DRAFT

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Dose-effectiveness Modifying Factors in Military and Space Radiation Medicine*

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Dose-effect relationships, and factors that modify these relationships, are fundamental to the characterization of biological responses to radiation, and to the utilization of radiobiological data and principles in the applied disciplines of radiation biology. The applied disciplines are radiation protection, radiation therapy, military medicine and space medicine. Quantitative data are essential if valid and accurate predictions of the degree of biological effect are to be made from physical measurements of dose parameters in a given radiation environment.

The object of this paper is to review in some detail a number of physical concepts and parameters, as well as biologically-determined dose effectiveness modifying factors, that must be taken into account in quantitative prediction of the degree of biological effect from a given exposure. Only dose-effect relationships of concern in Military and Space Radiation Medicine are considered; the analagous problems in Radiation Protection and Radiation Therapy are not dealt with. Emphasis is placed on concepts rather than on specific values for dose-effect relationships or dose-effect modifying factors.

Definition of Quantities and Units

Standard physical quantities such as exposure (in air or in tissue), absorbed dose, exposure rate, dose rate, fluence, flux, kerma, etc. have been defined recently elsewhere (1), and need not be redefined here. Definitions of QF, dose-equivalent and rem are also given (1), in the context of the application of these terms in radiation protection. The

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DRAFT

ICRU has not to date provided terms with meanings conceptually similar to those of QF, dose-equivalent and rem, for use in the applied disciplines of radiotherapy, military medicine and space medicine. In the absence of such terms, those defined for radiation protection purposes will be utilized below with meanings conceptually identical to those assigned these terms in radiation protection.

The term radiobiological effectiveness (RBE) is reserved for use in radiobiology, and is defined as the ratio of the absorbed dose of a "standard" x- or gamma radiation required to yield a given degree of a given biological effect, to the dose of an "unknown" (usually high LET) radiation required to give the identical degree of the same biological effect. The term QF, though conceptually similar, differs in that the QF has an assigned value, arrived at by a body of experts on the basis of several considerations in addition to the radiobiologically determined values of RBE for the particular effect in question. The term "dose equivalent" is not limited in meaning to the product of the absorbed dose and the QF. Rather, the dose equivalent is equal to the product of the dose and of any number of modifying factors that may be pertinent, including a quality factor, a distribution factor, and any other necessary modifying factors. Additional comments on the meaning of the dose-equivalent and rem will be given later in the paper.

Absorbed Dose and its Determination

The basic measured physical parameter that determines the degree of biological effect is the energy absorbed per unit mass, or the absorbed dose, expressed as rads. This is consistent with basic pharmacological principles, in that it is the dose of an agent that actually reaches the organ of interest that is determining with respect to the degree of effect. Thus

DRAFT

it is not the exposure (in air) or, in analogy, the amount of drug in a syringe or the amount of drug in a capsule given orally that is determining. It is the amount of energy absorbed, or in analogy the amount of drug actually injected or absorbed and reaching the organ of interest that determines the degree of effect. Thus while it may be expedient, convenient, or even necessary under some circumstances to express an exposure in terms of a quantity other than absorbed dose, one should not lose sight of the basic importance of absorbed dose.

If is, of course, true that absorbed dose under most conditions cannot be measured directly and must be estimated from other parameters. Some of the principal steps required will be outlined below. Low LET radiations will be dealt with first, following which neutron radiation will be discussed.

Under many circumstances the primary dose parameter available will be the exposure or "air dose" measured in an essentially free field. The relationship between the exposure in air and exposure in tissue* is a strong function of the energy of the radiation and the geometry of the exposure. This is depicted in Figure 1. The ratio of the exposure in tissue, to the free field exposure in air at a point corresponding to the proximal surface of the animal or phantom, is given. With unilateral exposure, the exposure in tissue at the proximal surface is higher than the exposure in air because of build-up and back scatter. The dose is attenuated rapidly in large animals so that even with relatively penetrating radiations, the exit dose may be considerably below either the exposure in air or the exposure in tissue at the proximal surface.

Thus with unilateral exposure, the exposure of the proximal tissues may

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*The exposure in R, measured in a small volume of air located within tissue.

considerably exceed that of the exposure in air and the exposure of distal tissue may be well below that in air. Also, if small animals are exposed to whole body irradiation under full backscatter conditions (e.g., in the location of proximal tissues in Fig. 1), the exposure in tissue could exceed considerably the exposure in air.

If the exposure is multidirectional (bilateral exposure is frequently employed), then the exposure in tissue at any surface is the sum of the proximal entrance exposure in tissue from one incremental exposure added to the exit exposure in tissue from the other. Thus the exposure in tissue at the surface and throughout the animal or phantom may be appreciably below the exposure in air. The exact factor by which it is lower depends on the energy of the radiation, the width of the specimen, and the precise geometry employed. If in addition to multiple exposures from the sides of the animal, some fraction of the dose is delivered from one or the other end of the trunk, the exposure in tissue may be lowered further by an appreciable factor because the effective "width" of the specimen is thus increased.

The exposure in tissue in R may be converted to absorbed dose in rads by applying a conversion factor approximating unity, the exact value of which depends on the energy of the radiation. The factor is approximately 0.95 for x-rays from a moderately filtered 250 kvp unit, and is somewhat greater for higher energy x- or gamma radiations.

The above factors apply in principle to neutron exposure. In this case the "exposure in air" becomes the "kerma in tissue measured in air." This is equivalent to the older "first collision dose", and means in essence the energy <u>released</u> per unit mass in a volume of tissue of very small

dimensions exposed to the neutron beam in a free field. The absorbed dose in tissue from fast neutrons is due principally to recoil protons from hydrogen and to gamma radiation from the interaction of thermal neutrons with hydrogen. Because the recoil protons are essentially all absorbed within the small volume of tissue, the kerma in tissue measured in air is frequently taken as approximating the dose (energy absorbed per unit mass) from the recoil protons. However, the kerma in tissue measured in air is usually an unacceptably poor approximation of absorbed dose from gamma radiation produced as a result of neutron interaction with tissue elements. This is because most of the energy of the gamma rays, unlike that of the recoil protons, escape unabsorbed from the small volume with no compensating absorption of gamma rays from the surrounding air. If the small volume of tissue is located within a large tissue mass, then the loss of energy from gamma rays originating in the small mass is compensated by absorption of gamma rays originating in surrounding tissues.

The absorbed dose in tissue from the recoil protons from neutron irradiation is frequently determined separately from that due to gamma radiation. Such a curve is shown in Figure 2, and the absorbed dose in tissue from the recoil protons is given as a fraction of the kerma in tissue measured in air. The curve was obtained for "fission neutrons" from an experimental nuclear device detonated in Nevada (2). Note that the absorbed dose to all tissues from recoil protons is well below the kerma in tissue measured in air. Note also that the neutrons of this energy are rapidly attenuated in tissue. The relatively high dose on the distal side of the phantom is due to the fact that in the field the neutrons are delivered essentially isotropically once they have gone through a few mean free paths in air.

DRAFT

The gamma contribution to the total dose shown in Figure 2 can be appreciable. The gamma arises principally from the H^1 $(n,\gamma)H^2$ reaction resulting mainly from slow neutrons generated by thermalization within tissues. For the curve shown in Figure 2, the gamma contribution raised the total dose at the midline by a factor of 1.6. Thus it becomes important, at least with energies comparable to those of "fission neutrons", to include gamma radiation in determining the total absorbed dose to tissues. The dose of gamma radiation cannot be deduced readily from the kerma in tissue measured in air, and is a strong function of the spectrum of impinging neutrons.

Specification of "The Dose" Received

It is necessary to specify, for pragmatic reasons, a single value for the dose received by an individual even though different tissues may have received different doses. This single value is designated the "nominal dose." If the absorbed dose to all tissues is essentially uniform, then the value of dose determined for any tissue is of course equal to the nominal dose. Frequently the absorbed dose to the mid-trunk of the individual is taken ("midline absorbed dose"), with no implication that this location is in any way uniquely determining with regards to the effects of total body response. The dose is usually non-uniform, however (e.g., Figs. 1 and 2), and there is thus no unique value of dose delivered. The nominal dose received under these circumstances is arbitrarily designated as the highest value received by any macroscopic volume of tissue other than bone.

The nominal dose received will usually be that delivered to a surface of the individual, the "surface dose" or "skin dose." These terms for dose to the surface tissues are usually adequate; however, more precise

DRAFT

specification may be necessary if equilibrium is not achieved within approximately 0.1 mm of the surface (true particularly of gamma radiations with energies of a few hundred kev and greater, and particularly if effects on the skin are of interest. Under these conditions the nominal dose, the highest dose received by surface tissues, is specified as that at equilibrium depth.

The nominal dose has been specified above as the maximum dose received by tissues other than bone; however, one might argue that conceptually the average dose or gram-rads/gram might be a more suitable parameter (see "Discussion" below). However, "whole body" effects are in reality determined by damage to specific organs such as the bone marrow, and thus there seems to be no basis for considering the "whole body" as the tissue or "organ" of interest for practical purposes. The average dose to some organs, e.g. the bone marrow, has usefulness in determining a distribution factor (DF) for non-uniform exposure (see "Non-uniform Exposure to Penetrating Radiations" below). In addition, average dose to the body is difficult to determine, and extremes of dose to non-sensitive tissue masses such as muscle would reduce even further any possible meaning of this parameter applied to the whole body. For these reasons, then, a specific dose at a specific location is designated arbitrarily as the nominal dose received.

Effects of Principal Interest in Military and Space Radiation Medicine

Of principal concern is the ability of the exposed individual to perform satisfactorily and to complete a given mission. Any type of effect or illness that would impair performance capability during a mission is of chief interest. Thus early effects (can occur minutes to hours after exposure) such as nausea, vomiting, diarrhea, or other more subtle

changes are of first concern. Effects that occur later (days to weeks) such as skin damage, infection, hemorrhage, etc. are also of importance but generally of lesser priority. Serious morbidity and mortality from radiations are in warfare of an importance commensurate with those from other harmful agents; these would of course be viewed with considerable alarm in peacetime space explorations. An increased probability of later effects derived from radiation exposure, such as lens opacification, life shortening, leukemia, and other malignancies are of lowest priority.

Thus the present paper is concerned with the effects of large doses of radiation in the sublethal to supralethal range, over a time span of minutes to at most weeks after exposure.

Dose-effect Relationships in Man for Whole-body Exposure

Mortality. The dose-mortality curve for man will be dealt with first, even though the limitations on the usefulness of such curves are appreciable. These include: (1) under most practical circumstances, it is not mortality but performance ability that is of chief concern; (2) such curves may provide an undue sense of accuracy, and dose parameters are not likely to be sufficiently well known to allow utilization of the curve with any degree or precision; and (3) the curve deals only with statistical probabilities in a large population, and does not allow one to predict accurately for the individual. These limitations should be borne in mind.

On the other hand, the concept of the median dose to produce any given effect has firm roots in pharmacology, and there are excellent reasons for using it. The obvious reason is that at the median point the rate of change of effect with dose is at its maximum, and therefore this endpoint can be calculated much more readily than can any other percent response. Further, the median dose provides an excellent quantitative point of departure from

which one can make estimates with any degree of accuracy warranted by the input data and the situation at hand. The same holds true whether the criterion of effect is mortality from the bone marrow syndrome, mortality from the bowel syndrome, nausea, vomiting, or other. The most clear-cut endpoint, that which is subject to the least misinterpretation, is the LD_{50}.

The earliest estimates of the LD_{50} for man were of the order of 400 to 450 roentgens; the geometry of exposure, uniformity of dose distribution, and location at which the "dose" was measured were not specified. Various estimates have been made over the course of the years, and these are summarized in Chapter 5 of reference 3. Estimates from the Marshallese exposed to fallout radiation indicated an LD_{50} corresponding to about 225 rads absorbed dose for uniform total body exposure (4). The early observation (5) that large animals have essentially a low LD_{50} and small animals a high LD_{50} lent weight to a relatively low LD_{50} for man. Estimates at that time from available data on human beings and on large animals resulted in an estimate of approximately 300 rads, absorbed dose for uniform whole body radiation (5). More recent estimates (3) based on currently available data on large animals, patients exposed therapeutically to penetrating radiations, and individuals exposed accidentally to large doses of radiation are shown in Fig. 3 (3). The estimated LD_{50} is 285 ± 25 rads, absorbed dose, uniform whole body γ-radiation, death within six weeks of exposure. These estimates of dose-effect relationships are now relatively firm, and the precision is probably much better than that of estimates of dose and of dose effectiveness modifying factors which, under practical conditions, will have to be applied.

DRAFT

Nausea and Vomiting. Dose-effect curves for nausea and vomiting in human beings exposed to whole-body radiation is shown in Fig. 4 (3). These signs and symptoms occur within minutes to hours following exposure and last a matter of hours to days at most. They are the so-called "prodromal" symptoms, and must be sharply differentiated from the much more serious gastrointestinal syndrome described below.

The Gastrointestinal Syndrome. The gastrointestinal (G.I.) syndrome, in contrast to "prodromal" symptoms of nausea and vomiting is encountered only at extremely high-dose levels, for example, in man exposed to whole-body radiation, when the dose exceeds 1,000 rads. Severe nausea and vomiting are accompanied by diarrhea. Damage to the gastrointestinal tract, the bone marrow, and other organs is severe, and continuous and severe morbidity can be expected to culminate in one hundred percent mortality, with or without treatment, in seven to ten days.

Early Skin Effects. Skin effects in general are not of serious consideration with whole-body exposure, since in general the dose for serious skin damage exceeds the lethal dose for whole-body exposure. Effects are due to local deposition of energy in the stratum germinativum and are essentially independent of the dose received by other tissues and other areas of the skin. The dose of x- or gamma radiation required for a given degree of effect is strongly energy dependent, and the dose required for a given degree of redness increases as the energy is increased. This, the so-called "skin sparing" effect of the higher energy radiation, is due to the fact that the radiations come to equilibrium at greater depths with higher energies and thus the dose to the stratum germanativum (taken usually as 0.1 mm in depth) is correspondingly lower. For instance, with Co^{60}

gamma radiation compared to 200 kvp moderately-filtered x-rays, for the same dose at equilibrium depth, the dose to the stratum germinativum is about 60 percent less with Co^{60} gamma radiation.

Dose-effect relationships established for 200 kvp x-rays, for erythema and for moist desquamation of the skin are given in Fig. 5 (3). This can be considered as representing the "worst" case for radiations likely to be encountered in military or space medicine, including fast neutrons and protons, i.e., no skin effects will be seen at doses below those indicated, all of which are in the lethal range if delivered uniformly to the entire body. (See additional discussion under "non-uniform Exposure" below.)

The above statements probably hold even if an RBE for protons or neutrons exceeding unity for skin effects is introduced. It is reasonably clear that the RBE (or QF) for penetrating fast neutrons or protons, for lethality, is close to unity; thus the LD_{50} for these radiations is approximately 285 rads (or rem). Thus using the curve in Fig. 5 for skin effects, and RBE of 2 for fast neutrons or protons for skin effects, severe skin damage is encountered with whole body exposure only if the lethal range is entered or exceeded.

Other Effects. It is quite possible that relatively small doses of radiation may impair performance and judgment capabilities, particularly as regards complicated tasks, by mechanisms unrelated to the signs and symptoms discussed above. Dose-effect relationships for man are not sufficiently well established to permit meaningful discussion at this time.

The RBE and QF of Fast Neutrons in Animals and in Man

The RBE for the "bone marrow syndrome" will be dealt with first, following which the RBE for symptoms and mortality related to bowel damage will be discussed. A number of experiments have been done with animals

under conditions in which the dose from neutrons was essentially uniform throughout the tissue of interest (bone marrow of the entire body). Thus the values obtained can be acceptably described as giving the RBE in the radiobiological sense, for mortality from the bone marrow syndrome. Values of the order of 2 have been obtained in mice in a number of experiments (6), although values as high as 4 or 5 have also been obtained (7). The differences may be due to differences in neutron energy and strain of mice employed, although part of the differences may be due to dosimetric discrepancies. Values of RBE for mortality are usually reported in terms of the doses of the two types of radiation required to yield an LD_{50}.

Initial studies with dogs (8), however, yielded an RBE for fast neutrons of approximately unity, and this value has been confirmed using fast neutrons of a different energy spectrum (9). In these experiments essentially uniform exposure of the entire animal was obtained by means of bilateral exposure, and the gamma ray contribution was relatively minor. Thus the value of unity can be considered to be an RBE in the radiobiological sense of the word.

On this basis, one would anticipate that the RBE for fast neutrons in man would be approximately unity. Data on human beings exposed to fast neutrons are insufficient as yet to confirm or reject this value. Data from accidents involving nuclear excursions are too sparse to provide meaningful input. Data from the Japanese exposed in Hiroshima and Nagasaki may, with further analysis, provide such data. The contribution of neutrons to the total dose received by human beings at a distance corresponding to the radiation LD_{50} for those exposed outside of structures is currently believed to be somewhat greater than 0.4 (n/γ ratio of about 0.8); the contribution of fast neutrons to the total dose at the LD_{50} distance in

Nagasaki was negligible. On the basis of these data, and the absolute estimates of total dose at the LD_{50} points, it can be inferred that the "RBE" for neutrons may be greater than 1. However, the dose estimates are not as yet sufficiently firm to allow a definite statement, and it is felt that the data do not presently warrant the employment of an RBE for man other than unity.

The RBE can be determined by itself only if uniform dose distribution is used for both the neutron and standard x- or gamma ray exposure. Uniform distribution of dose from neutron exposure is rarely, if ever, encountered in practical situations (e.g., Fig. 2), and one must deal in addition with a "distribution" factor. However, in assigning a quality factor (QF) for fast neutrons under practical conditions, it is still necessary to specify the factor separately for uniform exposure only, and to deal separately with a distribution factor. The nominal dose of neutrons is specified as the highest dose received by tissue other than bone.

Then:

Dose Equivalent = (Dose in rads) (QF) (DF) ---.

The QF for fast neutrons is presently specified as unity, from currently available data. Methods of estimating values for DF are dealt with below.

At times it may be expedient or necessary to utilize kerma in tissue determined in air as the "dose" of neutrons, and perhaps even to utilize the inverse ratio of their value to the exposure in air of x- or gamma radiation to derive some estimate of the ratio of effectiveness of a "neutron exposure" to that of a gamma exposure. This practice is undesirable from a quantitative viewpoint for a number of reasons. Such values for

"free-field exposure" in no way take into account such highly important and quite variable factors as geometry of exposure, degree of penetration in tissue, radiation quality, and dose distribution. Also, kerma in tissue measured in air does not include the dose from gamma radiations from interaction of neutrons with tissue elements. Thus, such a ratio must of necessity be highly unique to a specific exposure situation, and it must have minimal predictive usefulness for the ratio of effectiveness under other conditions of exposure. In any case, such a ratio is not in any sense a value of QF or RBE, and if used should be specified only in the most non-rigorous terms such as an "effectiveness ratio" or "potency ratio."

The RBE either for symptoms and signs, or mortality, from bowel damage is probably considerably different from that for mortality from the bone marrow syndrome (7, 9). Values from experiments on dogs (9) agree approximately with those obtained with mice, and the RBE for bowel damage appears to be of the order of 2 to 2.5. This serves to emphasize that the RBE is a radiobiologically-determined number, and that the number is specific for the biological criterion of effect or endpoint that is utilized in determining the number.

Dose Rate Factor (DRF)

The effects of low-LET radiation are markedly dependent on dose rate (or more accurately, total time of dose delivery); those of high LET radiations less so. This factor must be taken into account if the total exposure is delivered over a period of time exceeding 6 to 12 hours. The subject is covered in considerable detail elsewhere (3), and thus is not treated here.

DRAFT

Non-Uniform Exposure to Penetrating Radiations

Exposure to ionizing radiations is usually non-uniform under practical circumstances, and quantitative evaluation of the degree of effect from such exposure poses difficult but not insurmountable problems. Although it is easily seen that a non-uniform exposure to penetrating radiation requires a higher dose of radiation to at least some portion of the body to produce a given degree of a given effect, than is necessary with uniform whole body exposure, the full quantitative characterizations of dose and dose-effect relationships are necessarily more complex for non-uniform than for uniform doses. With non-uniform exposure, however, it has been shown clearly (10, 12) that, for death from the bone marrow syndrome, neither the entrance dose, the absorbed dose at the midline of the animal, the exit dose, the integral dose, nor the average dose will "normalize" and allow dose-effect predictions for the full spectrum of different dose distributions. Thus additional factors must be taken into account, and a weighted, dose averaging procedure must be applied to the bone marrow to predict dose-effect relationships, as will be brought out below.

With certain other effects, such as nausea and vomiting, it is principally the local dose to a specific organ, the gastrointestinal tract, that is the determining factor. Thus it is usually adequate in such circumstances to establish dose-effect relationships on the basis of the highest dose that is delivered to any major portion of the abdomen, or more specifically the epigastrium. For skin effects, the dose delivered to any sizable area of skin is determining.

Temporally, nausea, vomiting and skin effects are manifest earlier (hours to several days after exposure) than are the serious and potentially lethal signs and symptoms resulting from bone marrow depression and

pancytopenia (seen usually in the third to fifth week after exposure). Thus for any given dose distribution it is desirable to think first in terms of what organs or body region(s) received the largest dose, and to ascertain what signs and symptoms, if any, would be expected from this circumstance. It is next necessary to think in terms of the overall distribution of dose to the active bone marrow, to determine if any of the signs of infection and hemorrhage, and death, would be expected. In what follows, the evaluation of possible effects of relatively high doses received locally by the G.I. tract and the skin will be dealt with first*, following which consideration will be given to the expected severity of hematopoietic depression.

Nausea and Vomiting. Nausea and vomiting follows exposure of either the whole body, large segments of the bowel, or of the head. Lower doses are required for the equivalent signs and symptoms with uniform whole body than with local irradiation. Thus, a dose-effect curve for whole body radiation (Fig. 4) can be taken as giving the lower limit of doses at which a given incidence of these signs and symptoms can be expected. From this curve, 50% of individuals would be expected to show nausea and vomiting within two days following a dose of approximately 185 rads. Approximately 10% would be expected to show nausea and vomiting at about 70 rads.

As mentioned above, the dose to a large segment of the bowel, or to the head, to produce these signs and symptoms would be increased over those shown in Fig. 4. For exposure of a large segment of the abdomen, the dose to produce a given effect should be increased by a factor of approximately 1.5. For exposure of head alone, the dose required for a given level of

*All effects considered are for single, high-dose exposure occurring in one hour or less. For longer exposure times, the dose for a given effect would be higher.

effect should be increased by a factor of 5 to 10.

The Gastrointestinal Syndrome. The dose required to produce the gastrointestinal (G.I.) syndrome with local exposure of large segments of the bowel is somewhat higher than with uniform whole body exposure. This is because the additional complicating factors of bone marrow depression and subsequent neutropenia and infection, a component of the G.I. syndrome with whole body exposure, is reduced or absent with local bowel irradiation. If any large segment of the bowel has received doses of this high order of magnitude, not only will extensive signs and symptoms (nausea, protracted vomiting, diarrhea) be expected, but some mortality may be expected as well.

Early Skin Effects. Dose-effect relationships established for 200 kvp x-rays, for erythema and for moist desquamation of the skin are given in Fig. 5. The values hold for whole body exposure or local skin exposure. One can expect about a 50% incidence of erythema at a dose of about 600 rads, and 50% incidence of moist desquamation at a dose of about 2000 rads. The dose required for a given degree of effect on the skin is strongly energy-dependent with x- or gamma rays, and the dose required for a given degree of redness increases as the energy is increased (see above).

With fast neutrons and protons, an RBE or QF must be introduced. The value of QF for both these radiations is approximately 2. (3)

Mortality, Bone Marrow Syndrome. Mortality from the bone marrow syndrome, resulting from either uniform or non-uniform exposure, is the result primarily of depletion of the bone marrow with resultant failure of the marrow to deliver mature functional blood elements to the peripheral blood in adequate amounts (13). When the neutrophil (white cell) and platelet counts reach very low levels, usually in the third or fourth weeks following an exposure in the lethal dose range (dose range in which some,

but not all human beings so exposed will die within a period of six to eight weeks, in the absence of treatment), then fever and other signs of infection, and hemorrhage develop. Death ensues in some individuals, depending on the severity of the infection and of the bleeding.

With uniform whole body exposure (same dose to all bone marrow), the number of surviving stem cells in the bone marrow decreases exponentially with dose after a small "pseudothreshold" in the low dose range. When the number of stem cells reaches a critical low level, a few individuals so exposed will die of the consequent peripheral blood element depletion. As the stem cell survival level falls lower with increasing dose, more will die. At the LD_{50} of 286 rads for man, a certain number, N, of stem cells survive. A line showing the numbers of surviving stem cells relative to N (right hand ordinate) as a function of dose is shown in Fig. 6. The abscissa is the absorbed dose in rads. The curve is normalized so that the relative number of stem cells at the LD_{50} for man is 1.0.* The ordinate on the left shows the mortality levels for man corresponding to a given dose of radiation delivered uniformly to all of the marrow (3). Thus from the graph can be read off readily the mortality rate in man (untreated) exposed uniformly to a given dose of radiation and the corresponding relative number or fraction of stem cells surviving at that dose level. For example, the dose of 286 rads corresponds to a 50% mortality rate for man, and a relative fraction of stem cells equal to 1.0; 372 rads gives 95% mortality in man, and the relative surviving stem cell fraction is 0.4.

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*The dose-survival curve for bone marrow stem cells is known most accurately for the mouse, and the slope of the semi-log plot (right ordinate) in Fig. 1 corresponds to that established for this species. The model presented here to handle non-uniform exposure has been shown to apply to the rat and the dog as well as the mouse (references 1-3), using the same slope for stem cells. It is assumed in this paper that this curve also applies to man.

Fig. 6 provides a basis for dealing with non-uniform exposure if one has the dose distribution in man, and the distribution of bone marrow, assumed to parallel that of stem cells. Bone marrow distribution for the "standard man" is given in Table I (14). Dose distribution data are presumed to be available for any given exposure. Each sub-unit of bone marrow appears to act independently of other sub-units, as regards the response to radiation of stem cells in that sub-unit. Given the dose to a number of sub-units of marrow and the percent of bone marrow stem cells in that sub-unit (Table I), one can determine the relative number of surviving stem cells for each sub-unit using Fig. 6. Summing over the entire marrow yields the total relative number of stem cells in the body that would survive the exposure. The mortality level to be expected from this stem cell survival can then be read from the left hand ordinate of Fig. 5.

Example: A man has received a nominal dose of 375 rads.

50% of the bone marrow has received a dose of 250 rads;

25% of the bone marrow a dose of 200 rads, and

25% a dose of 375 rads. Then from Fig. 1:

0.5 of marrow X 1.5	= 0.75
0.25 of marrow X 2.6	= 0.65
0.25 of marrow X 0.4	= 0.1
Total	= 1.50

Thus 1.50 is the relative total number, or relative fraction of stem cells surviving.

From Fig. 6, left ordinate, one finds that a surviving relative fraction of 1.50 stem cells corresponds to an expected 80% survival rate in a population of individuals so exposed.

In the above simple example, only three subdivisions of the bone marrow were used. Much finer subdivisions of dose distribution can be used when data are available, and if, in addition, the complete distribution of dose and of bone marrow are known, a correspondingly more exact numerical integration can be performed.

On the other hand, one can gain a rough estimate quickly of the expected degree of severity of bone marrow depression, and therefore, the probability of mortality, from a given dose distribution. Since the curve for surviving fraction of stem cells shown in Fig. 6 is exponential, by far the largest component of intact bone marrow cells lie in the least exposed bone marrow. Thus a rough estimate of the largest dose received by any major segment of marrow allows one to determine from Fig. 3 the relative number of surviving stem cells in that segment of marrow. If it is above approximately 1.7 or 1.8, one can conclude that there is less than approximately 10% chance that death from the bone marrow syndrome will occur, regardless of what dose is received by the rest of the bone marrow. On the other hand, should the surviving relative number of stem cells in this segment of marrow be of the order of 0.5, then it is important that contributions from surviving stem cells in the rest of the marrow be calculated to give a worthwhile estimate of the chance of surviving the syndrome.

For any given non-uniform dose distribution, a dose of uniform whole-body irradiation that will result in the same mortality rate can be determined from Fig. 6. In the simple example for non-uniform exposure considered above, the calculated relative fraction of stem cells surviving, 1.50, corresponds to a survival rate in man of 80%, resulting also from a whole-body uniform exposure of 235 rads. Corresponding "doses" of uniform whole body exposure thus derived from Fig. 6, however, are in fact identical in

DRAFT

concept to dose equivalent, rather than absorbed dose. This is because in the averaging process for non-uniform exposure, each increment of dose was weighted by the amount of bone marrow irradiated at that dose level, and by the relative effectiveness of that dose increment to destroy stem cells. Thus, in the example above, a survival rate of 80% in man exposed to non-uniform radiation corresponds to a surviving stem cell level of 1.50 N, and a dose equivalent of 235 rems (based on survival rate at the LD_{80} level). The DF is thus (Dose of uniform radiation)/(nominal dose) = 235/375 = 0.63.

NOTE: The model dealt with assumes that, for a man to survive the hematopoietic crisis, his supply of the critical type (or types) of mature cells during this period (descended from surviving stem cells) must exceed the minimum required for survival (3, 6). In these terms, the model described here is based on the assumptions: (a) that the total number of mature cells is proportional to the total number of surviving stem cells, whatever their distribution in the body; and (b) that the requirement for mature cells follow-any non-uniform exposure is the same as that following the uniform exposure equivalent to it with respect to total stem cell survival.

This pair of assumptions appears, on the basis of data on non-uniform versus uniform exposure of mice, rats, and dogs, to be justified for exposures having a moderate degree of non-uniformity--extremes of local doses to any part of the body not exceeding a value of approximately 1,000 or 1,200 rads. Local blood vessel damage at higher doses becomes a significant factor, leading to increased requirements for both neutrophils and platelets. Also, high doses locally to the bowel can produce death in the absence of significant marrow damage (15).

DRAFT

Variation of Dose-effectiveness Modifying Factors as a Function of Dose

The basic dose-effect curve is the "standard" for any given type of effect, attained for low-LET radiations delivered uniformly to the entire body over a period of the order of one hour or less. If the LET or other exposure condition is changed, generally speaking the overall shape of the resulting dose-effect curve changes. Thus the appropriate dose-effectiveness modifying factor (the ratio of doses under different exposure conditions required to yield the same degree of the same biological effect) changes with dose. This is contrary to the popular notion that a given quality of radiation has a definite and unique RBE, fostered at least in part by the practice in radiation protection of assigning (for practical reasons) unique values of QF to a given quality of radiation. On the other hand, the error involved is not serious under circumstances presently considered. At the high doses of primary importance in military and space radiation medicine, the variation of dose-effectiveness modifying factors is relatively small over the dose ranges of interest. Thus for most purposes the variation can be considered a second order effect, at least until such time as dose-effect relationships for man become considerably more firmly established than they are at present.

The Order-dependence of Dose-effect Modifying Factors

If single values are to be assigned to dose-effect modifying factors, then their application must be order-dependent (non-commutative). Since single values of RBE (QF) are usually given for high dose-rate, single exposure, and since RBE (QF) are applicable only to uniform whole-body irradiation, the order of application must be: dose rate factor (DRF); the distribution factor (DF) and the quality factor (QF).

The non-commutativity of the factors can be most simply illustrated as

DRAFT

follows: Denote by $D_A(E)$, $D_B(E)$, and $D_C(E)$ the doses of three irradiation procedures A, B, C resulting in the same degree, E, of the same biological effect, and by $F_{AB}(E)$, $F_{BC}(E)$, and $F_{AC}(E)$ the factors of A relative to B, B relative to C, and A relative to C, respectively. Then,

$$D_C(E) = D_A(E) \times F_{AB}(E) \times F_{BC}(E) \qquad (1)$$

and

$$F_{AC}(E) = F_{AB}(E) \times F_{(BC)}E \qquad (2)$$

In analogy to the (DE) equation, let $D_C(E)$ be the dose of standard radiation and $D_A(E)$ that of the "unknown", which is assumed to be non-standard in two respects. The result of correcting $D_A(E)$ for one of the two non-standard conditions is to give the dose $D_B(E)$ of an intermediate, semi-standard procedure, B. Its value, as well as the factors involving it, depends on the order in which corrections are made. To illustrate, let the standard quality be gamma rays, the standard rate, 100 rads/min., and the effect, 50 percent lethality in 30 days. The following would be a reasonable set of iso-effect (50 percent lethal) procedures:

A. 200 rads of neutrons delivered at 1 rad/min

B. 1200 rads of γ rays delivered at 1 rad/min

C. 200 rads of neutrons delivered at 100 rad/min

D. 720 rads of γ rays delivered at 100 rad/min

If quality is corrected for first, the intermediate is B and the RBE (QF) is 6.0, and the factor for dose rate (DRF) is 0.6. Alternatively, if one corrects first for dose-rate, the intermediate is B^1 and the RBE corresponding to DRF is 1.0, while that corresponding to QF is 3.6. The product of the factors is in each case of course 3.6, as it must be from Eq. 2. It is obvious, however, that when two or more corrections are involved it is at least ambiguous to speak of "the" QF, "the" DRF, etc.

unless the order of application is specified.

Instrument Bias to Exclude "Ineffective Radiation"

From geometrical considerations above, it is quite obvious that beams of low energy, electromagnetic, or low energy neutron radiation (below perhaps 70 kev x- or gamma radiation--perhaps below 800 kev for fast neutrons) are very poorly penetrating and are decidedly ineffective with respect to producing damage to the bone marrow and thus in producing the bone marrow syndrome. Thus it is attractive to bias an instrument such that it will discriminate against low energy radiations in proportion to the effectiveness of that radiation. This would have the seeming advantage that, at least under some circumstances, it would provide a reading that is somewhat analogous to "rem", and obviate the necessity of using dose-effect relationship modifying factors. However, there is much to be said against the use of such a procedure. Any such biasing can be based on the effectiveness of the radiation for only a single type of biological effect, and the same bias in most circumstances would not apply with respect to other types of biological effect. For instance, if an instrument is biased on the basis of the effectiveness of the radiation to produce the bone marrow syndrome, that bias would be quite incorrect with respect to effects on the skin, the gastrointestinal tract, or the central nervous system. All or large fractions of these organs are superficial, and thus even poorly penetrating radiations can be quite effective. Further, the bias built in for a given type of biological effect, e.g., mortality, must be tailored to the particular geometry of exposure on which the bias is based. If the instrument bias is based on bilateral and uniform exposure, for example, the readings would not allow prediction of the degree of biological effect if one were dealing with non-uniform exposure. The most serious objection

DRAFT

to such a bias lies in the fact that once it is introduced, one can no longer derive a "pure" physical parameter from the readings of the instrument, but only readings with the particular built-in bias. Such readings can be quite misleading to individuals who are not knowledgeable as regards dosimetry and the factors that must be considered in deriving the degree of biological effect from physical parameters. A further objection is the fact that since such readings do not provide the basis for valid estimates of the necessary physical parameters, they do not allow one who is knowledgeable with respect to dosimetry and biological effects to give a meaningful interpretation of the readings of the instrument. Statements to the effect that the contribution of the relatively "ineffective" radiations thus biased out may be relatively small does not constitute a valid argument for or against such bias. A reading of a "rem meter" is at best a poor substitute for estimations of exposure or dose.

Discussion

It is seen from the above that predictions of the degree of effect can, under some circumstances, be estimated satisfactorily from curves showing absorbed dose versus expected degree of effect. Such curves for a given biological effect, however, must be specified for certain "standard" conditions of exposure, generally (1) low-LET (x- or gamma) radiation, (2) single dose (total exposure time of the order of one hour or less), (3) uniform whole-body exposure. It is assumed that satisfactory estimates of absorbed dose in tissue can be derived from measurements of exposure in air (x- or gamma radiations) or kerma in tissue measured in air (neutrons).

In the majority of practical circumstances, however, one or more of the "standard" conditions do not pertain. In these circumstances standard dose-effect curves are insufficient in themselves, and it is necessary to apply biologically-determined dose-effectiveness modifying factors in order

to satisfactorily predict the expected incidence of a given effect. The principal factors to be considered at present are the quality factor, the distribution factor, and the dose-rate factor. This can be represented mathematically as follows:

Dose-equivalent = (average absorbed dose) (QF) (DF) (DRF).

A better understanding of the necessity for dose-effectiveness modifying factors may be gained by a brief review of the development of the concept of absorbed dose. Concepts of exposure, exposure in tissue, and finally absorbed dose grew up in the context primarily of low-LET x-radiation. Dose is an "intensive" function and is energy per unit mass, or the sum of numerous micro increments of energy laid down in events*/unit mass. Thus it is basically a macro concept, gram-roentgens or gram-rads/gram, and thus represents an <u>average</u> of energy densities in the mass of interest. The dose alone provides no information nor restrictions with respect to the average size or distribution of sizes of events at the micro level, the extremes of dose distribution that gram-rads/gram may entail at the macro level, nor the distribution of energy deposition in time. Rather narrow restrictions are placed on these variables for the "standard" radiation delivered under standard exposure conditions, i.e., essentially all events are uniformly small in size, dose distribution at micro and macro levels are essentially uniform over the volume of tissue of interest, and the time rate of energy deposition is rapid (exposure time short). When any of the three distributions deviate significantly from those specified for the standard, then the <u>average</u> energy deposition, or absorbed dose, no longer is adequate for precise prediction of the degree of biological effect. It is then necessary to use additionally a dose-effectiveness

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*An event refers to the energy deposited in a mass of tissue of micro dimensions, as the result of the passage of a single charged particle and/or secondaries.

modifier for size distribution of events at the micro level (RBE), for distribution of energy at the macro level (DF), and distribution of energy deposition in time (DRF). Thus all three dose-effectiveness modifiers are conceptually similar.

It is necessary to examine further the concept and meaning of "dose-equivalent." When the absorbed dose in rads is multiplied by one or more of a series of modifying factors such as AF and DF, the actual meaning of the derived dose-equivalent is not obvious. It might be asserted that the modifying factors are pure dimensionless numbers and that, therefore, the product is still, dimensionally, dose. The difficulty with regarding the product of rads and modifying factors to be "dose" may be illustrated as follows. The risk* associated with the absorption of 10 ergs/g from a radiation having a QF of 2 is equated to that with 20 ergs/g from the standard x- or gamma radiation. Although the physical quantities involved are obviously different, both exposures are then regarded as resulting in the same "dose-equivalent" in rem. The physical meaning of "dose" has not changed, which is as it should be. The difficulty is resolved if it is realized that the concept of "dose-equivalent" involves equivalence of the biological effect or the probability of biological effect, rather than an equivalence of absorbed energy. In other words, the modifying factors convert the number expressing the dose in rads to another number that indicates the degree of real or potential biological effect derived from a dose-effect curve for the "standard" radiation delivered under "standard" condition of exposure. Dose-equivalent should then have units of probability of effect, or risk, and the conversion factors such as QF and DF should be

*Risk is taken to be synonymous with incidence of effect, rather than the product of incidence and severity of effect.

DRAFT

assigned the appropriate units of "degree of effect/rad" for the specific degree of the given biologic effect.

Should quantities and units with the same concepts and meanings as dose-equivalent, rem, QF, etc., but with different names, be coined for use in military and space radiation, and in radiation therapy, it would be well to establish an entirely new set of terms. In particular, the misleading term "dose-equivalent" should be avoided. A term should be chosen which implies no physical equivalence of the doses involved.

Specifically, it is suggested that the term "Effect-equivalent Standard Dose" (ESD) be substituted for "dose equivalent." This has the further advantage of obviating any need for the misleading and confusing term "rem." The ESD is in fact conceptually and dimensionally dose and can be expressed in rads. It might instead be expressed in R (since it is x- or gamma radiation), which might aid in setting it apart from the absorbed dose in rads. It could then be called "Effect-equivalent standard exposure", or ESE.

FIGURE CAPTIONS

Figure 1: Depth-exposure patterns in tissue, showing the relationship between the exposure in air and the exposure in tissue at different locations in depth, with different geometries of exposure.

Figure 2: Depth-dose pattern for "fission neutrons", from data obtained from nuclear devices detonated in Nevada. Note the non-uniform distribution of dose, and the discrepancy between kerma and tissue measured in air and absorbed dose in tissue.

Figure 3: Mortality Rate vs Radiation Dose for Man (3).

Figure 4: Nausea and Vomiting vs Radiation Dose for Man (3).

Figure 5: Skin Effects vs Radiation Dose for Man (3).

Figure 6: Dose-survival curve for man exposed uniformly to penetrating x- or gamma radiation (lower curve), and relative survival rate of bone marrow stem cells in any segment of marrow, or the total marrow, exposed uniformly to a given dose of radiation. The dose is given in rads; it is also given in terms of the (dose-LD_{50} for man), or (dose-286 rads). The survival rate of stem cells is normalized to the number surviving at the LD_{50} dose for man, uniform total-body exposure.

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Table 1. Comparative active erythropoietic bone marrow distribution in several mammalian species (1,3)

Grouping	Skeletal Structure	Man at age 10	15	40	Monkey	Dog	Rat	Mouse
1	Skull	7.5*	9.7	13.0	8.7	1.0	6	19.1
	Mandible	0.7	0.9	1.2	2.2	0.1	4	
2	2 Clavicles	0.9	1.1	1.6	0.7	-	-	-
	2 Scapulae	2.9	3.6	4.9	3.9	5.1	-	-
3	Upper limbs (total)	(9.5)	(6.5)	(2.2)	(12.2)	(11.1)	(11)	(5.7)
	2 Humeri	6.1	5.2	2.2	9.2	10.8	-	4.1≠
	2 Radii	0.8	0.3	0.0	1.5	0.1	-	-
	2 Ulnae	0.9	0.3	0.0	1.3	0.1	-	-
	2 Wrist-hands	1.7	0.7	0.0	0.2	0.1	-	1.6
4	Ribs	8.3	9.5	7.1	4.8	20.5	-	16.1
	Sternum	1.6	2.0	2.5	1.5	2.8	-	
5	Vertebrae (total)	(25.0)	(32.0)	(42.9)	(33.1)	(42.6)	(24)	(38.1)
	Cervical	2.1	2.7	3.6	2.2	6.7	-	-
	Thoracic	8.7	11.1	15.0	12.3	17.6	-	-
	Lumbar	6.7	8.6	11.5	17.0	15.0	-	-
	Sacroccocygeal	7.5	9.6	12.8	1.6	3.3	9≠	8.2≠
6	2 Hip bones	12.0	15.3	20.5	12.9	8.9		
7	Lower limbs (total)	(31.2)	(19.4)	(3.9)	(20.0)	(7.9)	35	(12.8)
	2 Femurs	17.5	14.0	3.9	13.3	7.2	19	6.0
	2 Patellae	0.5	0.2	0.0	0.1	0.0	-	-
	2 Tibiae	6.9	2.7	0.0	5.9	0.6	16	4.2
	2 Fibulae	1.0	0.4	0.0	0.5	0.0		
	2 Ankles-feet	5.3	2.1	0.0	0.2	0.1	-	2.6
	Total	99.6	100.0	99.9	100.0	100.0	89	100.0

*Percent of total active bone marrow

≠Includes clavicles and scapulae

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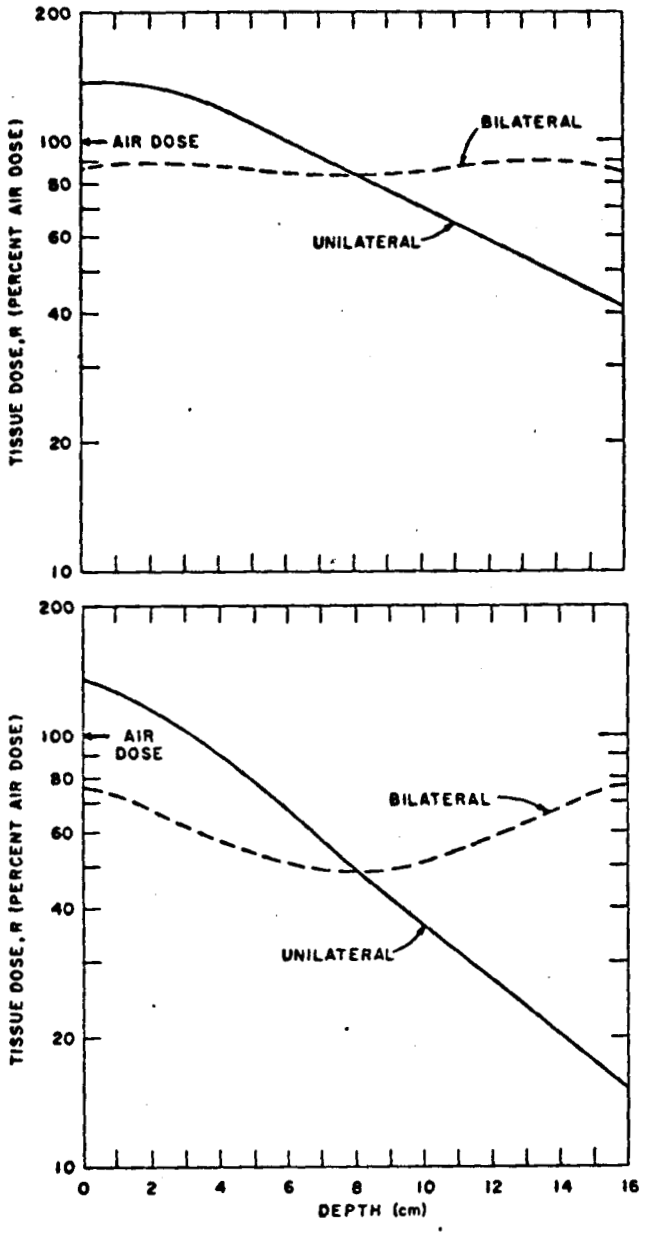
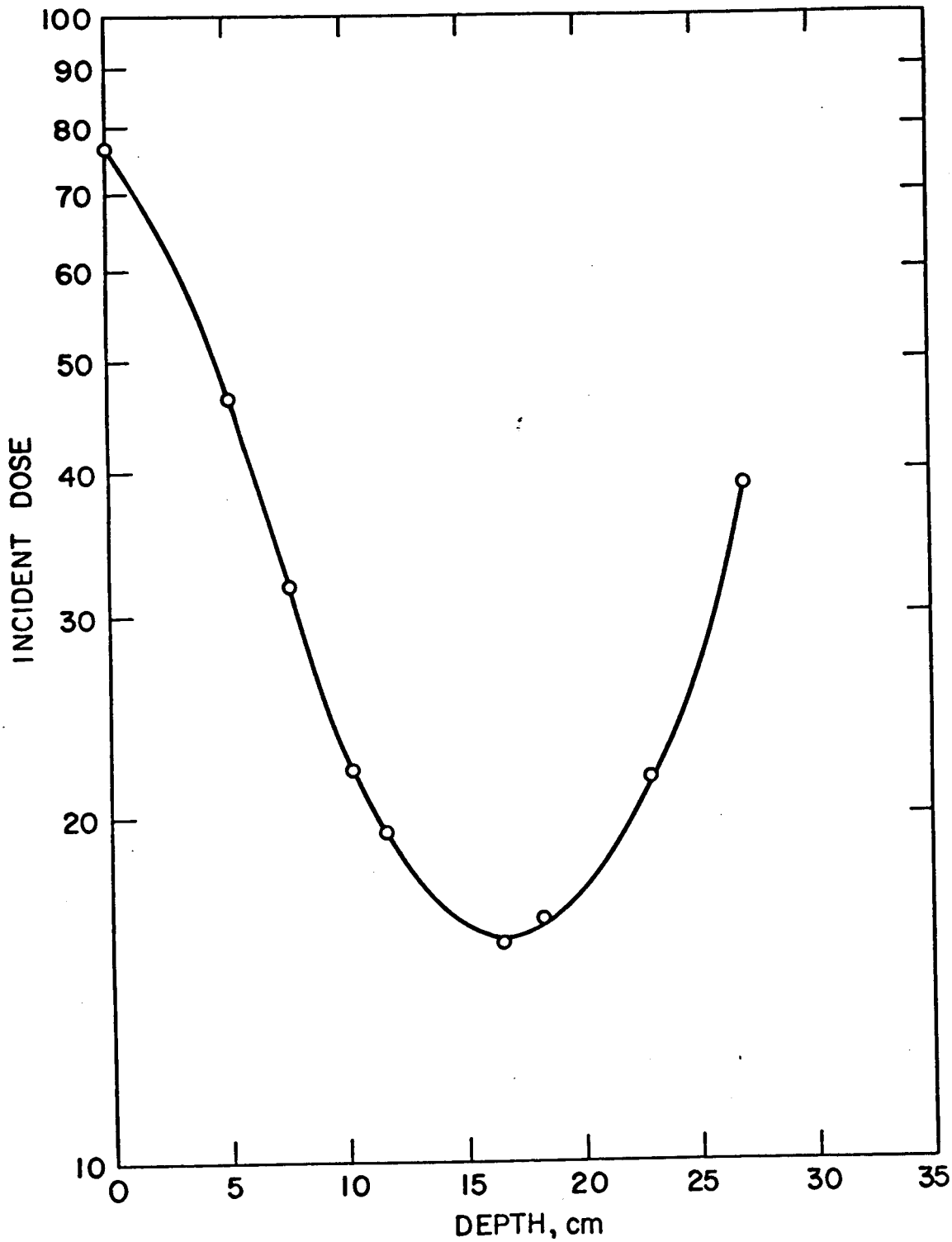
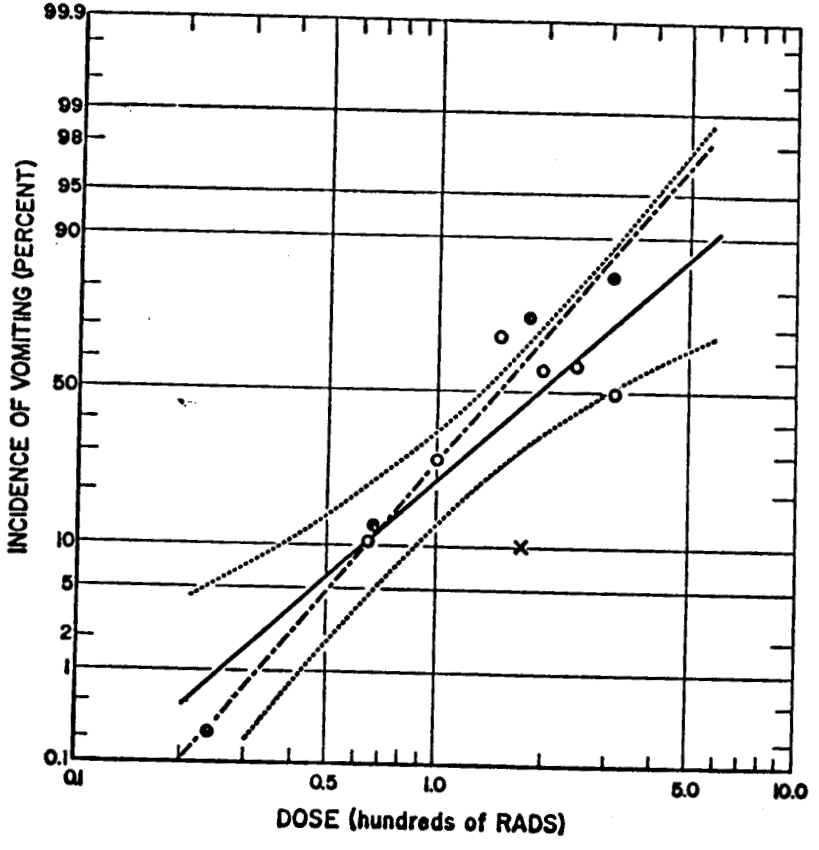
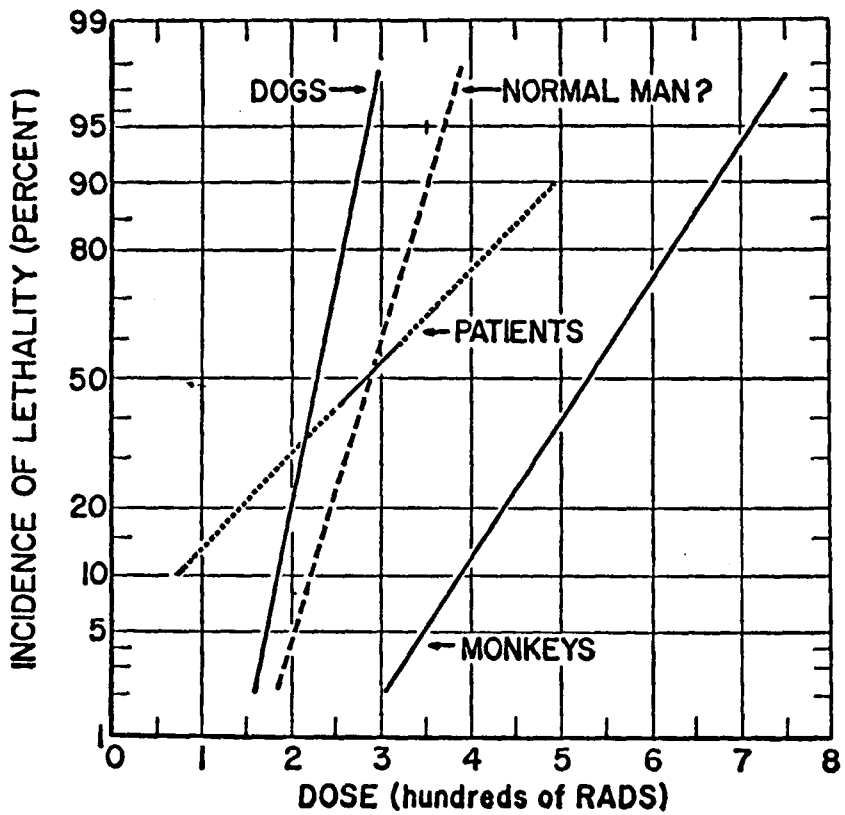


Temporary Fig. 1--Final to be supplied.


100
90
80
70
60
50
40
30
20
10
INCIDENT DOSE
0
5
10
15
20
25
30
35
DEPTH, cm


INCIDENCE OF VOMITING (PERCENT)
99.9
99
98
95
90
50
10
5
2
1
0.1
0.1
0.5
1.0
5.0
10.0
DOSE (hundreds of RADS)


INCIDENCE OF LETHALITY (PERCENT)
99
95
90
80
50
20
10
5
1
0
1
2
3
4
5
6
7
8
DOSE (hundreds of RADS)
DOGS
NORMAL MAN?
PATIENTS
MONKEYS