahn. In essence, this curve indicates that continuous exposure at dose rates of from 0.1 to 1 rad/day results in an actuarial life shortening in man of from about 1 to 2 days/rad. This is in good general agreement with Failla and McClement,[129] who estimated the life shortening effect in man to be approximately 1 day/rad of accumulated dose for chronic exposure at a dose rate not in excess of about 0.5 rad/day. A frequently quoted value for life shortening in man is 15 days/rad proposed by Jones,[130] who sets extreme limits of from 1 to 30 days. Curtis[65] applied animal data to man (on a direct per cent of life span basis) and estimated that the life shortening effect for acute exposures may be about 12 days/rad. He further showed that the extrapolated value for life shortening effect under low-level chronic exposure (0.3 rad/week) differed by a factor of about 20, depending on the method of extrapolation. It should be pointed out that the quantitative aspects of radiation life shortening in man are by no means as clearly defined as indicated in the previous discussion.

2. INCREASED INCIDENCE OF LEUKEMIA AND OTHER NEOPLASTIC DISEASES

Leukemia is a specific cause of death, the incidence of which is known to be increased in both laboratory animals and in man by acute radiation exposure. Statistical studies of the Japanese atomic bomb survivors[131] and ankylosing spondylitic patients given therapeutic X-ray treatment[132] suggest a linear dose-effect relationship at least with acute doses above about 100 rads. The leukemias observed in man are predominantly of the acute lymphatic and chronic myelocytic types; peak incidence occurs from 4 to 7 years after exposure, and an elevated incidence may continue for as long as 15 years. Assuming a linear relationship between dose and effect, an annual increase (averaged over a period of 15 years) over the natural incidence has been estimated to be about 100 cases per 10^6 persons per 100 rads of exposure for each year at risk.[133] In other words, a whole-body radiation dose of 1 rad may increase an individual's yearly average actuarial leukemia risk from the normal value of about 68 chances per million (U. S. population) to about 69 chances per million for the first 15 years after exposure. This relationship (shown graphically in Figure III-12) is based on acute exposures at high dose rates and, in the case of the Japanese, on the response of a nonselect population. Intermittent or continuous low-level exposure would not be expected to be as effective,[133] and the curve may be representative of the limiting condition.

Little can be said about the effect of radiation exposure on the incidence of other types of neoplasia except that a brief study of the Japanese atomic bomb survivors (1957 to 1958) suggests a linear increase in incidence with increasing dose, which seems to parallel the dose-response curve for leukemia.[134,135] These observations have led to an estimation of the human can-
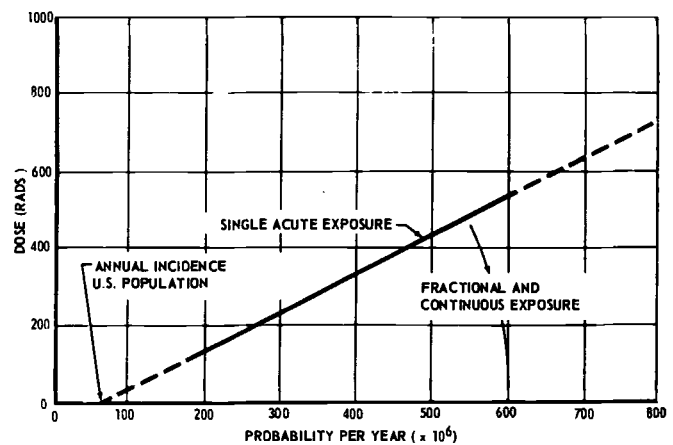
Figure III-12. Postulated dose-response relationship for radiation-induced leukemia in man.

cer doubling dose of prompt radiation exposure as about 400 rads.[134]

3. PRODUCTION OF CATARACTS

Either acute or chronic exposure of the optic lens will result in the formation of opacities which may progress to clinically significant cataracts, depending on the magnitude of the dose and the nature of the radiation. The most extensive and thorough study of the radiation-induced cataracts in man and the relationship to dose was published by Merriam and Focht,[136] who reported on 100 cases with cataracts and 73 cases which received radiation but did not develop cataracts. The radiations involved were 100 to 250 KVP X rays and gamma rays of radium. Cases were divided into three categories on the basis of exposure regimen: those receiving a single acute dose, those receiving multiple doses over a period of 3 to 12 weeks, and those receiving multiple doses over periods of greater than 4 months. The minimum cataractogenic dose (estimated at the position of the lens from phantom dosimetry measurements) for the three groups was 200, 400, and 550 rads, respectively.

Depending on the dose, the lens effect may be only a stationary opacity, with no visual impairment, or a progressive cataract, resulting eventually in significant impairment. The time of appearance of the opacity is highly variable and may range in the adult from about 2 to many years after exposure. Usually the higher the dose the shorter the time interval and the greater the likelihood of a progressive lesion and visual impairment. A single acute exposure is more effective and produces opacities sooner than the same dose given in divided or continuous exposures spread out over times ranging from 3 weeks to a few years. The human data are not adequate to support rigorous quantitative analysis of the dose-effect relationship. However, a histogram (Figure III-13) of cataract incidence as a function of dose for all of Merriam and Focht's cases in which treatment was protracted over periods of greater than 3 weeks does show that a relationship exists. Although they observed lens changes in one patient who
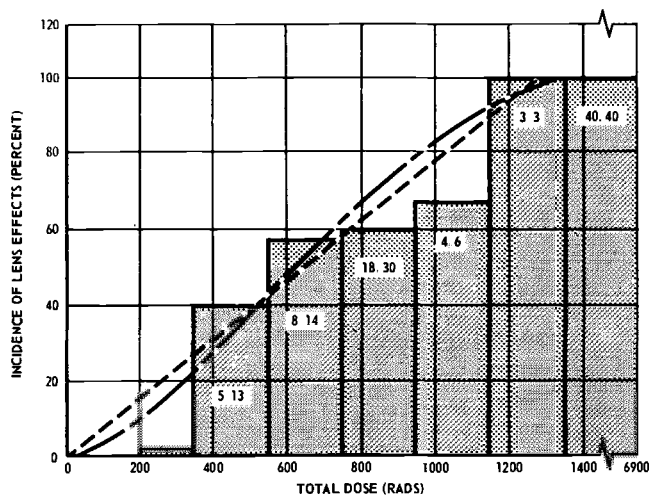
Figure III-13. Observed radiation-induced cataracts in man in relation to dose.[136]

received a single acute exposure of 200 rads, the minimally effective X-ray dose (200 KVP) for production of clinically significant cataracts appears to be between 400 and 1000 rads, if the exposure is divided or protracted. The data suggest that doses between 550 and 950 rads (average 750) delivered over periods of from 3 weeks to a few years may produce an opacity incidence of about 60 per cent. Of these, about 50 per cent may be progressive and result eventually in impaired vision. On this basis, one might estimate that about 30 per cent of flight crews who receive lens exposures of 750 rads of ionizing radiation (equivalent in effectiveness to 200 KVP X-rays) protracted over a career of a few years may develop clinically significant cataracts at some time during their lives. The ocular lens seems particularly sensitive to densely ionizing radiations. Recoil protons from fission neutrons (average linear energy transfer $\sim$ 50 kev/μ) appear to be as much as 5 to 10 times as cataractogenic as 200 KVP X-rays in experimental animals.

4. LATE OR DELAYED EFFECTS ON THE SKIN

As with all other organs and tissues of the body, somatic radiation effects are produced in the skin which may not show up until many months or years later. These so-called late or delayed effects are proportional to the accumulated dose. Regardless of whether early signs of damage are or are not produced, skin exposed to accumulated doses of a few thousand rads becomes chronically abnormal. This chronically abnormal condition manifests itself as thin parchment-like tissue which is sensitive to mild traumatic injury, has poor healing quality, and is prone to spontaneous break-down, ulceration, and neoplasia. This condition is referred to as chronic radiodermatitis and may involve atrophy, pigmentary changes, telangiectasia, ulceration, keratosis, and development of both malignant and nonmalignant tumors. The most common types of tumors produced are basal and squamous-cell carcinomas and occasionally sarcomas.[137,138] Twenty per cent of the cases showing indications of cancerous

changes do so in 15 to 30 years after exposure. Such changes, however, may occur as early as 7 to 10 years or as late as 50.[139] Atrophic changes may become evident within about 6 months to 5 years.[140]

It is not possible to review thoroughly the subject of chronic radiodermatitis. The reported cases number several hundred, many of which have resulted from cosmetic and therapeutic applications of low-energy radiation for various benign skin conditions, others from use of low- and high-energy radiation incidental to cancer therapy, and still others from occupational exposure in connection with therapeutic and industrial applications.[137] As would be expected, the doses required to produce chronic radiodermatitis are influenced by dose fractionation and protraction,[140-144] quality or penetrability of the radiation,[145] size of the exposure field,[140,141,146] and anatomic site or location irradiated.[140,144] Because of the wide variation in response produced by these factors and variability or lack of specific definition of exposure conditions, it is not possible to derive a general dose-effect relationship for late or delayed skin effects as it might apply to space flight operations even though observations of such effects are numerous. It is possible, however, to get a general impression of the dose range where significant late effects might occur. Sulzberger, Baer, and Borata[147] reported a systematic follow-up and examination of the skin of 1000 persons who 5 to 23 years previously had received superficial low-voltage X-ray treatments. The usual quality of irradiation used ranged from 60 to 100 kv with half-value layers of about 0.5 to 1 mm Al. For radiation of this quality, the tissue dose in rads would probably be about the same as the exposure dose in roentgens. They found no evidence of late effects in patients who received total exposures up to 1000 rads when given at weekly intervals in fractional doses of up to 85 r. Among patients who received weekly fractional doses totaling between 1000 and 2600 rads, the incidence of late radiation sequelae was estimated to be about 1.5 per cent. The effect was of the nature of very mild telangiectasia of cosmetic interest only. They concluded that superficial X-ray treatments in doses necessary for the cure of the usual malignant skin conditions may produce chronic radiodermatitis in 25 per cent of cases. There seems to be reasonable agreement that exposures required to bring about cures in these conditions are about 2200 to 2800 rads when delivered in a single dose.[141-143,148] From the just cited references it may be ascertained that the exposure doses required to produce cures of these conditions when fractionated over periods of 30 to 60 days are of the order of 6000 to 7000 rads. This would indicate that, when fractionated over a period of 30 to 60 days or longer, doses of 6000 to 7000 rads may result in a 25 per cent incidence of delayed radiation effects. Traenkle et al.[140,144] observed the influence of five different dose schedules on the cumulative probability of late radiation necroses over a 5-year period following therapy of skin cancer with 100 kv X-rays (HVL 1.5 mm Al, target-to-specimen distance 18 cm). In these cases, the doses were corrected for backscatter and may approxi-

TABLE III-2. INFLUENCE OF TREATMENT SCHEDULE ON CUMULATIVE
PROBABILITY OF LATE RADIATION NECROSIS[144]

Treatment Schedule	Frac-tionation	Total Dose (r or rads)	Over-all Treatment Time (days)	Equivalent Cumulated Dose (r or rads)	5-Year Prob-ability of Necrosis (per cent)
A	1000 r x 4	4000	8-10	2000	14
B	1000 r x 5	5000	10-12	2392	34
X	500 r x 9	4500	12	2112	
Y	400 r x 13	5200	18	2212	3
Z	300 r x 18	5400	25	2134	

mate the tissue dose in rads. Their observations are summarized in Table III-2.

Calculation of cumulated biological dose from the time-dose formula developed by Strandqvist[149] gave essentially the same value for all treatment schedules. The fact that the probability of necrosis was considerably higher with schedules A and B than with schedules X, Y, and Z while the equivalent cumulated doses were approximately the same suggests that the size of the individual dose fractions might be a factor in determining the probability of late effects on the skin. These data and the previous discussion, however, support the general impression that a dose to small skin areas (upper limit ~ 100 cm²) of 4500 to 5500 rads of radiation of the quality of 100 kv X-rays (half-value layer 1 mm Al), if fractionated in relatively equal doses over periods of greater than 30 to 60 days, may not be expected to cause more than ~ 5 per cent probability of delayed skin effects. This estimate, however, is based on exposure of small areas. Since the number of cells at risk is directly proportional to area, it would seem prudent to lower these values by as much as 50 per cent when applying them to space radiation conditions where exposures may involve a substantial fraction of the total body surface.

D. Genetic Effects

Exposure of the germinal epithelium to ionizing radiation will increase the probability of the occurrence of gene mutation that may be detected among the offspring of the irradiated individual. It seems reasonably well established that the probability of production of mutations increases linearly with increasing radiation dose for doses above about 25 rads. Within limits, however, the dose-effect relationship is dependent on the radiation dose rate.[150] Essentially all of the available information on mutagenic effects of radiation comes from animal studies and little is known about man. There is little doubt, however, that the basic observations in experimental animals apply, in general, to man.

Spontaneous mutations are always occurring in the gene pool of any population, and the radiation induced ones are additive to these in such a gene pool. Mutations regardless of their origin are a matter of continued concern, as it is possible for the mutation rate to be greater than the rate of elimination of such mutations in the gene pool of a population. Even though the potential genetic effects of space radiation are of very little significance to the general population because of the extremely small number of individuals that

will be exposed, they may be of interest to a particular space crew member.

The type and frequency of mutations are dependent on the post exposure mating time. If mating occurs soon after exposure (within about 60 days in man[151]), fertilization may result from irradiated mature germ cells (spermatocytes, spermatids, and spermatozoa). The mutation rate for recessive genes in these cells may be twice that in exposed immature germ cells (spermatogonia or stem cells[150]). Furthermore, irradiated mature germ cells carry a high incidence of dominant lethal gene mutations which are seldom seen in irradiated immature cells.[152] Mutations observed in late matings (beyond about 60 days after exposure) are predominantly recessive, and the mutation rate is to some degree dose-rate dependent at dose rates of 1 rad/min or less. Below about 1 rad/min, the mutation rate may be lower by a factor of 4 or more as compared to high dose rate exposures.[150]

On the basis of Russell's observations of radiation mutation rates in mice[153] and the assumption of 10^4 genes in man, Grahn[128] estimated that the probability of a given immature germ cell exposed to 100 rads carrying a mutation lies between 1 in 20 and 1 in 5, depending on whether exposure is chronic or acute. Furthermore, the chances of a recessive gene expressing itself in the first generation are about 1 in 25. The chances, therefore, that an individual exposed acutely to 100 rads will have an immediate offspring that expresses a mutational abnormality may be less than about 1 in 100. It should be kept in mind, however, that abnormalities may be expressed in later generations.

While it is somewhat premature for conclusive evidence to have been obtained from the Hiroshima and Nagasaki exposures for the F_1 generation, such data as are available have not shown any significant changes in the mutation rate. However, a slight decrease in the birth rate of these populations has been reported.[154]

E. Factors Modifying Radiation Effects

The dose-effect relationships discussed previously are based largely on observations of animals and occasionally man exposed to so-called conventional radiations (low- and intermediate-energy X and gamma rays, beta particles, and neutrons) available on earth. There is no counterpart on earth for the heterogeneous mixtures of radiations to which space crews may be exposed. Space radiations consist of variable fluxes of

heavy and light charged particles (galactic primaries, alpha particles, protons, and electrons), each having specific energy characteristics which may be dependent on time and position. There are also secondary radiations produced by interaction of the high energy charged primary particles with the spacecraft and with the tissues of the body. Secondary protons, neutrons, high energy gamma and X-rays, pions, and muons result from these interactions.[155] Extrapolation of existing observations to the complex radiations and exposure conditions inherent in the space environment presents the greatest single difficulty in attempting to establish radiation risk criteria for manned space flight.

Many physical and biological factors modify the dose-response relationships for both early and late effects. Some of these factors may make space exposure conditions less hazardous and others more. The most important factors are those related directly or indirectly to the quality and nature of the radiation and the variability of exposure conditions. Among these are nature and relative biological effectiveness (RBE) of the radiation, topical and depth-distribution of dose, and protraction (dose rate) and fractionation of exposure. Other factors may involve design and operational conditions and medical management.

1. NATURE AND QUALITY OF SPACE RADIATION

a. General Considerations

The absorbed dose of any ionizing radiation is the energy imparted to matter by ionizing particles per unit mass of irradiated material at the place of interest, and the unit of absorbed dose is the rad which is equal to 100 ergs/g.[116] One would expect the quantity of absorbed energy to determine the biological effect regardless of the type of radiation. Numerous experiments have demonstrated, however, that equal rad doses of radiations of different nature and quality do not always produce equal biological effects. These observations have necessitated the concept of RBE (relative biological effectiveness) to relate all types of radiation to a standard (high energy X or gamma rays), thereby providing a common denominator of effect.

The RBE may be defined as the ratio of the dose (rads) of high energy X or gamma rays required to produce a specific biological effect to the dose (rads) of another radiation required to produce the same level of effect. The unit of RBE dose is the rem, and the biologically equivalent dose (in comparison with X or gamma rays) of a specific radiation for the production of a specific biological effect is:

RBE dose (rems) = dose (rads) x RBE.

The concept of RBE is further complicated by its dependence on the effect observed (whether acute or chronic, etc.), the biological test system used, conditions of exposure, and other factors. The dependence of RBE on energy and type of radiation is related in a very general and complex manner to the ionization density or linear energy transfer (LET) along the

primary track in tissue or water. LET is expressed most commonly in kev/μ of track length and varies inversely with energy and (for particulate radiation) directly with the charge.[156] The mean LET of 200 to 250 KVP X-rays is about 3 kev/μ. Figure III-14, adapted from Sondhaus,[157] shows an idealized plot of RBE versus mean LET (relative to an RBE of unity for X-rays of LET=3 kev/μ) for four different general types of response. Type I shows a decreasing RBE with increasing LET. This response is characteristic of simple systems such as enzymes, viruses, etc., exposed in the dry state. Type II shows a peak value of about 2 for the RBE at a LET of between 100 and 200 kev/μ. This type of behavior is generally characteristic of simple bacterial and plant cells, as well as chromosome effects and mutations. Type III shows a peak RBE value of from 3 to 4, corresponding also to a LET value of about 100 to 200 kev/μ. This type is somewhat characteristic of animal cells and complex biological systems especially with regard to early effects. The type IV response shows RBE values of 10 or greater for LET's of above 100 to 200 kev/μ and has been observed in dry seeds, spores, and other biological systems. In general, the type III response seems to be most pertinent to the case of human exposure at least with regard to early effects. Notice especially that curves II and III show a maximum RBE in the LET range of about 100 to 200 kev/μ and then decrease. As the ionization density along the individual particle tracks increases, more energy is deposited in the radiosensitive microscopic critical volume of the cell than is needed for destruction. This "wasted" energy shows up in the dose-effect relationship as a reduced quantity of effect per unit dose (i.e., as a reduced RBE). If this somewhat speculative interpretation is true, then it may be anticipated that the amount of irreparable or cumulative damage produced by densely ionizing particles may be greater than that produced by the standard low LET radiation. This suggests the possibility of relatively higher
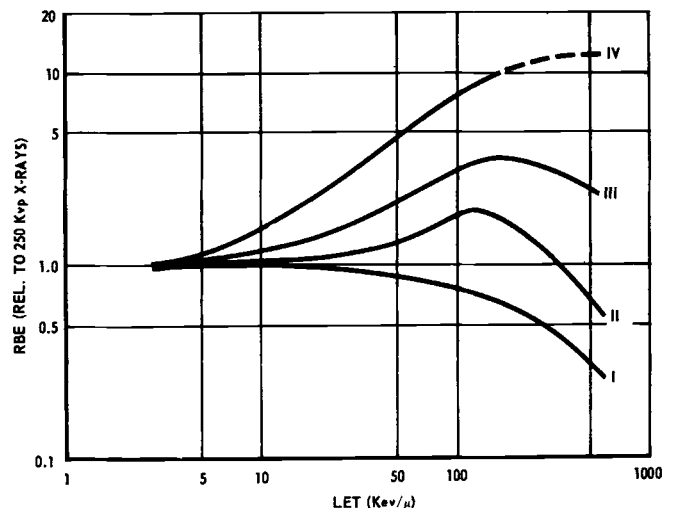

Figure III-14. Variation of relative biological effectiveness (RBE) with linear energy transfer (LET) for various types of biological systems.[157]

RBE values for chronic or delayed, compared to early, effects and less dose rate dependence of RBE for high LET particles compared to the standard.

The previous discussion, however, relates to RBE as determined by observing the ratio of effectiveness of a particular radiation to a standard in radiobiological experiments (usually on simple test systems) under a specified set of conditions. It is well known that RBE does not depend on LET alone but on a variety of other parameters including biological end point observed, dose rate, dose fractionation, etc. In defining official RBE values for radiological protection practices, the various authoritative bodies have assumed the worst possible combinations of influencing parameters and have chosen the highest values reported.

A special RBE committee organized by the International Commissions on Radiological Protection and on Radiological Units and Measurments has published a review of the RBE concept and its application in radiation protection.[158] To avoid ambiguities resulting from different usage of the term RBE, the committee endorsed the ICRU's recommendation[159] that the symbol QF (for quality factor) be used instead of RBE to designate the linear energy transfer-dependent factor when applied to radiation protection. They endorsed also the recommendation that the term "RBE dose" be replaced by "dose equivalent" (DE) and that the unit of dose equivalent be the rem. In this case, DE (rems) = D (rads) x QF. These recommendations will be adhered to in the following sections of this report. The committee concluded also that present knowledge was not sufficient to justify a more sophisticated treatment of the RBE concept or departure from the currently used values for the relationship between QF and LET shown in Table III-3. A first approximation to the QF versus LET relation (for LET's up to 100 kev/μ) was given as:

$$QF = 0.8 + 0.16 \, L,$$

where L is the LET in kev/μ of track.

The QF-LET relationships given in Table III-3 are limiting values applicable to low dose exposure and risk of late effects in routine occupational health pro-

TABLE III-3. RECOMMENDED VALUES FOR THE RELATIONSHIP BETWEEN QF AND LET

LET∞[1] (kev/μ in water)	QF
3.5 or less	1
3.5 - 7	1 - 2
7 - 23	2 - 5
23 - 53	5 - 10
53 - 175	10 - 20

1. LET∞ is defined as the energy loss per unit distance of the charged particles originally set in motion by electromagnetic radiation or neutrons or charged particles originating from a radiation source and is the same as the "stopping power."

tection practice. They do not apply to early effects of acute or emergency exposure at high doses and high dose rates. Their applicability to space radiation exposure, therefore, is limited to risks of late or delayed effects, preferably those resulting from the low dose-rate component. No specific recommendations were made regarding a QF-LET relationship for early effects

of acute exposure. Perhaps the best that can be done at present is to assume conservatively that curve III of Fig. III-14 applies generally to early signs of radiation damage under acute exposure conditions or that the relationship of QF to LET for chronic exposure applies also to the acute case.

b. Primary Charged Particles in Space

(1) Protons—Figure III-15, taken from data of Schaefer,[160] shows the LET of protons as a function of kinetic energy. Since a LET of 3 to 3.5 kev/μ corresponds to a QF of unity, protons of greater than
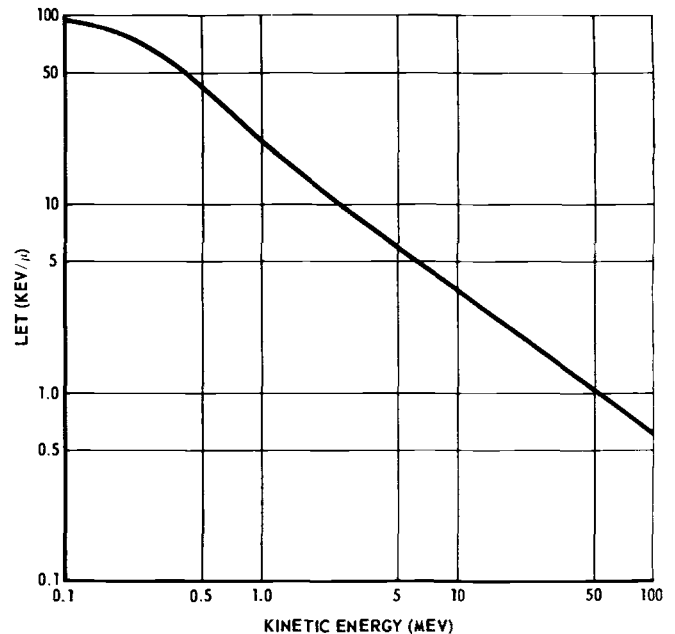

Figure III-15. Linear energy transfer (LET) of protons as a function of kinetic energy.[160]

about 10 Mev should have a QF of approximately 1 or less. A few experimental observations of the RBE (not QF as defined earlier) of high energy protons (157 to 730 Mev) for production of various effects in animals have been reported.[161-165] The end points used were largely early or acute responses. The observed values ranged from 0.5-0.6 to 1.4, with the majority ranging from 0.7 to 0.8. The energy spectra of protons in space are, however, extended continua of negative slope. As these proton beams travel in absorbers, including the human body, a complex transition occurs in the spectral configuration, shifting the low energy cut-off all the way down to zero energy. This results in intratarget energy spectra that are continua extending from zero energy up to many hundred million electron volts and higher. As a consequence, the tissue ionization dose in such radiation fields is delivered by a heterogeneous LET spectrum. Therefore, for a quantitative assessment of the dose equivalent (DE) in rem units at depths of interest in a target irradiated by a heterogeneous proton beam, the local configuration of the energy spectrum has to be evaluated for each point and the corresponding mean local QF estab-

lished. This subject has been treated extensively by Schaefer[160, 166-172] for both Van Allen belt and solar flare protons. These references may be consulted for computational methods, assumptions, and details. Although high QF values of around 10 were assigned for protons of 0.5 Mev and less (LET maximum 93 kev/μ, Fig. III-15), this analysis shows that the mean local QF for space protons can never greatly exceed unity because of the small fraction of the total dose delivered at high LET. For solar flare protons with light prefiltration (2 g/cm²), a maximum QF of 1.46 occurs in the surface of the target. For Van Allen protons, the maximum is 1.2 or less. Figure III-16 shows the entire mean local intratarget QF pattern for an actual case (not specifically identified) calculated for a 20-cm spherical tissue phantom inside 2, 4, and 8 g/cm² of shielding.[160,172] This figure indicates a maximum QF of 1.46 in the skin surface. An increase of 46 per cent in the rem dose to the skin would be of no significance under ordinary circumstances. It may be important, however, under emergency exposure conditions involving operations outside a spacecraft during a solar flare.

(2) Alpha Particles—Freier and Webber[54] reported that the rigidity (momentum per unit charge) spectra of alpha particles and protons above approximately 30 Mev were about equal in abundance in 7 of the 10 solar events in which the fluxes of both were measured during the 1956-1961 period. Their calculations of dose (in rads) inside various thicknesses of spherical shielding showed the alpha component to contribute substantially to the total. The average alpha particle dose for 9 of the 10 flares inside a 2 g/cm² shield was approximately 20 per cent of the proton dose, excluding the February 23, 1956, event for which the alpha dose was 230 per cent of the proton dose. As with a heterogeneous proton beam, assessment of the rem dose from solar alpha particles at depths of interest in a target requires evaluation of the local energy spec-

trum for each point to establish the mean local QF. In the case of alpha particles, it is quite possible that a relatively much greater portion of the dose absorbed in the skin surface will have a high QF. This merely suggests that the alpha particle component of solar flare radiation should not be ignored.

(3) Electrons—Significant fluxes of primary electrons are confined predominantly to the geomagnetic radiation belts. Near the center of the outer Van Allen belt, the natural flux is very high. The electron spectrum, however, is a continuum with steep negative slope and very few particles have energies greater than $\sim$ 1.6 Mev. Exposure from this source is not considered significant, since the minimum thickness of the structural material of a spacecraft is sufficient to essentially completely eliminate the primary flux. Exposure from primary electrons is not necessarily insignificant, however, for operations outside the spacecraft or for unnatural electron belts created by high altitude nuclear detonations in which there may be appreciable fluxes of electrons with energies up to 6 to 8 Mev. In any event, the QF for electrons of all energies above 0.03 Mev[158] is assumed to be unity.

(4) Heavy Primary Nuclei—The heavy particle component of galactic cosmic rays may contain stripped nuclei of atoms as heavy as tin. Although the flux of such particles is not great, they may have kinetic energies of many billions of electron volts. Because of their high energy and charge, heavy primary galactic cosmic rays may produce inelastic collisions (star formations) and dense ionization tracks (thin-downs) at any depth in the body. Cells in which such events occur undoubtedly will be killed, since they will be subjected to doses of several hundred rads of very high LET radiation if the concept of dose can be assumed to have any meaning. The discrete nature and high ionization density of these events would certainly influence the biological response.

The previously cited RBE committee[158] states specifically that the RBE concept obviously cannot be applied when the concept of "dose" itself fails and cites as examples the special type of effect produced by passage of a single particle of high LET and nuclear star formation where several ionizing particles are emitted from a common center.

The biological effects of high LET particulate radiations are being studied vigorously using presently available high energy accelerators.[173-175] Chase et al.[176] have observed the effects of heavy primary cosmic-ray particles on the greying of hair of black mice flown in high altitude balloons. Curtis and co-workers have used microbeams of high energy deuterons to simulate the ionization track of heavy primary thin-downs and to study their effects on the visual cortex of the brain[177] and the ocular lens[178] of mice. The dose required to produce histologically observable damage in the brain decreased rapidly with beam diameter until approximately 4 x 10⁵ rads were required for beam diameters approximating that of primary cosmic particles. The dose required to produce observable effects in single cells of the lens was not dependent on beam diameter, but the probability of progression to a per-
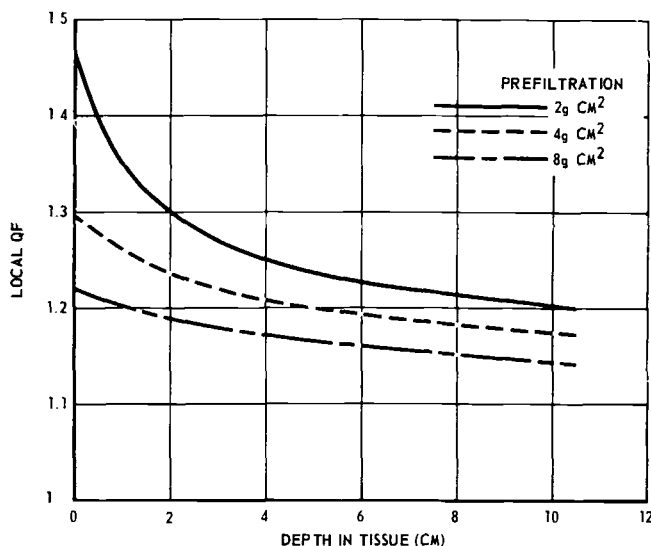

Figure III-16. Variation of local quality factor (QF) of solar flare protons as a function of prefiltration and depth in a 20-cm tissue-equivalent sphere.[160,172]

sistent cataract seemed to require a beam diameter large enough to damage a cluster of cells. Curtis[179] has concluded that exposure to heavy primary cosmic rays does not constitute a serious hazard in manned space flight. Others feel, however, that the less dramatic chronic or delayed effects may be of particular importance in assessing long-term damage from extended exposures.[172]

c. Secondary Radiations

Absorption of radiation in matter, whether it be the materials of the spacecraft or the human body, involves transfer of the incident energy to the atoms of the absorber. This process may lead to production of a variety of secondary radiations including recoil protons, neutrons, electrons, and X and gamma rays. All of these and other more exotic radiations are produced in high energy cascades. The QF of secondary recoil protons will be the same as for primary protons of comparable LET. The electromagnetic radiations, including bremsstrahlung from beta particles, produced by primary interactions do not differ significantly from standard X-rays and may be assumed to have a QF of unity. With increasing shield thickness, the secondary neutron dose from high energy particle interactions approaches and may eventually exceed the dose from the primary flux. The QF of neutrons is dependent on their energy and the observed biological effect. For neutrons of maximum effectiveness ($\sim$0.5 to 2 Mev), the experimentally observed RBE for acute effects varies from about 1 to 4, depending on the animal species and the biological end point,[180] and for chronic or delayed effects the QF is assumed to be approximately 10.[158]

As a comprehensive reference to the nature, production, and significance of secondary radiations, the reader is referred to the report of the Proceedings of the Symposium on the Protection against Radiation Hazards in Space held in Gatlinburg, Tennessee.[61]

2. DEPTH-DOSE DISTRIBUTION AND PARTIAL-BODY EXPOSURE

Because of nonuniform shielding characteristics of the spacecraft and a decreasing depth-dose distribution as a result of the spectral characteristics of the primary radiations, exposures in space will not be uniform whole-body irradiation. In general, nonuniform exposure, whether as a result of topical shielding or a decreasing depth-dose distribution, is much less effective than uniform exposure for production of both early and late manifestations of radiation damage. There are, however, specific effects that are exceptions to this generalization. A given radiation dose delivered locally at the depth of the ocular lens may be as cataractogenic as the same dose received incidental to a uniform whole-body exposure. Other exceptions are epilation from local exposure of the head and decreased fertility from local exposure of the testes.

The quantitative modification of effect by nonuniform dose distribution is dependent on the topical
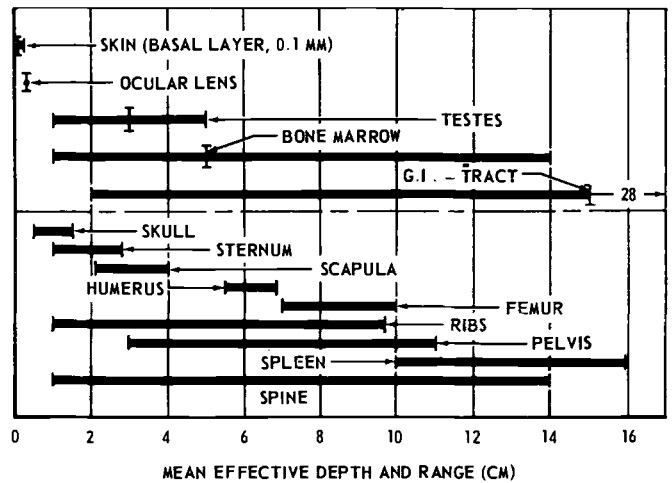

Figure III-17. Depth-distributions of various critical organs and tissues and their assumed mean effective depths.

region and depth irradiated in relation to the location of certain sensitive critical organs and tissues of the body. The problem is complicated by the fact that some critical organs (e.g., bone marrow, gastrointestinal tract) are distributed widely and others (ocular lens, skin) are specifically located with respect to region and/or depth. The upper portion of Figure III-17 shows graphically the depth-distribution of various critical tissues and organs and their assumed mean effective depth. The lower portion shows the depth-distribution of the principal structures in which hematopoietic activity occurs, and Table III-4 gives an estimate of the relative distribution of active bone mar-

TABLE III-4. DISTRIBUTION OF THE HEMATOPOIETIC TISSUE IN THE HUMAN SKELETON[181]

Skeletal Structure	Active Marrow (per cent)	Range in Depth (cm)
Cranium and Mandibles	13	0.5 - 1.5
Ribs	15	1 - 9.5
Scapulae	5	2.0 - 4.0
Clavicles	2	1 - 3.0
Sternum	3	1 - 3.5
Sacrum	9	3 - 9.0
Pelvis	23	3 - 11
Vertebrae	30	1 - 14

row among the various skeletal structures.[181] The degree of biological effect produced by exposure to a nonuniform depth-dose distribution is influenced also by geometric factors.[182] As an example, unilateral exposure is less effective than bi- or multilateral exposure because nonuniformity of dose distribution is greater in the former case.

The depths of critical tissues in relation to proton depth-dose distribution (in a spherical phantom behind 2 g/cm^2 of shielding) for the inner Van Allen belt and the May 12, 1959, solar event are shown in Figure III-18.[125,183] Further complications arise also from the fact that the spectral distribution (and thus the depth-dose distribution) of protons inside the spacecraft is dependent on inherent shielding and, in the case of flares, the spectrum varies from flare to flare and with time after onset. Figure III-19 shows Schaefer's cal-
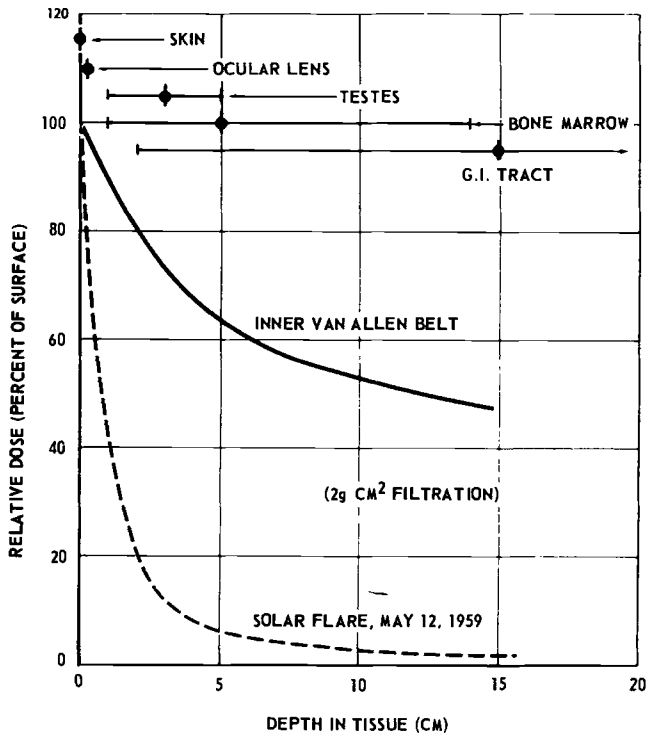
Figure III-18. Depth of critical organs and tissues in relation to proton depth-dose distribution (in a spherical phantom behind $2g/cm^2$ shielding) for the inner Van Allen belt and the May 12, 1959, solar event.[128,183]

culations[170] of relative proton depth-dose rate in a spherical phantom inside 2, 4, and 8 g/cm^2 of shielding at 2, 4, 16, and 48 hours after onset for Bailey's typical large flare event.[184]

Various methods of expressing dose have been proposed to try and normalize biological effects of radiations under conditions of nonhomogeneous dose distribution. The volume or integral body dose concept proposed by Mayneord[185] has been used extensively. Others have proposed exit dose,[186,187] midline tissue dose[188,189] and mean marrow dose,[181,189,190] which in man would correspond roughly to the absorbed dose at 5 cm (the mean effective depth of the bone marrow). No method of measuring or expressing exposure seems to provide an entirely satisfactory basis for predicting the degree of biological effect in animals of all sizes and for radiations of all qualities. For early bone marrow depression and lethality, the mean marrow dose probably reflects the biological damage most directly.[181,189,190] Alpen and Jones[189] investigated the effects of concomitant superficial X-irradiation upon the lethal effects of 250-KVP X-rays in dogs and found that neither surface dose, midline dose, or integral body dose normalized the LD_{50} values when the exposure consisted of different ratios of 50 to 250 KVP X-rays. These results, extended by Wilson and Carruthers[181] to include estimates of mean marrow dose, are shown in Table III-5.

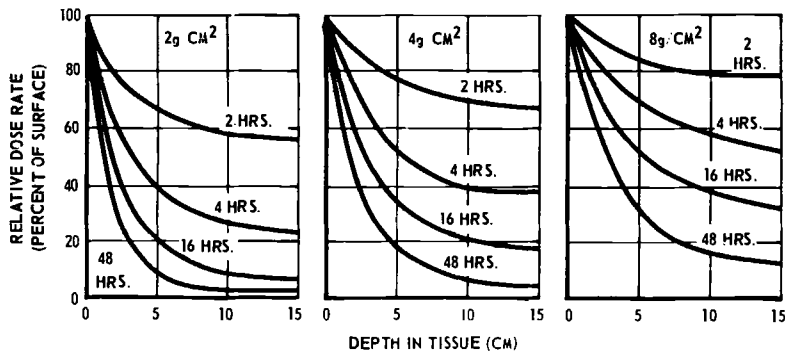Jackson,[191] using a Co^{60} gamma-ray source and ro-

Figure III-18. Variation in proton depth-dose rate in a spherical phantom as a function of shield thickness and time after onset for Bailey's typical large solar flare event.[170]

TABLE III-5. COMPARISON OF LD_{50} OF DOGS EXPOSED TO VARIOUS QUALITIES OF RADIATION WHEN DIFFERENT METHODS OF EXPRESSING DOSE ARE EMPLOYED[181]

Radiation Quality	Exposure Regimen[a] (r)	Surface Dose (rads)	Midline Dose (rads)	Integral Dose (megagram rads)	Mean Marrow Dose (rads)
250 KVP X-rays	275	224	206	2.25	165
250 KVP X-rays	226	184	169	1.85	
50 KVP X-rays	1000	485	34	0.73	
Total	1226	669	203	2.58	145
250 KVP X-rays	205	167	153	1.68	
50 KVP X-rays	3000	1455	101	2.20	
Total	3205	1622	254	3.88	150
250 KVP X-rays	281	....	228	.... .	169
100 KVP X-rays	664	....	316	....	153
1000 KVP X-rays (330 eff.)	270	....	235	....	195
1000 KVP X-rays (450 eff.)	303	....	250	. ....	222
Co^{60} gamma rays	376	....	335	....	300

[a]Exposure air dose measured at the position of the midline of the animal before placement.

TABLE III-6. VARIATION OF LD50 WITH BODY REGION AND VOLUME EXPOSED

Species	Exposure Conditions	Exposure Dose (r)	Integral Dose (kg-rads)	Reference
Rats	Co-60 gamma rays, whole body uniform..	830	170	(191)
	Co-60 gamma rays, whole body (midline dose 25 per cent of surface dose)	2590	260	(191)
Rats	X-rays, whole body uniform..	700	175	(194)
	X-rays, abdomen shielded.	1950	275	(194)
	X-rays, abdomen irradiated, rest shielded	1025	134	(194)
Rats	X-rays, whole body exposed.	750	150	(195)
	X-rays, upper body exposed	1750	130	(195)
	X-rays, lower body exposed	1080	136	(195)
Dogs	X-rays (275 r, 250 KVP), whole body	275	2250	(189)
	X-rays (226 r, 250 KVP; 1000 r, 50 KVP), whole body....	1226	2580	(189)
	X-rays (205 r, 250 KVP; 3000 r, 50 KVP), whole body....	3205	3880	(189)
Dogs	1000 KVP X-rays, whole body exposed	250	2500	(196, 197)
	1000 KVP X-rays, upper 54 per cent of body exposed	1775	9600	(196, 197)
	1000 KVP X-rays, lower 46 per cent of body exposed	855	3900	(196, 197)

tational exposures behind properly shaped shields, studied acute lethality in rats exposed to a depth-dose distribution simulating that calculated for the proton spectrum of the June 16, 1959, solar event inside 10 g/cm^2 inherent filtration and compared the results with those of uniform Co^{60} irradiation (Table III-6). Under the depth-dose exposure conditions, the midline dose to the animals was 25 per cent of the surface dose. The average LD_{50} surface dose for nonuniform exposure was approximately 3 times that for uniform exposure (2590 and 830 rads, respectively). The respective midline LD_{50} doses were 650 and 830 rads, and the ratio of volume or integral absorbed dose (nonuniform to uniform) under the two conditions was 1.5. The tissue depth at which the LD_{50} doses were the same was approximately half-way between the surface and the midline, which probably corresponds grossly to the mean effective depth of the bone marrow of the rat. More studies of this type in which the ratio of midline to surface dose is varied from about 5 to 80 per cent are highly desirable. These results and those reported in Table III-5 would seem to justify using the average absorbed dose at 5 cm depth as a first approximation of the early hematopoietic effects of radiation exposure involving a nonuniform depth-dose distribution.

Variation in thickness of the inherent shielding of the spacecraft will cause topically nonhomogeneous dose distribution resulting in what is commonly referred to as partial-body exposure. If a part of the body is shielded, exposure to a given radiation flux will be much less effective than if the total-body is exposed. Naturally, the effect of partial-body exposure may be expected to vary qualitatively and quantitatively with the region and area or volume of the body exposed. Effects of partial-body exposure have been studied extensively in animals, and such data as exist in man confirm the general conclusion that topically nonuniform exposure is less effective than uniform exposure for production of both early and late manifestations of radiation damage. Animal experiments have been conducted in which the upper portion of the body was shielded and the lower portion irradiated, and vice versa. Individual tissues and appendages have been

shielded (liver, spleen, pelvis, head, all or portions of the gastrointestinal tract, etc.) and the rest of the body exposed. In all cases of partial-body shielding, lessening of radiation effect resulted. Observations have involved both early[192-197] and late [198-202] manifestations of radiation damage. Tables III-6 and III-7 summarize respectively some of the experimental observations of variation in LD_{50} and degree of life shortening with body region and volume irradiated.

There is no generally applicable way of quantitating dose-effect relationships for the more general radiation

TABLE III-7. VARIATION OF DEGREE OF LIFE SHORTENING EFFECT WITH BODY REGION AND VOLUME EXPOSED (MICE)

Exposure Conditions (250 KVP X-rays)	Integral Dose (kg-rads)	Decrement in Life Span (days/kg-rad)	Reference
300 r Whole Body	7.8	16	(199)
560 r Whole Body	14.6	8	(199)
1200 r (4 × 300) Whole Body	31.2	8	(199)
750 r Bilateral Thorax	6.3	2	(199)
1800 r Right Thorax.	7.7	14	(199)
600 r Right Thorax and Pelvis...	5.6	3	(199)
1200 r Right Thorax and Pelvis....	11.1	8	(199)
1800 r Right Thorax and Pelvis....	16.7	10	(199)
100 r Whole Body	2.3	26	(201)
200 r Whole Body	4.6	24	(201)
400 r Whole Body	9.2	18	(201)
200 r Upper 50 per cent of Body....	2.3	9	(201)
400 r Upper 50 per cent of Body. .	4.6	11	(201)
800 r Upper 50 per cent of Body...	9.2	6	(201)
200 r Lower 50 per cent of Body....	2.3	18	(201)
400 r Lower 50 per cent of Body....	4.6	22	(201)
800 r Lower 50 per cent of Body....	9.2	13	(201)

effects under conditions of partial-body exposure. Ideally, it would be desirable to correlate degree of effect with mean effective dose to the exposed organs. At present, the extent to which specific organ exposures contribute to such effects as the prodromal reaction, early lethality, leukemia incidence, life shortening, etc., cannot be evaluated quantitatively. Even if such evaluation was feasible, it would not be possible, because of the wide variation in distribution of various critical organs, to determine the mean effective organ dose under all possible exposure conditions. In the only mathematical treatment of partial-body exposure,

Blair[203] concludes that the integral body dose for lethality will tend to be the same for whole-body or partial-body exposure when the region and mass exposed are sufficiently great that the average sensitivity of the exposed tissues is the same as for the whole body. He points out, however, that the rule will fail in either direction when the average sensitivity of the exposed tissues is not the same as for the whole body.

The integral body dose concept, therefore, may be of some value when mean effective regional or organ doses cannot be ascertained. It cannot be denied that some organs are more sensitive or critical than others and deserve more protection. The available information indicates that the abdominal region of the body is perhaps a factor of 2 or more sensitive than other parts for both early and delayed generalized effects and thus may deserve more shielding consideration for this reason. Also, the surface-to-volume ratio is small in this region and a given mass of shielding would provide protection for a relatively greater body mass and with less restriction of essential motion.

As approximately 50% of the hematopoietic tissue is contained in the pelvis and vertebrae,[181] effective partial-body shielding of the lower region including the gastrointestinal area will result in a significant portion of undamaged bone marrow which will provide transplant or seeding sources for recovery of this tissue. Such shielding may depress the incidence or severity of the prodromal syndrome as well. The consequences of this partial-body protection may be reflected in human performance capability. Therefore, partial-body shielding may be of some value in maintaining a high degree of crew performance, particularly during periods of exposure to high radiation intensities.

Practical use of the concept of partial-body protection with a given mass of shielding is a complex problem. The radiation type, level, and duration of exposure require consideration as well as the general early and late radiation effects. Protection of an individual organ such as the eye against specific radiation effects requires special attention. All of these factors may influence the design or operational requirements of the space system. Undoubtedly compromises will be necessitated in the trade-off studies deriving the desired optimized system.

3. DOSE FRACTIONATION AND PROTRACTION

a. General Considerations

Radiation exposures in space will not be delivered at a constant dose rate but rather will consist of occasional acute exposures delivered at a relatively high but varying dose rate imposed on a continuous low-level component. The periods of acute exposure will result from penetration of the radiation belts and interception of radiations from solar flare activity. The chronic low-level component will result from primary galactic cosmic rays and the secondary radiations produced by their interaction with the materials of the spacecraft. In general, a single acute exposure delivered at a high dose rate is more effective than the same dose when fractionated or protracted.
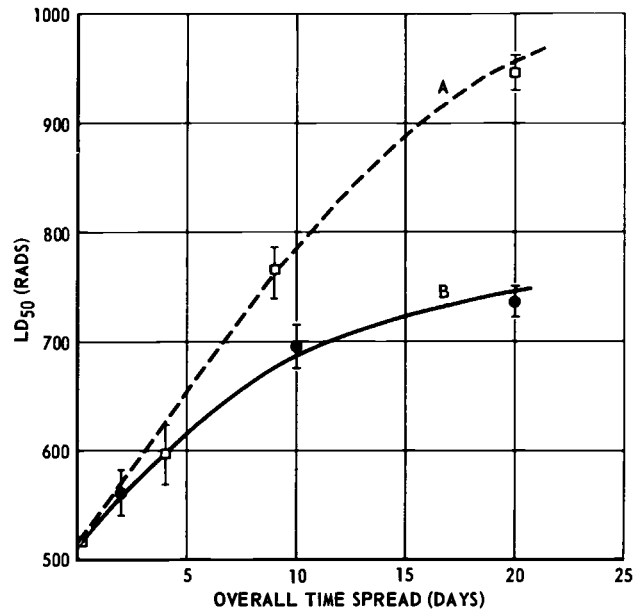
Figure III-20. Effect of fractionation of the dose of acutely delivered 250 KVP X-rays on the LD$_{50}$ of mice.[204] Curve A, dose given in equal daily fractions; Curve B, dose given in two equal fractions separated by increasing intervals.

That fractionation and protraction of dose result in decreasing effectiveness of acute radiation exposure is shown by Figures III-20 and III-21. Figure III-20, taken from Paterson et al.,[204] shows the increase in LD$_{50}$ of mice for irradiation (250 KVP X-rays, 45r/min) given as equal daily fractions spread over increasing overall times (curve A) and for irradiation given as two fractions separated by increasing intervals (curve B). Curve A shows that the LD$_{50}$ rises steeply with increasing fractionation so that over-all extension of the exposure time-spread to 20 days essentially doubled the LD$_{50}$ dose. Curve B shows an increasing LD$_{50}$ with increasing intervals between exposures. The upper curve of Figure III-21 (to be discussed later) shows the effect of dose rate (protraction) of Co^{60} gamma radiation on the LD$_{50}$ of mice. The points (with fiducial limits) are the data of Thomson and Tourtellotte.[205] The curve representing the data is not the one proposed by them.
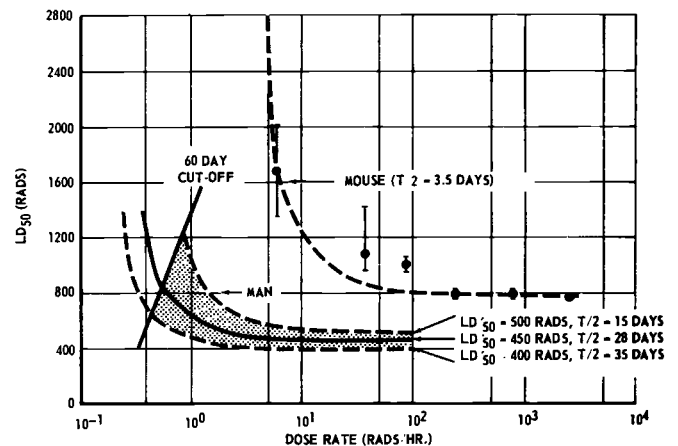

Figure III-21. Effect of dose-rate of Co^{60} gamma rays on the LD$_{50}$ for mice[205] and a theoretically derived dose-rate effect on the LD$_{50}$ for man.

The points themselves show, however, that the LD_{50} of their animals was relatively insensitive to dose rate above about 200 rads/hr but, with increasing dose protraction, it increased rapidly reaching 1400 to 2000 rads at a dose rate of 6 rads/hr. These and many similar observations on both acute and chronic radiation effects suggest, therefore, that dose-response relationships under space exposure conditions will depend on the delivery rate of both the continuous and acute components of dose and on the frequency and magnitude of the acute incidents.

Numerous animal experiments have been conducted in an effort to clarify the quantitative relationships between various radiation effects and dose fractionation and protraction. Many of the reports of these experiments are summarized, elaborated, and referenced in publications by Blair,[206-209] Sacher,[210] Sacher and Grahn,[211] Storer,[212] and others.[213-215] It is generally agreed that the early-effects response of animals to fractionation and protraction of dose results from operation of the animal's compensation or recovery processes. It is further agreed that a residue of each increment of damage remains, manifesting itself statistically as a late or delayed effect. That is, recovery never brings the organism back to the precise state from which it was displaced, leading to the concept of an irreparable or irrecoverable component of radiation injury.

b. Dynamics of Generalized Early Radiation Injury

A number of formulations of the dynamics of radiation injury and repair have been proposed.[206-216] The first and most widely used is that proposed by Blair.[206-208] His model is based on the hypothesis that radiation injury develops in proportion to the dose rate and is repaired spontaneously at a rate proportional to its magnitude, except for a residual irreparable portion proportional to the total accumulated dose. The model is represented mathematically by a differential equation[206] which can be solved for net or residual radiation injury as a function of time after an acute exposure and as a function of time during continuous exposure at a constant dose rate. Following acute exposure, the effective or net injury in terms of equivalent residual dose (D_{ea}) is given by:

$$D_{ea} = D_o [f + (1-f) e^{-t/\tau}],$$

where D_o is the total dose, f is the irreparable fraction of injury, t is elapsed time (days), and τ is the mean repair time of the reparable fraction and is equal to the repair half-time (in days) divided by 0.693.

The equivalent residual dose (D_{ep}) during protracted exposure at constant dose rate is given by:

$$D_{ep} = \gamma [ft + \tau (1 - f) (1 - e^{-t/\tau})],$$

where γ is dose rate (rads/day), t is exposure time (days), and τ and f are the same as above.

Use of these expressions to estimate equivalent residual dose under specific exposure conditions depends on knowing appropriate values for the irreparable fraction (f) and the repair half-time of radiation damage. These values are controversial and dependent on exposure conditions and methods of determination even for experimental animals. They, of course, are un-

known for man and can be obtained only by extrapolation from animal data with full recognition of the uncertainties involved. Michaelson and Odland[217] used an apparent relationship between basal metabolic rate and observed recovery half-times in different species of experimental animals to obtain an extrapolated value for man. Based on this relationship, the recovery half-time was estimated to be between 15 and 22 days. A comprehensive treatment of existing animal data on repair rate and correlation with time of minimum white blood cell count (including human data from the Japanese bombings) by Davidson[218] led to an estimation of the human repair rate of 25 to 35 days. The spread in the estimated value ranges, therefore, from 15 to 35 days. The most commonly used repair half-time is 28 days, which corresponds to a repair rate of 2.5 per cent per day.

The basis for estimating the irreparable fraction (f) of radiation injury is even less secure. The Blair formulation leads to the inference that f would be treated as a constant. Although there is general agreement as to the existence of a permanent or very slowly repaired component of radiation injury, animal experiments show quite conclusively that it is not a constant under all conditions of exposure. There is evidence that f following acute exposure may vary with the size of the dose and that exposures at low dose rates result in smaller values of f than do exposures at high dose rates. Some reported observations of the per cent irreparable injury in various species are shown in Table III-8. It is obvious from these data that little

TABLE III-8. SOME REPORTED VALUES OF IRREPARABLE RADIATION INJURY (f)

Species	Condition	Irreparable Injury (per cent)	Reference
Mice	Co-60 gamma rays (divided acute doses)	5.0	(216)
Mice	200 kv X-rays (continuous)	5.0	(206)
Mice	Fast neutrons (daily doses)	2.3	(207)
Mice	Gamma rays (continuous low-level)	1.4	(207)
Mice	Gamma rays (single acute)	7.5	(207)
Mice	250 kv X-rays (divided acute doses)	9.6	(219)
Mice	250 kv X-rays (divided acute doses)	7.9	(220)
Mice	Fast neutrons (divided acute doses)	9.8	(221)
Rats	200 kv X-rays (chronic acute doses)	1.9	(207)
Rats	1000 kv X-rays (single acute doses)	3.6	(207)
Guinea Pigs	Gamma rays (chronic low-level)	2.9	(207)
Dogs	200 kv X-rays (chronic)	3.0	(207)
Average		5.0	

can be said about the actual value of f other than it appears to be of the same order of magnitude for the various species and appears to be no more than about 10 per cent regardless of exposure conditions. This has resulted in the arbitrary choice of 10 per cent as the irreparable component of radiation damage for man.

If it is assumed that death occurs when the equivalent residual dose equals the instantaneous exposure LD_{50}, the equation for protracted exposure at constant dose rate can be tested by application to the observations of Thomson and Tourtellotte[205] on the dose-rate dependence of the LD_{50} for the mouse shown in Figure III-21. The upper dashed line shows the calculated dose-rate dependence of the LD_{50} for their mice

assuming a repair half-time of 3.5 days, an irreparable fraction of 0.1, and an instantaneous exposure LD_{50} of 770 rads. The fit to the data points leaves something to be desired, which led the authors to propose a different expression and to conclude that dose-rate dependence of LD_{50} could not be accounted for by a single recovery constant over the entire range. The lower part of Figure III-21 shows the same calculation for dose-rate dependence of the LD_{50} of man assuming a repair half-time of 15 to 35 days, an irreparable fraction of 0.1, and an instantaneous LD_{50} of 400 to 500 rads. This is shown primarily to give some indication of the sensitivity of the expression to only two of the present uncertainties in applying the concept to man.

Using an average repair half-time of 28 days ($\tau = 40.4$ days) and an irreparable fraction of 0.1, the equivalent residual dose after acute exposure becomes:

$$D_{ea} = D_o [0.1 + 0.9e^{-0.025t_a}], \quad (Eq. 1)$$

or

$$D_{ea} = a(t_a) D_o, \quad (Eq. 2)$$

where $a(t_a)$ is the multiplier appropriate to time t_a, and D_o is the total acute dose received during the exposure period at a dose rate above the chronic ambient dose rate. It has been suggested[73] that repair from a brief exposure (defined as one occurring over a period of a few seconds to 4 days) may not begin immediately and, therefore, the calculation of recovery should not begin until 4 days after the beginning of the dose. The use of such a 4-day waiting period has the further advantage of simplifying calculations for periods of rapidly changing dose rates. D_o can be taken as the total acute dose during a 4-day period following the onset of the elevated dose rate, and the detailed distribution of the dose in time need not be considered. The time t_a is measured from $t_a = 0$ at 4 days after the beginning of the acute exposure. Should the elevated rate continue for more than 4 days, successive 4-day periods are treated individually by separate application of the equation. Likewise, the equivalent residual dose at time t_p from protracted exposure at constant dose rate becomes:

$$D_{ep} = \gamma [0.1t_p + 36.4 (1 - e^{-0.025t_p})] \quad (Eq. 3)$$

or

$$D_{ep} = b(t_p) \gamma, \quad (Eq. 4)$$

where $b(t_p)$ is the multiplier appropriate to time t_p since the beginning of the exposure.

Calculation of the total equivalent residual dose during a mission subject to a complex radiation exposure pattern consisting of periods of acute exposure superimposed on a continuous low-level ambient background may be accomplished by application of these equations to the individual exposure events and summation of the separate contributions to the total dose. Note that a different time zero is required for each acute exposure incident. Values for multipliers a and b as a function of t_a and t_p for acute and protracted exposures, respectively, are shown in Figure III-22 as an aid to calculation of equivalent residual dose from a complex radiation profile. Figure III-23 shows the results of the application of this method to the derivation of the
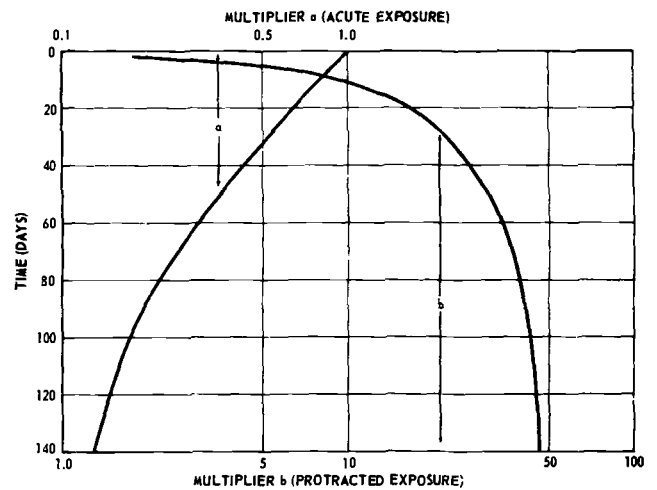

Figure III-22. Multipliers a and b as a function of t_a and t_b, respectively, used in calculating equivalent residual dose from acute and protracted exposure.

residual dose from an assumed 140-day orbital mission with a complex exposure pattern.

It was assumed that the mission involved a 200-nautical mile orbit (30° inclination), an average spacecraft shielding factor of 2 g/cm^2, and interception of a Bailey model flare event on the 17th, 27th, and 57th days. Under these conditions, the chronic or ambient background radiation dose at a tissue depth of 5 cm would be about 0.013 rad/day and each flare event would result in an average acute exposure dose rate of
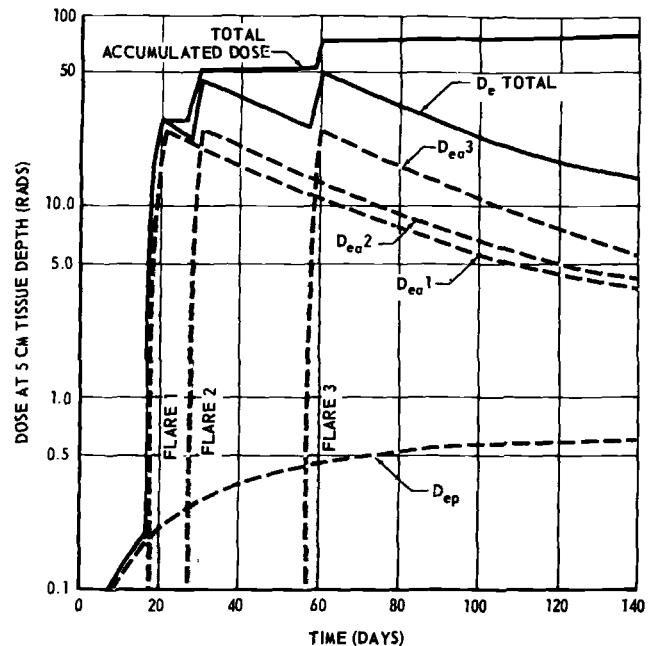

Figure III-23. Application of equivalent residual dose estimation to a hypothetical mission with a complex radiation exposure profile.

about 8.5 rads/day for a period of 3 days. Figure III-23 shows (for this specific case) that the maximum equivalent residual dose at the average effective depth of the bone marrow would be approximately 50 rads immediately after the third flare.

The equivalent residual dose concept was used by Davidson[218] as a basis for defense planning against fallout occurring in the course of military actions and by the National Committee on Radiation Protection and Measurements[73] as a basis for civil defense operations. It has been employed also by Schaefer,[222] Baum,[223] and Odland and Michaelson[224] to suggest radiation exposure criteria for manned space flight operations.

Unfortunately, enthusiasm for the extremely practical features of the equivalent residual dose concept must be moderated for a number of reasons. It should be noted that the assumptions on which it is based and the constants employed have not been validated in man and are somewhat in conflict with a considerable body of present day radiobiological data. Furthermore, limited observations of fractionated exposure of man have indicated a disproportionately sensitive response of the hematopoietic system to a second acute exposure as long as 2 to 3 months after the first.[106,225] Also, below normal peripheral blood counts have persisted in radiation accident victims for many months post exposure.[78] In its present state, the equivalent residual dose concept is applicable only to generalized acute manifestations of radiation injury (as evidenced by hematopoietic end points and lethality in experimental animals), and lack of specific human data suggests prudent restriction of its use.

Other early responses may be expected to show different dynamic dependency on time-intensity-dose factors. Undoubtedly, the probability and degree of prodromal symptoms will be lessened by dose protraction, and considerable information is available on the dynamics of early skin response, which shows a strong dependency on dose fractionation and protraction.

c. Dynamics of Early Skin Response

(1) Dose Protraction—The effect of dose fractionation and protraction on acute radiation response of human skin has been studied extensively in connection with therapeutic radiology. Many of these observations are referenced in sections III.B.2.c and III.C.4. The work of Duffy, Anderson, and Voke[113]
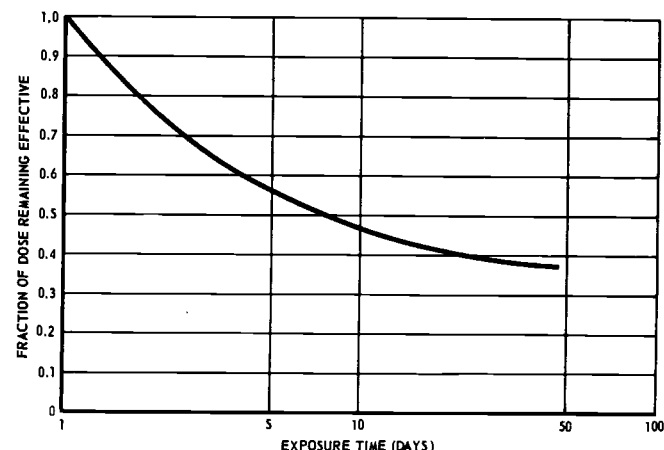
Figure III-24. Fraction of skin dose remaining effective as a function of time over which the exposure is spread.

and MacComb and Quimby[114,115] may be used to estimate the effect of dose fractionation and protraction on early skin response. These investigations involved determining the amount of 200 KVP X-irradiation (LET ~3 kev/μ) which, when delivered in equal fractions, with any specified intensity, produced the same skin reaction as a standard pigmentation or very slight erythema dose (525 r or ~650 to 700 rads, to an area of ~70 cm^2) delivered in a single exposure. The results
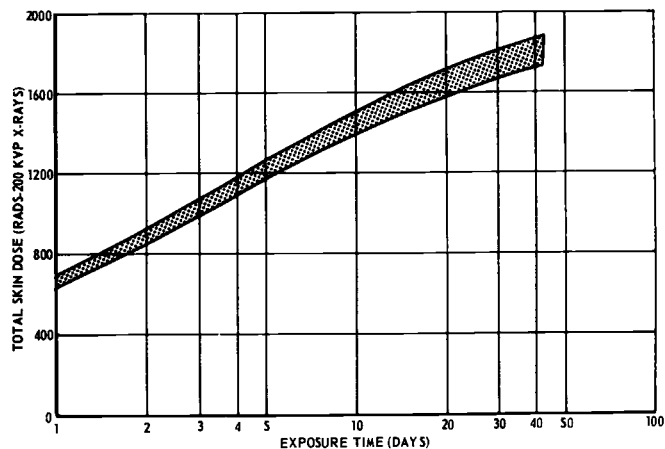
Figure III-25. Total skin dose (of a radiation with a QF of unity) required to produce slight erythema as a function of time over which exposure is spread.

show that the rate of recovery from each of a series of exposures is not the same but changes as a function of the accumulated effect in the skin. It appears that if sufficient radiation is administered in a given time to produce the threshold response, it makes no difference whether it is delivered in small doses with short intervals between or in larger ones with longer intervals. It appears, therefore, that the manner of dose fractionation and protraction is not highly critical. On the basis of these concepts and the observed repair rates,[114,115] Figure III-24 shows the fraction of the skin dose that is still effective as a function of time over which the dose is delivered. The curve is applicable for dose rates from 25 to 1000 rads/day. Since the manner of fractionation is not critical, it makes little difference whether the dose is given in increments throughout the time period or delivered continuously. Figure III-25 shows the total skin dose of 200 KVP X-rays required to produce slight erythema as a function of time over which the radiation is delivered, taking the single acute exposure threshold as 650 to 700 rads. Figure III-26 shows the maximum daily doses that can be given and not exceed the total doses specified in Figure III-25 for different periods of protraction. This is for daily fractionation in equal exposure increments and is the simplest and the preferred exposure schedule.

The possible practical use of these figures to space operations can be visualized by hypothetical examples. Assume a crew member had to perform a job outside the spacecraft requiring 10 working hours where the dose rate at 0.1 mm depth in the skin from a radiation having a QF of 1.5 (Figure III-16) was estimated at
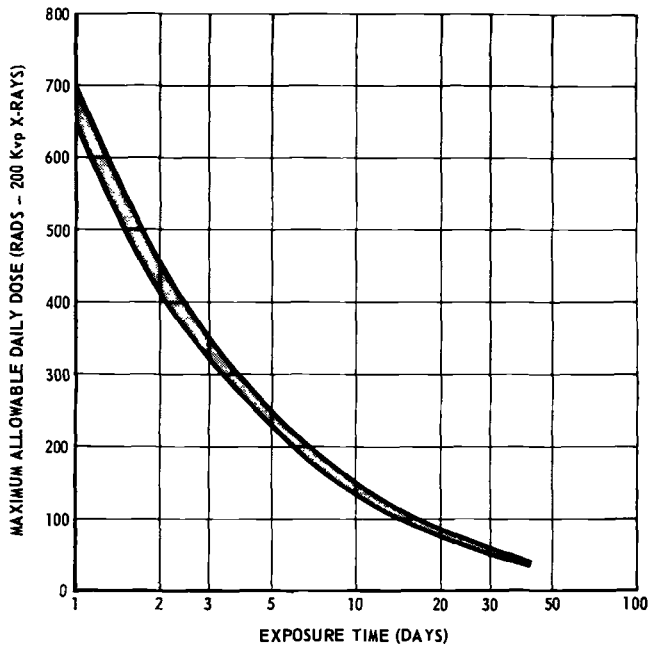
Figure III-26. Maximum daily radiation dose (QF=1) that can be given and not exceed slight erythema threshold as a function of period over which exposure is protracted.

100 rads/hr. Over how many days would the work have to be extended so as not to exceed the slight erythema reaction threshold? The total dose he will receive in doing the job will be 1000 rads or 1500 rems. Referring to Figure III-25, one determines the exposure time (in days) over which the total exposure must be spread in order not to exceed the threshold. Since the curves are in rads of radiation having a QF of unity, it is necessary to make the proper rad-to-rem conversion in using the data. The allowable exposure time for 1500 rems is 10 to 14 days. Referring now to Figure III-26, one determines the maximum delivered daily dose that can be accepted. For the slight erythema threshold, it is 107 to 150 rems/day. The daily working time at a dose rate of 100 rads/hr will be 40 to 60 minutes.

Another example is illustrated in Figure III-27 in which the curve for total exposure dose versus exposure time for slight erythema (Figure III-25) is plotted along with the integral proton plus alpha particle dose, in rem, for the triple flare event of July 10, 14, and 16, 1959, derived from the dose rate data under 1 and 2 g/cm² spherical shielding reported by Freier and Webber.[54] The integral dose data were converted to rems by multiplying by a QF of 1.5. As shown, the plot assumes the mission began on the morning of July 10, 1959. Inside 1 g/cm² of shielding, the second flare (July 14) would have exceeded the skin erythema dose. Shielding of 2 g/cm² would have provided adequate protection against early skin response.

(2) Area Exposed—In considering the debilitation that might result by exceeding the skin erythema threshold, it is very important to consider the size of the area exposed. If indeed 650 to 700 rads of 200 KVP X-rays are a true erythema threshold, then no erythema should appear until that dose is reached regardless of whether the area exposed is a few cm² or

the total body surface (~1.8 m²). The threshold for production of a second-degree thermal burn is about 3.8 cal/cm² and independent of area. A second-degree burn over an area of 1 cm² is not serious; however, such a burn over 80 per cent of the body surface is usually fatal despite heroic therapy.

Jolles and Mitchell[118] studied the effect of area on the skin "tolerance dose" of 180 KVP X-rays (HVL, 1.25 mm Cu; FSD, 40 cm). As an end point, they used moist desquamation of the treated area which could be healed with routine dressings within 4 weeks. The range in area investigated was from 19.6 to 300 cm², and observations included both single and fractionated exposures. On the surmise that the ability of the skin to tolerate radiation damage depended in some way on the undamaged tissue surrounding the exposed area, they empirically related the "tolerance dose" to the cube root of the perimeter divided by the area (i.e., TD $\infty \sqrt[3]{p/a}$). This implies a shape as well as a size effect of the tolerance dose.

Conversion of their exposure doses to skin doses by correcting for backscatter as a function of field size showed that the majority of their surmised p/a effect was due to enhanced skin dose from backscatter. There was, however, a small area effect not accounted for by dose correction. This amounted to about 20 per cent when extrapolated from an area of 70 cm² to an area of about 5 per cent of the body surface, beyond which there was little or no change. If the erythema threshold is exceeded, the possibility of increasing decrement in performance as a result of increasing discomfort and trauma with increasing area affected suggests that it may be wise to decrease the curves shown in Figures III-25 and III-26 when the potential area exposed involves 5 per cent or greater of the total body surface.

Their observations of effect of exposure protraction on skin response were corrected for backscatter also and compared with the curve for total skin dose as a function of protraction time (Figure III-25) derived from the data of MacComb and Quimby.[114,115] Although the curves had slightly different shapes, when
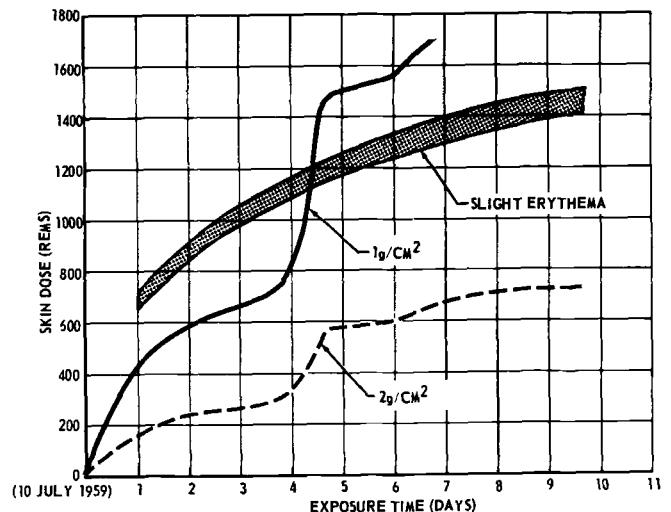

Figure III-27. Application of the dynamic skin response concept to the triple solar flare event of July 10, 14 and 16, 1959.

normalized at the point of minimum error, they agreed to within about 15 per cent or less for protraction periods out to approximately 6 weeks. This adds a degree of confidence to the skin dose protraction function used in Figure III-25.

4. SPACECRAFT DESIGN AND OPERATIONAL FACTORS

The inherent shielding and internal environment of a spacecraft are determined by engineering design criteria dictated by the structural and operational requirements of the particular mission. Other operational conditions (e.g., weightlessness) are imposed by the nature of the ambient space environment. Still others (e.g., nature of the cabin atmosphere) are imposed by operational and engineering decisions. These requirements and conditions constitute factors which can influence the degree and nature of the radiation problems of manned space flight. The nature or extent of influence some of these factors may have on radiation response is not known. Recognition and general discussion of a few of the more obvious ones seem justified, however, as a matter of completeness.

a. Inherent Shielding in Spacecraft Design

Singularly, shielding is the most important factor in radiation protection through modifying the response by minimizing exposure. Radiation shielding has developed to the stage of a highly complex and sophisticated science[61] which cannot be covered here. Generally speaking, however, it is important to recognize the potential of the shielding mass inherent in any space system for the protection of space crews. Any decrease in exposure decreases the probability of radiation effect; partial-body exposure is less effective than total-body, and some regions of the body are more radiosensitive than others. This leads to the obvious possibility, when compatible with engineering and operational design, of arranging structural elements, equipment, and supplies to minimize radiation response of the crew.

b. Temperature

The temperature of the interior of a manned spacecraft is designed to a comfort level of 20°C. Under a number of possible situations, a wide range of variations of the interior temperature of the vehicle can occur. If such occurred during exposure, radiation effects may be altered in relation to the extent of the temperature change from the adaptive temperature level.

The relationship between temperature *per se* and radiation effects is difficult to evaluate in mammals because of overriding secondary responses. Any temperature change from the adapted or comfort level constitutes a stress. Stapleton and Curtis[226] and more recently Kimeldorf *et al.*[227] have shown that exhaustive exercises enhances radiation lethality. Smith *et al.*[228]

found an increased lethality with cold stressing of nonacclimatized mammals.

Certain of the temperature effects can also be attributed to the induced changes in circulation or in oxygen tension. Carty[229] quite early showed that sensitivity to radiation is dependent upon blood flow to the exposed area and that the beneficial effects of chilling the skin can be ascribed to vasoconstriction leading to decreased blood flow with a decreased oxygen tension in the vascular bed of the exposed region.

If any generalization as to influence of temperature variations on the radiation effects in man is possible, it is to the effect that all such changes from the acclimatized value may tend to potentiate response to radiation exposure.[230]

c. Barometric Pressure

It is well established that man has thoroughly adapted to altitudes of approximately 15,000 feet where the barometric pressure is 8.29 psi and the Po_2 89.6 mm Hg.[231] He can also acclimate to an altitude up to approximately 10,000 feet with a barometric pressure of 10.1 psi and a Po_2 of 109.2 mm Hg quite readily. Extensive data as to the consequences of rapid and short-term exposure with and without adequate oxygen to altitudes corresponding to a pressure of approximately 5 psi are available.[232] However, data as to the consequences of prolonged exposures to reduced pressures such as 5 psi with 100 per cent oxygen are scanty and such as are available are contradictory.[233,234] A barometric pressure of 5 psi and even 7 psi with adequate oxygen causes the environment to become an unnatural one for man, since there are no data which show that man can become completely adapted to such an environment. Therefore, it must be assumed that the reduced pressure of the interior of the spacecraft may stress the crew and as a consequence possibly influence radiation response.

d. Oxygen Effect and Hypoxia

The existence of a relationship between oxygen tension and radiation effect has been definitely established. The sensitivity of certain bacteria to X-rays is directly dependent on oxygen concentration. The maximum sensitivity ratio between the oxygenated and anoxic states may be as much as 3. The oxygen effect appears to decrease with increasing LET of the radiation. It is suggested that oxygen enhances the radiation effect by reacting with ionized target molecules which, in the absence of oxygen, might be restored to their normal state.[235] Hypoxia has been shown to reduce mortality due to radiation in many biological systems,[236] i.e., yeast, tumor cells, etc., and the original work of Dowdy[237] with rats is well known. The 30-day LD_{50} for rats irradiated in 5 per cent oxygen is approximately twice that for animals exposed in air. Similar work with mice indicated significant protection, but the limits were narrow. Mice irradiated in 7 per cent oxygen were protected, but 5 per cent oxygen was not sufficient to sustain life during the irradiation period,

and 10 per cent oxygen did not provide protection.

Chemically-induced hypoxemia has been shown to provide various degrees of protection, and in some cases the data are conflicting. p-Aminopropriophenone, which produces methemoglobinemia, has given 72 per cent survival in mice receiving a lethal exposure, and results with sodium nitrite, vasopressin, and carbon monoxide were similar.[238-240] Carbon monoxide reduced the radiosensitivity of mice, rabbits, and rats, but carbon dioxide has not been effective.[238,240-242] There is some evidence also that hypothermia, possibly because of the lower temperature itself and possibly because of the decreased blood flow resulting in a lower oxygen tension, increases the survival rate in newborn rats and mice.[238,243,244] It is of interest that the protective effect of cysteine is enhanced in mice breathing 10 per cent oxygen even though the Po_2 of 76 mm Hg alone does not provide protection.[286]

Interest in possible tumor therapeutic applications of increasing radiation sensitivity with increasing oxygen tension has led to therapeutic trials with oxygen pressures up to 3 atmospheres.[245] Wright and Howard-Flanders[246] showed that the radiosensitivity of rat tail tissues increased rapidly with increasing oxygen pressure from 0.1 to 0.4 atmosphere. Sensitivity continued to increase, though less rapidly, up to 3 atmospheres. The pioneering work of Gray et al.[247] suggests that the maximum increase in radiation sensitivity that can be produced by oxygenation is a factor of about 3 over that of the anoxic state.

Conclusions from the existing data, in terms of man and in particular manned space flights, are not possible at the present time; however, the apparent relationship between available oxygen and radiation damage may be a factor in considering space cabin atmospheres.

e. The Gravity-Free State

The possible influence of weightlessness on radiation response in man is completely conjectural at this time. The environmental hypodynamic studies of Graveline et al.[248] and the bedrest studies of others[249,250] have indicated that the possible physiological effects of the gravity-free state may be far reaching if the assumption is made that bedrest and the hypodynamic environment are valid but limited analogs of such states. The results of these investigations have shown the following more important consequences:

(a) Loss of cardiovascular compensability.
(b) Loss of muscular tone and mass.
(c) Bone calcium depletion.
(d) Nitrogen imbalance.

If these changes are considered in toto, they indicate that the possible effects of weightlessness in man may be gradual but general debilitation which results in a loss of his physical stamina. In some respects, these effects resemble the general ones of radiation. There is a possibility also of a synergistic effect between the gravity-free state and acute radiation exposure for production of fatigue, nausea, vomiting,

and other signs and symptoms associated with the prodromal radiation response. Therefore, in the interests of ensuring suitable radiation safety under all possible conditions, it must be assumed that the gravity-free state may potentiate the space radiation effects in man.

5. MEDICAL TREATMENT

There are two basic approaches to the modification of early radiation response through medical treatment: prophylaxis and therapy. As unimpaired crew performance during manned space operations is the desired objective, prevention of early effects will allow its achievement. Thus, prophylaxis is the preferred approach, but if such measures are impractical or are unavailable and serious exposure occurs, therapeutic measures must be resorted to.

a. Prophylaxis and Chemical Protection

That certain chemical compounds provide some measure of protection from acute radiation exposure has been demonstrated repeatedly.[237,251-254] The mechanism of protection is poorly understood, but the most widely accepted theory is that the chemical agents compete for and react with the potentially harmful free radicals which result from the ionization of water. Experimental evidence also exists which suggests that protection is afforded by (a) local tissue hypoxia (i.e., a decrease in the amount of oxygen available for reaction with the free radicals); (b) reaction with and protection of biological sites normally the target of free radicals and ions; and (c) alterations in tissue metabolism, repair, or permeability.[237,255-258] One or more of these modes of action may play a role in protection, depending upon the nature of the specific chemical agent.

The case for various modes of chemical protection is founded, in part, on experimentation demonstrating roughly equivalent protection with chemicals of widely different molecular structure and reactivity. Many sulfur-containing compounds, metabolic and enzyme inhibitors, certain pharmacologically-active substances, anoxia-producing compounds, alcohols, etc., have been reported as having protective effect.[237,255,256,259-261] Compounds containing a free basic amine group and a free sulfhydril group with the two separated by not more than three carbon atoms are particularly effective. Studies with mice and mercaptopropylamine showed 100 per cent survival 30 days after exposure to a normally lethal dose, but only 26 per cent survival when the animals were protected by a 50 per cent larger dose of mercaptobutylamine.[262,263] Mice given AET [5-(2-aminoethyl)-isothiuronium dibromide] intraperitoneally and exposed to a single acute whole-body exposure of 700 r demonstrated at least 90 per cent survival after 30 days. Control animals could not survive more than 2 weeks under the same condition. Further AET gave proportional protection throughout an exposure range of 500 to 1000 r.[264] The

complexity and uncertainties in the mechanism are exemplified by difference in protective action of the dextro and levo forms of 5,2-aminobutylisothiourea dihydrobromide. The former isomer is effective at low dose levels (0.5 mg/mouse) against a radiation dose of 900 r, but an 8 fold increase in the chemical dose results in an $LD^{30}/_{50}$ of only 1100 r. The levo form of this compound is only about one-third as effective as a protector against radiation, but the isomers cannot be differentiated in terms of their toxicity.[265] Of interest in consideration of sulfur-containing compounds is the ineffectiveness of cystine, methionine, sodium sulfide, etc., to provide protection.[237,254]

PAPP (p-aminopropriophenone) is representative of one type of anoxia-producing chemical that has been shown to enhance survival in animals and is discussed briefly in the anoxia section. Changes in tissue metabolism seem to be the basis for the protective effect of pharmacologically-active compounds such as hormones, neurodrugs, etc., but by and large, protection has not been explained. The survival rate of mice has also been increased by injection of relatively inert compounds (i.e., powdered quartz, glass, etc.[266]).

In light of present knowledge, the practical application of chemical protection is beset with difficulty. In general, the more effective compounds are toxic, they afford little or no protection against chronic exposure, the timing of dose administration is critical, and the animal data cannot be extrapolated to man with any degree of certainty. Further, all physiological or functional systems are not equally protected and some systems receive no protection. Individually and collectively, these shortcomings impose severe limitations on the value of chemical prophylaxis.

If some of the protective action is indeed due to reaction of the protector with free radicals, then the administration of the dose must account for the relatively rapid rate at which most protective agents are metabolized and the time of free radical formation (on the order of 1 microsecond[255]).

The toxicity of many of the compounds no doubt is due to their competitive reaction with cell processes in the absence of radiation-induced free radicals, and herein may lie the major difficulties in protection against fractionated chronic exposure. In one chronic study with mice exposed to 50 to 100 r/day until death, combinations of AET, MEA (mercaptoethylamine), serotonin, and PAPP did not increase survivability over that of controls.[267] The investigators felt that cumulative toxicity of the chemical agents offset any beneficial effects derived from protection against radiation injury. Additional possible evidence of cumulative toxicity as a result of long-term administration of MEA and serotonin has been reported.[268] Others suggest that the biological effects of chronic and acute radiation exposures are different in degree and that compounds which afford protection against acute exposure may not necessarily be the most effective in chronic situations.[255]

The more promising of the radioprotective drugs have been tested, singularly and in various combinations, in irradiated monkeys.[269-273] Although significant protection against acute radiation death has been achieved, the effectiveness of such drugs in man has not been demonstrated, and it appears presently that prevention of acute radiation damage by means of drugs has not reached the stage of practicality.

b. Therapy

Radiation injury, like any other, is treated symptomatically as dictated by the severity and type of symptoms, patient history, etc., and by available facilities. In situations where the prodromal reaction, serious bone marrow damage, gastrointestinal injury, and shock are evident, a number of measures may be required. Antiemetics, sedation, intravenous feeding, bedrest, excellent nursing care, strict asepsis, and prophylactic antibiotics may be indicated. In very severe cases, tubal gastrointestinal decompression, fluid replacement, antihypotensive agents, and bone marrow transfusions may be indicated as desperation measures.[77,106,274,275]

Therapeutic mitigation of the prodromal syndrome has been tried extensively without confluent success. Good results have been claimed (and in many instances disclaimed) following administration of sodium chloride; various members of the vitamin B complex, especially pyridoxine; vitamin C; parenteral liver therapy; antihistamines; hormones (e.g., ACTH); antiemetics; and a host of other drugs.[89]

Treatment of patients with the hematopoietic radiation syndrome presents the same problems as the management of any other pancytopenia. However, the irradiated patient may have an advantage in that the aplastic state of the bone marrow may be reversible. Bone marrow transplantation should be effective during the suppressive phase of marrow function. Homologous bone marrow transplants have proved disappointing because of immune reactions;[276] however, autologous marrow should not induce immune responses when reintroduced into the subject. Patients whose hematopoietic tissues were rendered hypoplastic by radiotherapy and afterward given autologous marrow showed more rapid repopulation of marrow sites and recovery of peripheral blood than those not given autologous transfusion.[277] Since it is now possible to store bone marrow and to keep it viable for relatively long periods of time,[278] autologous marrow banks for space crews may be a possibility worth continuing consideration. While there is no doubt that under certain circumstances the availability of autologous marrow will not be life-saving (in the dose range of acute gastrointestinal and central nervous system lethality), in the range of hematopoietic lethality it may make the difference between life and death. Since there is some risk and considerable trauma and discomfort associated with bone marrow excision, equating the risk involved with the potential benefits to be derived should be considered. This requires an evaluation of the extent or degree of the need for autologous marrow storage in terms of operational factors.