

Predicted Levels of Human Radiation Tolerance Extrapolated
from Clinical Studies of Radiation Effects

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INTRODUCTION

Whatever the merits of the pros and cons of present day debates concerning manned space exploration, results of clinical studies of radiation effects in man himself do not support the contention that man is too radiosensitive an animal for this task. Man, other animals, electrical components, machines, etc. are all radiosensitive but have different tolerance levels that can be measured by the failure probabilities of variously performing systems. These may be immediately or only remotely important biologically or operationally. Evaluation of the space radiation hazards to man depend equally upon the accuracy of our physical knowledge of the levels and kinds of radiation that he may encounter and our biological knowledge of human radiation responses. Biologically, our knowledge is qualitatively good but not quantitatively accurate for man. Most quantitative radiobiologic estimates must be extrapolated from or with the aid of studies in animals where radiation exposures can be controlled experimentally and radiation effects quantitated by destructive techniques not applicable to clinical studies. The suitability of these animal models for prediction of the kinds and levels of human responses has been gauged by many clinical studies

of victims of radiation accidents and of patients undergoing elective radiation exposure in the therapy of their disease. Unfortunately, for our purposes, there have been few radiation accidents where men have been exposed to known amounts of radiation. On the other hand, in therapeutic exposures, although the dose is well known, the radiation effects are often confused by the pre-existing disease process.

Never the less, my associates² and I have been directing the major part of our efforts at the Medical Division in Oak Ridge toward defining human radiosensitivity from such clinical studies of radiation effects (refs. 1 - 9). These studies were begun in 1959 when our first human total-body irradiator was constructed for radiotherapy of patients with uniform exposures to omnidirectional beams from an array of gamma ray emitting radioisotope sources. Since then, with the continuing support of the AEC and with support from NASA commencing in 1964, we have expanded these studies of human therapeutic and biologic effects of single rapidly delivered exposures with low dose

¹The studies upon which this chapter is based have been supported since 1959 chiefly by the USAEC and augmented by NASA since 1964.

²Gould A. Andrews, R. M. Kniseley, C. Lowell Edwards, R. Tanida, F. Goswitz, Frank Comas, H. Vodopick, E. Balish, G. Kingdon, G. Littlefield, R. Ricks, W. Beck, T. Stokes, P. Aaron, E. Frome, E. McDow, A. Webb, A. Sipe, Mrs. Sutliff, and support staff.

rate exposure studies of protracted or fractionated radiation effects. Here we are now using another facility (Fig. 1) constructed solely for such exposures which in some instances have taken as long as ten days -- about the time for a round-trip lunar exploration. Coincidentally, the skin dose from ^{60}Co gamma rays in this low-exposure-rate total-body irradiation facility ("LETBI") accumulates with 1.5 R/hr exposures: the same rate that skin dose from protons would have, according to Dye and Wilkinson (ref. 10), in the worst week ever recorded for solar flare activity in space. As can be seen in Figure 2, derived from their study, the intestinal doses from the therapeutic and solar forms of irradiation and their respective rates of accumulation are widely divergent. The relatively small accumulated intestinal dose from solar protons offers little or no chance for untoward physiologic effects occurring from such radiation exposures in space.

We have broadened these direct therapeutic observations where possible by retrospective studies of clinical data obtained from other American and Canadian investigators and radiotherapists who kindly made these data available to this project. To obtain some basis for relating these results obtained with photons to those that might occur after exposure to high LET particles, we have been following closely the continuing studies of the ABCC staff at Hiroshima on the effects of mixed fission neutron and gamma irradiation that occurred in the Japanese atom bombings (see later).

This paper could end right here if the question to be answered for determining permissible exposures in space was only: What is the photon flux that "man" can "tolerate" and function in, while living under almost continuous exposure

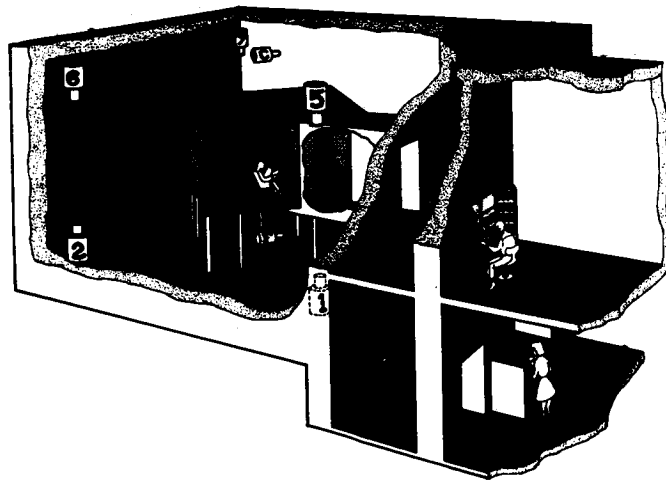
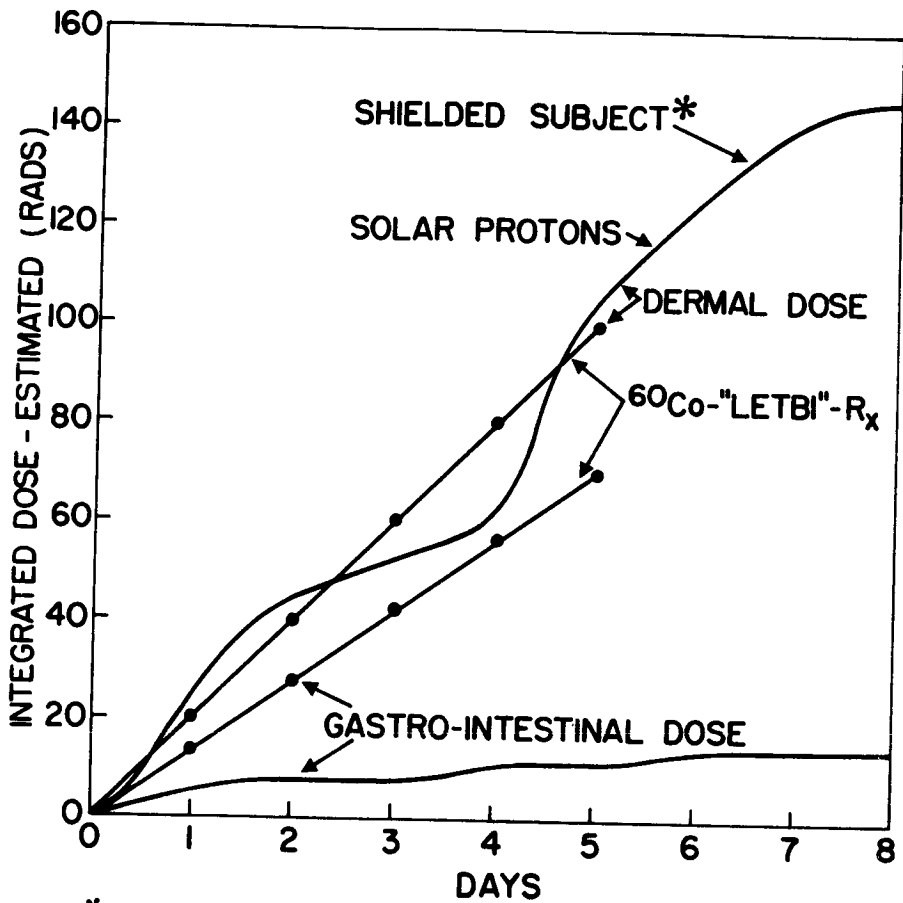


Figure 1. Cut-away diagram of the low dose-rate, total-body irradiation facility used in Oak Ridge to study the effects of protracted exposures (100 to 250 R of ^{60}Co gamma rays accumulated at 1.5 R/hr for 5 to 10 days). The location of some of the eight ^{26}Cl sources are shown (numbered) with the smaller trimming sources (C and F) surrounding the inner treatment room where the patient resides. The control room and data processing areas are adjacent to the 36 x 36 x 18 ft radiation containment room.



*Dye, D. L. and Wilkinson, M.: Radiation Hazards in Space, Science 147:19-25, 1 January 1965.

Figure 2. The rate of dose accumulations in the skin and intestinal tract of patients exposed to 1.5 R of ^{60}Co gamma rays/hr contrasted with those estimated for those organs of an hypothetical astronaut shielded by a space vehicle in the solar proton fluxes that occurred between 10 and 17 July 1959.

conditions? We know that patients (ours as well as others) "tolerate" total accumulated exposures of photons up to 250 R (average [estimated] bone marrow doses of 150 rads) and daily exposures at rates of 28 to 33 R at 1.5 R/hr. "Toleration" here, of course, is used by me at the subjective level; only a rare patient under these exposure conditions has shown gastrointestinal distress or complained of being sick or tired. Hematologically, however, exposures of this magnitude cause therapeutic depressions in blood leukocyte or platelet levels; percentage-depressions that would not be desirable from an occupational medicine point of view. Recently, as reported in another paper (ref. 11) in this symposium, we have demonstrated, using physiologic monitoring, that, unbeknownst to the patient being irradiated at these "tolerance" levels, he becomes exercise-intolerant or more easily fatigable even though no symptoms of the prodromal radiation syndrome or GI sickness occur. Although we believe we are defining in these retrospective and on-going studies a less-than-ten-day continuous irradiation "tolerance" level for man, we also know that many more human observations are needed before we can predict with certainty how radiosensitivity of various biologic systems change when exposures occur slowly over extremely large time periods and to relatively non-reparable high LET radiations. The late biologic consequences of irregular, numerous small exposures to high, as well as low, LET particular radiations remain our most serious problem because they are the restrictive criteria on which safe levels of occupational exposures must rest.

The word "tolerance," of course, has many definitions and many inferences that change in relation to the bodily functions being considered. The term

is used by me as the biologic summation of initial response, recovery from damage, and ignorable damage remaining in the total body or a specific organ system for various periods of time. For example, the one most commonly used level of radiation tolerance for any animal species is its radiation-induced lethality expressed in terms of the exposure (R) or dose (rads) that is expected to kill 50% of that kind of animals within 30 or more days ($LD_{50/30}$; $LD_{50/60}$).

THE HUMAN LETHAL DOSE PROBLEM

There is world-wide willingness to accept the estimate that the dose that will kill the unattended normal man with 50 percent certainty within 60 days of exposure ($LD_{50/60}$) is 450 R and that the mechanism of death is damage to his hematopoietic system and defense mechanisms against infection. The degree of acceptance of this 450-R value is surprisingly high in view of its history and its lack of valid support from reported human data (ref. 12). The importance of establishing this number for man was recognized during and immediately after World War II (ref. 13). It is the obvious point of reference for relating the radiosensitivity of man to that of other mammals whose radiation sensitivity has been well established by years of extensive research - most commonly by determining precisely the LD_{50} and its confidence limits for the species (ref. 14). This number, which is reproducible experimentally in laboratories around the world for each species, has rightly become the simplest expression for mammalian radiosensitivity. Because of the ease of its experimental determination, it has also become the end point most commonly used in radiobiological studies of relative effectiveness of various kinds of ionizing and nonionizing radiations and various kinds of radioprotective

agents and postirradiation therapy.

Just how this estimate of 450 R for man's total-body radiation tolerance was made has never been revealed publically. The assumption has been made (ref. 15) that Warren and Bowers based their estimate on lethality data obtained by the Joint Commission of the Medical Departments of the U. S. Army, Navy, and the Manhattan Engineering District in Japan during 1945. Most such accounts must be apocryphal since there was a tenfold error in the Hiroshima bomb-yield estimates that would have biased this number upwards and made it impossible to reconcile with the lower exposures in Nagasaki. These corrections, called "T65 doses" (ref. 16) are the ones now in use at ABCC in retrospective evaluation of human responses in these bombings.

Attempts to increase this estimate to 600 R, in the belief that the suggested human LD_{50/60} implied a depth dose of 450 rads of photon energy,

have been fought off successfully by several investigators, notably by Cronkite and Bond (ref. 17) on the basis of their observations of the hematopoietic responses of the Marshallese natives, inadvertently irradiated by fallout after a Bikini atom bomb test (ref. 18).

The LD₅₀, by definition, forms the best single measurement of the upper or acute lethal boundary of total-body radiation tolerance (see Fig. 3). There have been several attempts to check the 450-R estimate from human case histories after both accidental and intentional radiation exposures. These are tabulated in Table 1 to show how all studies have produced values lower than the original estimate and seem to indicate that 450 R is too high to be considered an estimate of midline depth-dose (absorbed radiation energy). The table also includes the results of two recent attempts to obtain

Table 1

EDUCATED GUESSES AND SOME CLINICAL AND STATISTICAL ESTIMATES OF HUMAN TOTAL-BODY RADIATION TOLERANCE

	LD _{50/60}	
	Exposure	Dose
A. NORMAL MAN		
1. Warren and Bowers (ref. 12)	450 R	
2. Cronkite and Bond (ref. 17)	350 rad	
3. Langham (ref. 15)	430 R	(285 rad)
4. Jablon et al. (ref. 19)	405 rem*	
B. PATIENTS		
1. Mathé et al. (ref. 20)	400 R	
2. Langham (ref. 15)	380 R	(250 rad)
3. Lushbaugh et al. (ref. 4)	370 R	(245 rad)
C. NORMAL MAN + BLAST AND BURN TRAUMA		
1. Lushbaugh and Auxier (ref. 21)	260 rem [†]	

*RBE for fission neutron component = 5.

[†]RBE for fission neutron component = 2.

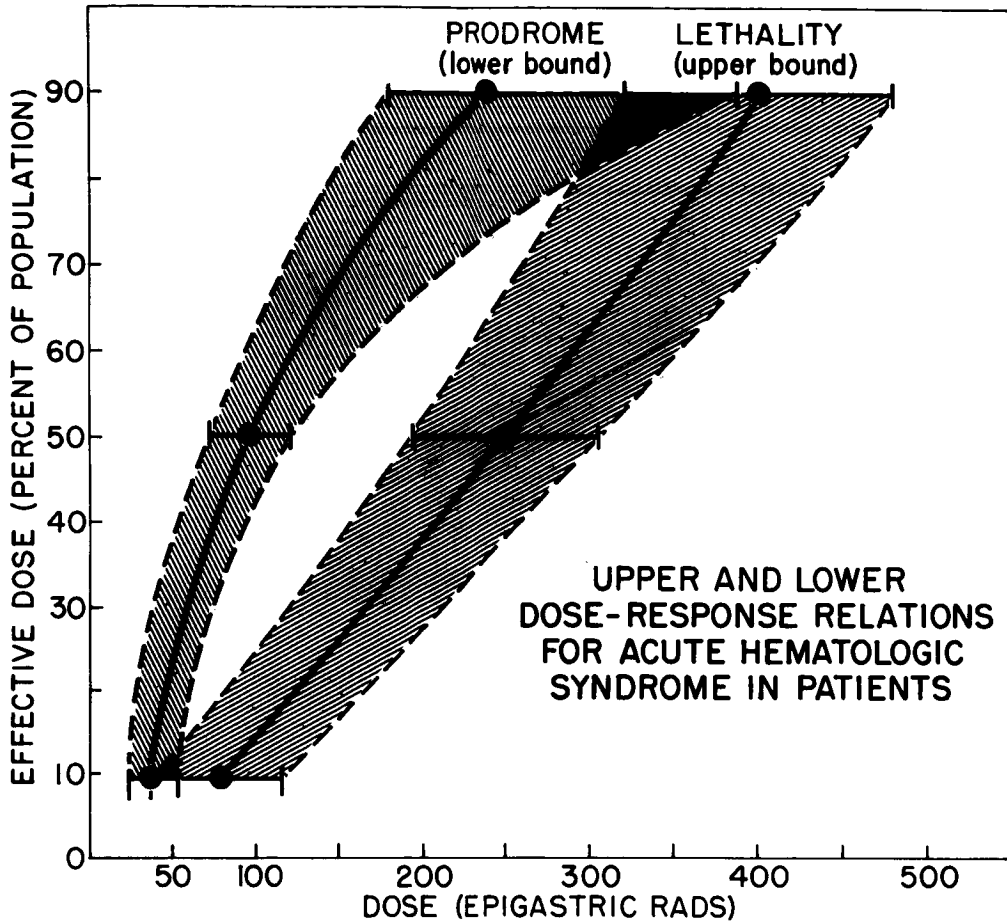


Figure 3. Acute hemopoietic syndrome is defined graphically by estimates of effective single doses for radiation-induced anorexia and lethality in patients. The probit regression lines have shaded fiducial limits. Depth dose is shown in "epigastric" rads to indicate that it is the fraction of the free field of photon radiation absorbed in the midline, midplane of the upper abdomen. This reference dose is usually 64 to 68 percent of the exposure in an average-sized man.

estimates of the human LD_{50} from the Hiroshima-Nagasaki exposures to mixed fission neutrons and gamma radiation (refs. 21 and 19). Many large animal experiments using fission neutrons, particularly those of Alpen (ref. 22) and Bond (ref. 23) and co-workers have provided a strong basis for forming the opinion that in "large" animals like man, dogs, swine, and cattle the RBE or QF for high LET radiation is 1.0 for acute hematopoietic death (ref. 15). In studies of human dermal responses to fast neutrons (refs. 24 and 25), RBE values of from 2 to 4 are needed, as in lower animals, to equate neutron dose for skin erythema with that of the reference (low LET) radiation. A QF value of 3 for high LET radiation ($>3.5 \text{ keV}/\mu$) has, however, been suggested only for damage to skin, intestines, and germinal epithelium (and not for prodromal responses, early hematologic responses, as well as hematopoietic death [ref. 15]). This recommendation seems to me to depreciate the well-known, experimentally-proven fact that sublethal cellular injury induced by high LET radiations is irreparable and as permanent as the cell in which it occurred. It would seem biologically more conservative, particularly from a safety point of view, to assume that in human tissues, including marrow, the damage caused by a dose of high LET radiation would be poorly repaired as it is in similar small animal tissues, and that hematopoietic as well as skin and intestinal crypt stem-cells would suffer equally in respect to actual dose from the same high LET radiation.

The answer to this problem is still disputable, but the more recent observations in the Japanese lend weight to the other side of the question for the first time. Lushbaugh and Auxier (ref. 21) used data from an unpublished study of the effects of various kinds of shielding upon survival in both

cities in relation to the T-65 dose estimates of the free-field fluxes at the 50 percent survival points. They obtained an LD_{50} estimate of 260 rem using an RBE of 2. This estimate was expected to be low because it should reflect the additive effects of heat and blast combined with radiation-induced damage. The more recent study by Jablon et al. (ref. 19), relates the estimated individualized doses received by $\sim 100,000$ survivors in the two cities with their clinical history of epilation and oropharyngeal hemorrhages. The human pharyngeal-epithelial and tonsillar-adenoidal barriers to infection have not been given much consideration in recent discussions of the acute hematopoietic syndrome. Yet it is an excellent objective end point for measurement. This painful, hemorrhagic sore throat is a symptom complex known as agranulocytic angina that stems from pharyngeal ulceration, bacterial invasion, granulocytopenia, and thrombocytopenia. By using this system complex as the measurable quantum of damage from total-body irradiation, any additive effect of other forms of concomitant trauma was avoided in the ABCC study. As can be seen in Table 2, the isoeffective exposures are only equal in rem when an RBE much greater than unity is used for the neutron component of the exposures. The isoeffective exposure dose (ED_{50}) of 405 rem that was found is remarkably close to the original human LD_{50} estimate. It is an even closer estimate of the exposure field strength that would be required for a mid-line human dose of 285 to 300 rads suggested as the possible human $LD_{50/60}$ by Langham (ref. 15) and Cronkite and Bond (ref. 17). The 310 rem, estimated as the isoeffective estimated dose for epilation in both cities using an RBE of 4 for neutrons, is likewise remarkably close to the widely accepted clinical value of 300 R

Table 2

FIFTY-PERCENT ISOEFFECTIVE EXPOSURE DOSES
FOR HUMAN SKIN AND BONE-MARROW DAMAGE, ESTIMATED IN SURVIVORS
OF NEUTRON AND GAMMA IRRADIATION IN HIROSHIMA (H) AND NAGASAKI (N)

	Neutron RBE Used	Resulting Estimates of Isoeffective Doses*	
		H (rem)	N
Epilation	1	190	300
	4	+310	310+
	5	350	310
Hemorrhage	1	200	375
	4	360	390
	5	+405	405+

*Approximated from graphic data of ABCC Study by Jablon et al.
(ref. 19).

of X radiation as the radiation exposure causing epilation in man. These correspondences seem to demonstrate an internal consistency in the data and their analyses that indicates, to me at least, that neutrons do have an RBE greater than 1.0 for acute hematologic, as well as for skin, effects in man. It would seem difficult to pass the ABCC study off lightly because it does not agree with large animal observations. We should not ignore Mathé's observation (ref. 20) that the man who died after neutron exposure in the Yugoslavian radiation accident had much more extensive marrow destruction than was to be expected on the basis of his estimated dose of 430 rads. There seems to be less official reluctance to accept the use of a large RBE for neutrons and other high LET radiation when late-effect end points are considered. Most fractional-cell-survival studies demonstrate well the relative irreparability of sublethal cellular damage after high LET radiation exposure and provide a firm experimental basis for assuming a large QF for such effects as genetic damage, leukemogenesis, and carcinogenesis after single exposures. When coupled with the decrease in

"damage efficiency" that occurs in most biologic systems with increasing protraction or fractionation of the same total exposure, the RBE increases further (ref. 26). There is not much clinical information about high LET radiation in man other than that about the well-known effects of alpha-particle exposures in victims of radium poisoning and in uranium miners. The data under study by ABCC provides unquestionable verification for the large QF for fission neutrons for leukemogenesis and thyroid carcinogenesis (ref. 27) after single exposures.

In Figure 3 the acute hematopoietic syndrome of irradiated man is defined as the probability of response estimates in respect to total-body photon exposures. Here, probability of lethality forms the upper bound and that of acute GI distress of the prodromal syndrome forms the lower bound of the envelope. How these dose-response relations shift when exposure is prolonged or fractionated is our continuing problem.

Retrospective studies of a large volume of clinical data extracted from hospital charts of 2000 patients given therapeutic total-body irradiation have given us dose-response relations for the symptoms and signs of the prodromal syndrome. The statistically determined single exposures that can be expected to produce these symptoms in 50 percent of the patients so exposed are shown in Table 3 along with the increased levels of the exposure required for the same incidence when the exposure period is lengthened.

When total-body exposure occurs promptly in less than one day, the effective dose for 50 percent incidence of these response (ED_{50}) are: anorexia, 147 R; nausea, 210 R; vomiting, 277 R; and diarrhea, 348 R. The log-normal frequency distribution of these responses in respect to dose indicates that

Table 3
 ACCUMULATED ESTIMATED EXPOSURES* FOR
 50 PERCENT INCIDENCE OF PHYSIOLOGIC SYMPTOMS

	Exposure Length (Number of Patients)		
	<1 Day (504)	<8 Days (103)	>8 Days (1083)
Anorexia	147	309	600?
Nausea	210	397	750?
Vomiting	277	745	>900?
Fatigue	223	400?	
Diarrhea	348	800	

*Midline upper abdominal dose (RAD = 0.66 Exposure R).

? = Guesstimate; 20 to 30 R/day is apparent threshold of dose rate.

the exposures required for their 10-percent incidence would be about one-fourth of that for a 50-percent incidence (ref. 4). The probability dose-response curves predicting the population incidence of these responses are steepest for anorexia and become progressively less steep for nausea, vomiting, and diarrhea in that order. This family-like relationship of the probability curves for the occurrence of the effects from mild to severe suggests that individual variation in ability to repair the underlying physiologic damage is progressively greater for each step in severity. If true, this analysis predicts that a radiosensitive person who shows, for example, nausea at a low dose would be more likely to show other symptoms and signs of greater damage per unit of irradiation than a radioresistant person in whom nausea did not occur without a much greater exposure. Except for the low-radiation-damage threshold of the human spermatogonia type B of about 15 rads, these gastrointestinal physiologic effects are the most radioresponsive. In the context of space exploration, these early gastrointestinal effects appear to be the most likely symptoms

to occur with small exposures and therefore to be the most likely to reduce performance capabilities. Their occurrence would be improbable, however, when the exposing radiation flux was less than 20-30 R/day and the radiation was poorly penetrating, two conditions that, on the basis of previous space radiation measurements, seem to have a high probability. Nothing is known to suggest an RBE for high LET radiation for production of these physiologic effects. Although one might guess that the quality factor (QF) might be greater than three, the results of studies on the effect of dose protraction upon the size of the effective exposure dose (shown in Table 3) in 1,085 patients given small, daily total-body exposures, suggest that between 20-30 R/day are required for 30 or more days to cause these symptoms; exposures of from 10 to 20 R/day produced nausea infrequently even when these exposures were delivered rapidly at approximately daily intervals for three to four weeks; exposures of about 5 to 6 R/day were physiologically symptomless.

Although all of our statistically validated human information in this area is derived from exposures to photons, there is no reason to believe that fission neutrons delivered in small daily doses for prolonged periods to the sensitive midabdominal trigger-zone would produce damage that would ever summate in the acute onset of gastrointestinal distress. This opinion would seem correct, particularly if chronic exposures are constrained by current planning limits of 0.15 rem/day through reactor shields (ref. 15).

Recent observations obtained during the physiologic monitoring of patients in our LETBI unit during and after low-exposure rate (less than

1.5 R/day and low total daily exposure of less than 30 R/day) confirm these analyses of patients' charted histories that reveal the absence of acute GI distress under these conditions (ref. 11). They indicate, however, that increased fatigability can occur with small daily exposures of this magnitude. These studies are still too fragmentary to be considered a statistically sound basis for predicting the incidence of radiation-induced fatigue at low-exposure rates. So far, however, using bicycle ergometry, we have observed performance capability has decreased after single, prompt exposures (150 R) and after low-exposure rate, fractionated, 15 daily exposures of 10 R (150 R). These measurements, based on pulmonary impedance pneumography, seem to show that this form of performance decrement follows a cyclic-time course with a periodicity depending on the initial rate of induction of radiation damage. The long duration of the effect after one exposure could conceivably be enhanced by subsequent, remotely-spaced exposures but we are uncertain of this. This effect could be a threat to performance during long-duration space missions if small radiation exposures and muscular inactivity worked together to reduce physical strength and conditioning

EFFECT OF MULTIPLE EXPOSURES ON LETHALITY

Almost nothing is known in truly quantitative terms about the effect of protraction or fractionation of human exposures upon the size of the isoeffective lethal dose. The Space Radiation Study Panel used an unpublished study of Focht, Nickson, and Langham in its evaluation of this problem (ref. 15) to see if clinical data obtained from the medical records of the Heublein total-body irradiation unit, Memorial Hospital, could be fitted to a Strandqvist-type of mathematical model. In

this retrospective study the relative roles of the basic disease and of the protracted low-dose-rate radiation in causing death could not be determined. Whether or not a patient died during or within 60 days of his treatment was recorded only as yes or no quantal information and graphed in relation to total accumulated exposure and duration of exposure. The three graphic areas defined by exposure and time were delineated by the incidences for >90% death, 50% death, <10% death. The best fit of these data to three parallel lines for the 90, 50, and 10% probabilities of death were then computed by Langham (unpublished) using a "Strandqvist" (ref. 28) power function model:

$$\text{Isoeffective (fractionated) LD}_{50} = 345 t^{0.26}$$

Where 345 is the assumed nominal single lethal dose in rads (midline absorbed photon energy) for a single protracted exposure to about 530 R of X radiation over one week; t is used for exposures longer than 1 week's duration and the exponent of t is the power-function or slope constant of the log-log regression line. This model and its parameters were graphed (Fig. 4) by the author to show how this model predicts these isoeffective lethal dosage levels (90, 50, and 10%) will increase with increasing durations of exposure up to a year. The amount of repair predicted by this model for photon irradiation is remarkable. It is of interest that the power function (or slope constant) derived from the best fits was 0.26, a number remarkably similar to that factor for normal skin damage and tumor cures (ref. 28) and hematologic damage (ref. 29). As shown in the figure, this model predicts 50% survival at 18 rads/wk or ~3 rads (marrow dose)/day/year. The slope of this regression line for increase in LD₅₀, as marrow

LASL MODEL OF HUMAN LETHALITY FOR FRACTIONATED EXPOSURES—AFTER FOCHT AND NICKSON

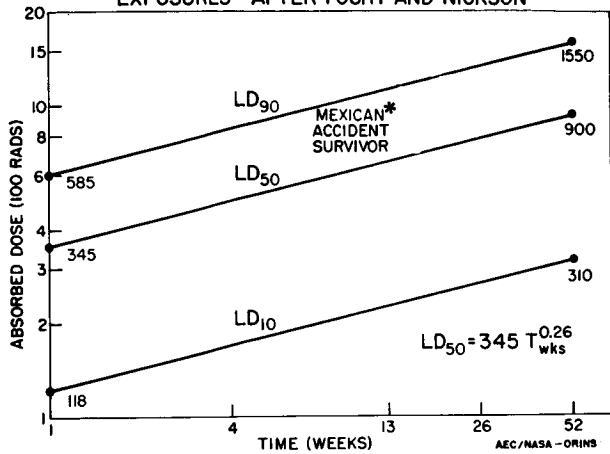


Figure 4. The Los Alamos Scientific Laboratory (LASL) model for human lethality computed from clinical total-body irradiation data of Focht and Nickson using the method of Strandqvist to determine the power function for duration of exposure in weeks.

dose is protracted, would be steeper if fatal diseases were not present in the study population. A recent study of clinical and accident data indicates that this slope may be increased as much as 2 or 3 times if the exposed persons have normal-health hematopoietic systems (ref. 29).

Low-dose-rate exposure at the rate suggested by these combined observations (about 10 R/day if the Yuhas correction of 3 is accepted) is, however, apparently not tolerable for man for a year. In fact, the events in the 1964 Mexican accident can be interpreted as demonstrating that in only 100 days of such irradiation an exposure close to that for lethality will be accumulated at ~10 R/day (ref. 30). One of the victims in this accident was literally irradiated to death in 115 days, during which time she received an estimated 2,000 to 3,000 rem of cobalt-60 gamma radiation (15 to 25 R/day [see Table 4]). Her husband, who is still surviving at the time of this writing seven years

after the accident (shown by the asterisk in Figure 4) received his daily exposures (984 to 1,717 rem in 106 days) during the night while sleeping. His wife and his mother were irradiated continuously day and night as they worked about the house where an unrecognized radiography ⁶⁰Co source was stored. The four deaths in this family of five were found at autopsy to be from severe hematopoietic damage that led to hemorrhage and infection. All but the survivor acted as though they had a plague-like disease. The survivor, however, had surprisingly few symptoms and signs of illness in contrast to the severe radiation-induced atrophy of his bone marrow that was subsequently demonstrated by marrow biopsy. What symptoms he had were chiefly referable to his low-grade anemia rather than his severe leukopenia.

Table 4
1964 MEXICAN ⁶⁰CO RADIATION ACCIDENT
(Martinez et al., 1964)

	Exposure (days)	Estimated Exposure (rem)	Approximate Exposure Rate Ranges (rem/day)	After Survival (days)	
Son	24	2940-5165	125-250	5-12	18
Wife	115	1996-2938	17-26	0.7-1	2
Daughter	99	1373-1872	14-19	0.5-0.8	30
Mother	90	1818-2897	20-32	0.8-1.3	80
Survivor* (Husband)	106	984-1717	9-16	0.4-0.6	(7+ years)

*April 1971.

In Figure 5, two ways are shown in which the dose-response relations may shift when exposure is protracted. There are: (a) a decrease in the slopes of the shifted probability lines caused by greater repair of radiation damage accumulated slowly (revealed as a greater variation in the response rates of the population); and (b) a simple displacement of dose-response envelope without a change in the slope of the lines for the probability of response. This dose-response displacement is to be expected when exposure is to high LET radiation where cellular damage is nonreparable. In Figure 6, the results are shown when the LASL study is used to predict the level of human lethality for the exposure rates of 6, 20, and 30 rads/wk. This probability estimate, shown by the solid line superimposed on those of Figure 5, supports the many observations made in mice irradiated at low-dose rates that the hematopoietic system has a remarkable ability to recover from slowly delivered photon irradiation. Recently, Yuhas, et al. (ref. 29) obtained additional evidence supporting this remarkable reparability of the normal human hematopoietic system when its exposure is made in small fractions. He derived a multifactorial regression model for human blood-cell responses to multiple as well as single total-body therapeutic exposures using approximately 2,000 clinical case histories. Individual charts were carefully selected that met strict criteria for numbers of blood examinations, dosimetry, precise diagnoses, and evidence that the individual was not in the terminal stage of his disease. The dose-response patterns of 123 single exposures and 395 multiple exposures were studied in four diagnostic groups of patients: chronic myelogenous

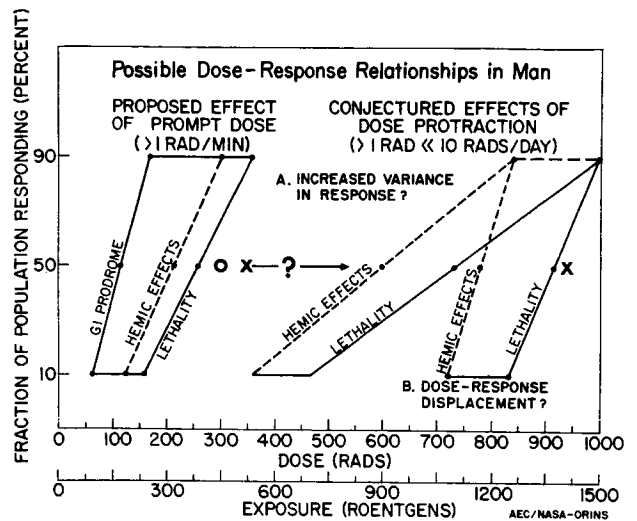


Figure 5. A graphic representation of two possible ways that clinically recognizable lower and upper dose-response probability boundaries of the hematopoietic syndrome may shift when exposure is protracted over a year.

- A. Variance in the incidence of a response is increased as reparability increases as after low LET photon irradiation.
- B. The dose-response envelope is displaced upwards without change in the slope of probability lines, commensurate with proliferation capacity of unhit target cells in the presence of irreparably damaged targets as after exposure to high LET particles. The prodromal symptomatology, lower bound of the prompt exposure probability envelope becomes undetectable when the daily fraction of the exposure is less than 15 R and therefore is replaced by symptoms referable to anemia or infection. (See Table 3.)

leukemia (CML), chronic lymphocytic leukemia (CLL), lymphosarcoma (LS), and nonleukemic patients with normal blood values. The percent of WBC remaining at the nadir was found to be related to a power function on total exposure and the duration of the therapy in days:

$$\% \text{ WBC} = K [100] \cdot [D]^{-b_1} \cdot [T]^{b_2}$$

K = a constant, required for extrapolation to the ordinate at zero dose because no effect was seen below 25 R

D = total exposure in R

b_1 = the slope of % WBC on D

T = the time of protraction in days

b_2 = the slope of % WBC on a given D or T

The slope of percent WBC on exposure was found to be essentially equal to -1.0 in all diagnostic groups (Table 5). In persons with normal marrow, percent WBC on time (T) at a given exposure (D) increased as the 0.63 power of the number of days separating the first and last fractional exposures used. In CML, CLL, and LS this exponent was found to be 0.39, 0.23, and 0.22.

Table 5
SLOPE CONSTANTS AND TESTS OF THE STATISTICAL SIGNIFICANCE OF THE YUHAS MODEL (REF. 29)

Diagnostic Group	Single Exposures		Multiple Exposures		
	b_1	Correlation Coefficients	b_2	Correlation Coefficients	P Value
"Normal"	1.04	0.57	0.63	0.535	<0.025
CML	0.999	0.82	0.392	0.569	<0.0001
CLL	0.917	-	0.221	0.583	<0.0001
LS	1.119	0.42	0.231	0.567	<0.0005

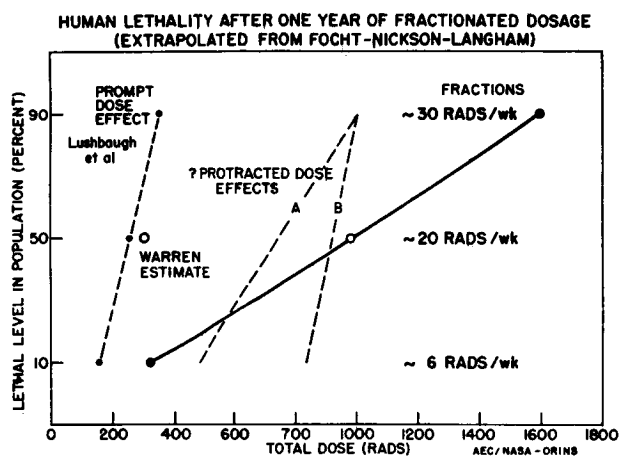


Figure 6. The conjectured effect of a year-long dose protraction upon the displacement and slope of dose-response probability regression lines (shown in Figure 5) contrasted with the prediction of the LASL model using actual data. (For further explanation, see text.)

The values for the slope constants shown in Table 5 have biological implications: The negativity of b_1 indicates that as dose increases, the percent survival of peripheral WBC decreases. The correspondence of this value for each group to 1.0 may indicate that, in the different cellular systems involved in these diseases, differences in radiosensitivity are not significant. This result is surprising in view of the widely held clinical

belief that the leukocytes in CLL, for example, are much more radiosensitive than the cells comprising the WBC in CML or in "normal" persons. This apparent deviation from clinical "fact," however, can be explained by the significant differences found in the values for b_2 . The larger this positive slope constant the more effective the length of exposure protraction is in increasing percent survival; according to these values, in the "normal," protection of the white blood cell level by dose protraction is three times that found in CLL and LS (see Fig. 7). In the latter groups, dose protraction should not, according to this analysis, decrease the effectiveness of the total dose as much as in the "normal" group and as, to a lesser extent, it will in the CML group. These interpretations implied by the analytical results agree well with most clinical observations and suggest, in keeping with experimental observations, that normal tissues are spared more than abnormal ones by dose protraction. This concept is in fact the rationale for fractionation and protraction of

radiation therapy of malignant tissues amidst normal ones. These observed differences in peripheral WBC survival, after the same radiation exposure, probably result more from different efficiencies of recovery mechanisms than from inately different cellular radiosensitivities in these diseases (ref. 29).

It is commonly assumed that hematologic effects reflected by changes in peripheral blood counts correlate quantitatively with lethality. This correlation, however, has not been demonstrated either clinically or experimentally. Therefore, a regression model for the effect of dose-rate upon hematologic parameters, such as blood granulocyte levels, cannot be used with much assurance as the regression model relating dose-rate and lethality. The obverse is also true. Bateman (ref. 31), however, has shown well, at least in my opinion, that dose-rate data for such end effects as human dermal responses, and lethality of mouse, rat, swine, and sheep can be fit as a linear function of the reciprocal cube root of dose rate. This empirical observation stems in large part from the way the Strandqvist model and its numerous modifications all approximate the power-function exponent of 0.33. Applying the model to the data of others where a dose-rate effect is easily demonstrable, Bateman showed that:

$$ED_{R_1} = D_{\infty} \left(1 + \frac{k}{\sqrt[3]{R_1}} \right)$$

where D_{∞} is the single dose requirement when exposure is at an infinitely rapid rate, ED_{R_1} is the isoeffective dose at some lesser rate (R_1). The size of k , the slope constant for dose-rate effect as a function of the cube root of R , seems to be related to the size of the single-exposure

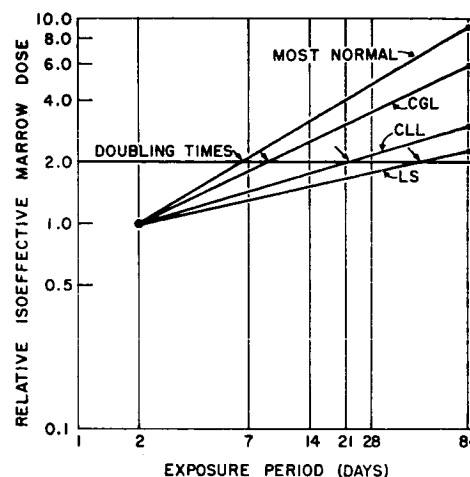


Figure 7. Graph of the rate of blood cell recovery predicted by the Yuhas multifactorial dose - WBC response model based on clinical data of total-body irradiated patients with no marrow disease ("most normal"), chronic granulocytic leukemia (CGL), chronic lymphocytic leukemia (CLL), and lymphosarcoma (LS). The data have been normalized to relative isoeffective marrow dose for two-day protraction for each set to compare the relative doubling times (straight arrows) in terms of exposure duration: 7 days, normal; 9 days, CGL; 22 days, CLL; and 42 days, LS.

dose given at conventionally rapid (therapeutic) rates. The size of k also expresses the recovery kinetics of the animal species and the cellular system involved. For example, in Bateman's study of lethality, k was 1.6 for swine, a species known to have remarkably efficient total-body repair, and 0.65 for sheep, an animal model of slow, inefficient radiation repair kinetics. Also, apparently the more radiosensitive a biologic system is (i.e., the smaller the dose is that is required to be effective) the less well it repairs the effects of this small dose; thus the size of k is variable within the same species, as it depends on the specific recovery mechanisms and kinetics of the damaged biologic system.

The Bateman model was used to construct a nomogram for human dose-rate tolerance using some of the biologic end points whose derivation and validity have been discussed above. This nomogram is shown in Fig. 8. Some of the assumptions are based on animal observations when normal human observations are not available. The extrapolations extend beyond 100 days even though the observations upon which they are based do not extend this far. They are extended to a year in the figure to correspond to the temporal requirement of deep-space exploration. Extrapolations of clinical data using the models of Strandqvist, Yuhas, and Casarett (refs. 32, 33) do not fit this reciprocal of the cube root scale of dose rate beyond one to three months after which they curve rapidly upward, away from the lines shown in the figure, indicating again perhaps the surprisingly great reparability that most tissues have of acute radiation damage induced at extremely low dose rates. Such a conclusion is, however, too optimistic for occupational radiation protection and long-mission planning guidelines since it predicts that no discernible acute responses will occur in marrow, gut, or skin below rather high dose-rate thresholds. In the absence of much objective clinical support for the quantitative relations implied by the nomogram, such reparability on the part of all men cannot be assumed. Even so, the extrapolations for the dose-rate response relation of infertility and sterility, severe hematologic effects, and hematopoietic death shown in the figure are more conservative than those of the Yuhas model, for example, as shown in Figure 7, that predict a ninefold increase in an isoeffective dose for hematologic damage to normal human marrow if exposure were fractionated over a 3-month period.

Until we obtain additional evidence that normal human marrow can actually repair as rapidly as this, the clinically conservative approach is to accept the worst predictions of the model; the doubling times of 21 to 42 days for CLL and LS, which, interestingly enough, approximate the rate that the Bateman model predicts in the nomogram (Fig. 8) by the line for "severe" hematologic response for patients.

In the dose-rate nomogram the accumulated isoeffective exposures are shown in the figure in R of photons. The encircled star, \odot , however, along with the line for "Late Effects," which has no slope, should be considered as dose in rem. The Late Effects lines are intended to define on the nomogram the dose-rate tolerance boundary or the safe occupational upper limits for human tolerance to low-dose-rate exposure if remote and late effects, rather than prompt effects, must be considered (ref. 34). The other steeper lines in the nomograph indicate possible dose-rate effect on the size of accumulated doses for such undesirable prompt effects as the 50 percent risk of death within 60 days. Such exposures have a low probability of ever occurring in space exploration, but, as we have indicated, are the kind on which we have the most clinical information. Much more clinical information, however, is needed before the creditability of any of these lines, their slopes, and dose-rate relations can be established statistically. The nomogram does, however, support the opinion that, except for the remote possibility of some unforeseen, uncontrollably large exposure, man is more than sufficiently radioresistant to make the risks of an early acute radiation effect on one short space mission intangibly small in relation to the other non-radiation risks involved.

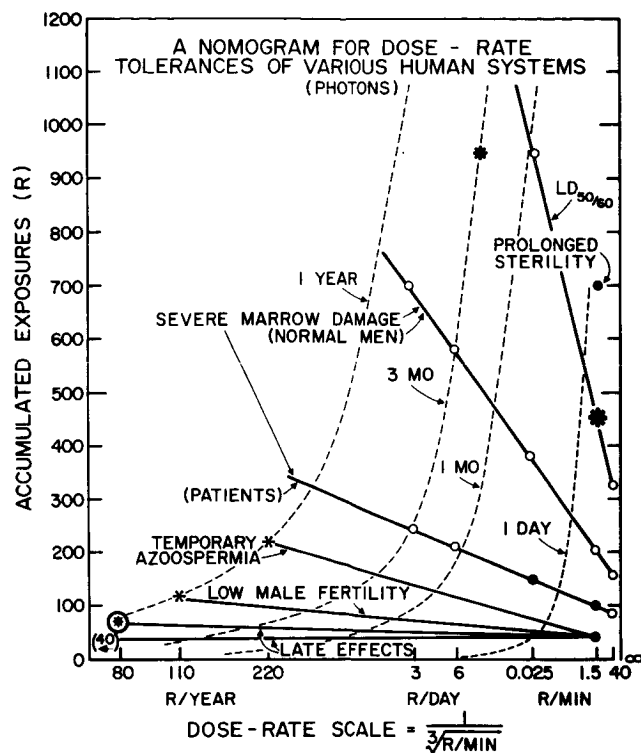


Figure 8. A nomogram predicted by the Bateman model of the effect of one-day, one-month, three-month, and one-year-long exposures on the size of accumulated exposure required to produce constant levels of several kinds of somatic damage; 60-day lethality, severe damage to normal marrow, assuming man and sheep are equally radiosensitive large animals. The smaller asterisk at ~ 1000 R on the 3-month isotime line locates the Mexican radiation accident survivor (see text). The lines for severe marrow damage are extrapolated from clinical data points (solid circles) and computed points (open circles) to show damage to diseased marrow, temporary (reparable) cessation of sperm production, reduced male fertility and late effects such as increased rate of cancer induction. The largest asterisk represents the original $LD_{50/60}$ estimate for man and has a regression line with a slope constant $k = 0.65$ running through it. Constants (k) are assumed of 0.24 for the recovery capability of diseased and 2×0.24 for normal hematopoietic systems. The lines for sterility and low fertility are based on the human data (ref. 15 [solid circles]) and canine data (small asterisks) on the one-year isotime line of Casarett and Hursh (refs. 32 and 33). The "Late Effects" lines are extracted from the Space Science Board Report (ref. 34).

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