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Reflections on Some Recent Progress in Human Radiobiology

C. C. LUSHBAUGH

MEDICAL DIVISION[1]
OAK RIDGE ASSOCIATED UNIVERSITIES
OAK RIDGE, TENNESSEE

I. Introduction

Since the discovery of radioactivity late in the 19th century, man has become increasingly aware of the potential for ionizing radiation to cause biological damage. This aspect of the use of radiation was not anticipated at first, but one year after the discovery of X-rays, reports of their harmful effects in man began to appear in medical journals. For example in 1901, Becquerel and Pierre Curie produced radiation dermatitis and ulcers on themselves in one of the first biological experiments in man with ionizing radiations. Gastrointestinal distress (now called the prodromal response) occurred first in an X-ray technician in 1897. Walsh reported then the first shielding experiment where a man unwittingly cured himself of radiation-induced nausea by wearing a lead apron, but another man failed to cure his headaches by using a wooden shield while working along

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side of a Crookes tube. Radiobiology has come a long way since then and now has explanations for some of these historical clinical events, but the mechanisms for many such phenomena are still not completely known. The explanation of some phenomena like the relative radiosensitivity of animal species is still almost completely conjectural.

Nonetheless, a vast amount of clinical data accumulated in the last 70 years contains information that defines the radiosensitivity of man in practical terms mutually understandable by physician and health physicist. These observations are used successfully by one group to avoid irreparable damage to the whole patient receiving radiotherapy for cancer, and by the other to avoid occupational exposures that could lead acutely to severe debilitation or death, and chronically to premature death by acceleration of aging and other cellular processes like leukemogenesis and oncogenesis.

Attempts made recently to integrate our knowledge of the pathological aspects of radiation damage for animals (Bond *et al.*, 1965) and man (Langham, 1967), reveal many problems that are still either only partially resolved or have quite controversial answers. Radiobiological problems appear to exist at present at all levels of human pathological analysis; histology (light and electron microscope), biochemistry, physiochemistry, and physics. In terms of modern radiobiological jargon, these problem areas are total body, organic, systemic, cellular, subcellular, and enzymatic levels. In the last five years, advances in radiation dosimetry as well as in radiobiology have defined these problem areas better and today many similarities and differences between man's responses and those of experimental animals have been quantitated as well as qualified. Altogether these conceptual details, even though incomplete, are beginning to form a clearer picture of the many facets of radiation damage that are fundamental to understanding the radiosensitivity of man.

The major deterrents to progress in this field have been our inability to gather direct evidence in man experimentally and to devise a meaningful, single expression for his absorbed dose and a way to measure it that is agreeable to both clinician and radiobiologist. Until the recent development of tissue culture techniques capable of growing human cells *in vitro,* there has been no way to compare man's cellular radiosensitivity directly with that of animals in simultaneous well-controlled experimental situations. Almost all of our radiobiological knowledge of man has perforce been deductive; only skin damage (Strandquist, 1944) and probability of a 5-year "cancer cure" (Friedman and Pearlman, 1968) have been used as experimen-

TABLE I

ALPHABETICAL LIST OF RADIATION ACCIDENTS[a] BY COUNTRY AND CITY

Country and city	Date	Number of exposures	Number of fatalities (F)-serious injuries (I)		Classification
			(F)	(I)	
Argentina					
La Plata	5/3-4/68	18	0	1	B,1
Belgium					
Mol	12/30/65	1	0	1	A,3
Bikini					
Japanese Fishermen	3/1/54	23	1	22	C,1
Marshallese	3/1/54	267	0	110	C,1
Eniwetok	5/14/48	4	0	4	C,1
Mexico					
Mexico City	4/1/62; 7/22/62	5	4	1	B,1
Puerto Rico					
Mayaguez	7/24/62	7	0	0	B,1
Russia					
Unknown	1953	2	0	2	A,2
Moscow	6/8/60	1	1	0	B,1
Unknown	11/9/60	1	0	1	C,2
United States					
Albuquerque, New Mexico	11/8/60	2	0	1	B,2
Chicago, Illinois	2/18/65	1	0	1	B,2
Idaho Falls, Idaho	1/3/61	3	3	0	A,2
Lemont, Illinois	6/2/52	4	0	0	A,1
Lockport, New York	3/8/60	9	0	2	B,3
Los Alamos, New Mexico	6/6/45	3	0	0	A,1
Los Alamos, New Mexico	8/8/45	2	1	0	A,1
Los Alamos, New Mexico	5/21/46	8	1	1	A,1
Los Alamos, New Mexico	9/7/48	1	0	1	C,1
Los Alamos, New Mexico	12/30/58	1	1	0	A,3
Madison, Wisconsin	1961	1	0	1	B,1
Oak Ridge, Tennessee	6/19/58	5	0	5	A,3
Pittsburgh, Pennsylvania	10/4/67	3	0	2	B,2
Richland, Washington	4/7/62	3	0	0	A,3
Wood River Junction, R.I.	7/24/64	3	1	0	A,3
Yugoslavia					
Vinca	10/15/58	6	1	5	A,2
		384	14	161	

[a] See list of references to these accidents at end of Reference List.

tally observable human test systems *in vivo*. Clinically, however, there are available abundant careful observations of the effects of both intentional (therapeutic) and accidental irradiation of man. These observations, made from all points of view, suffer, however, from having been made of either sick persons under multiple forms of therapy where most parameters of dose were usually well known or of well persons accidentally exposed to radiations of unknown intensities resulting in doses that have only been estimated in retrospect. These data, poor as they are, when interpreted in the light of modern experimental animal radiobiology, serve us to describe man's radiosensitivity and to define the areas of our uncertainty about his dose-response relations.

This large clinical experience has been used extensively to provide a firm basis for the USAEC occupational radiation health program that has proved to be so remarkably successful since exploitation of atomic forces was begun. It has also been useful in retrospect in interpreting biological damage in atomic disasters—intentional, accidental, or incidental. In our time this biological dosimetric information has been put to the test in about 25 accidents involving more than 406 individuals (Table I). Few recent observations in accidents have changed our radiobiological concepts founded on past clinical observations, although many have helped establish more precise dose-response relations than have previously been known for man. All the studies show that, without doubt, all mammals including man react in a similar fashion to radiation exposure, differing apparently only in relation to amount, rate, and kind of exposure (Bond *et al.*, 1965).

II. Human Biological Dosimetry

Unfortunately, accidents by definition are not designed but occur in spite of the best precautions. Since they occur only when they are not anticipated, they usually occur when the film badge is in the victim's locker, the gamma alarms and interlocks are not working, or the victims have ignored warning signs. As a result dosimetry *immediately* after an accident is either nonexistent or so poor that no physician can base his plan of therapy upon it (Andrews *et al.*, 1965). Instead his treatment of the victim must be reactive to the sequence and progress of anatomical and physiological events (signs and symptoms), and in this sense these events have become "biological dosimeters." The only scientifically unbiased human biological dosimeter, however, promises to be the tissue culture technique using human lymphocytes of the victim within a few hours after the acci-

dent (Bender and Gooch, 1962). All clinical "biological dosimeters" still reflect the bias of the practitioner who has integrated his observations over a lifetime of practice without reference to dose-response probability distributions and their statistics. One such inviolate "end point" he has evolved is, for example, radiation-induced vomiting that "clinically" is believed to occur only after exposures to greater than 200 r but not to lesser amounts. Such commonly used threshold assumptions in medicine appear to be closely related to rough estimates of the amount of "dose" that causes more than half of patients to respond. It is assumed generally to be equivalent to the "effective dose for 50 percent response," ED_{50}, but is actually used as an "all-or-none" clinical sign. Although clinical diagnoses are commonly based on probabilities that one disease or another is more likely to be present than some other one, physicians as a group commonly do not think probabilistically about the distribution of responders in a human population exposed to differing amounts of a deleterious agent. These resulting "all-or-none" response thresholds have become such common concepts in clinical practice that a patient's failure to respond to a higher-than-threshold dose is usually interpreted as a mistake in dose estimate, while his vigorous response to a lower-than-threshold dose is often ascribed to extraneous nervous influences upon him. Hence, retrospective statistical searches for dose-response relations (Lushbaugh *et al.*, 1967) using the techniques of probit regression analysis of clinical data seem medically naive even though there does not seem to be a more objective way to establish the biological relations of symptoms to dose and thereby establish unbiased rationales for therapeutic and occupational limits of radiation exposure.

In spite of the deductive manner of their development, however, most biological radiation effects at the morphological or anatomical level can be used as approximate dosimetric end points because most of them require direct exposure and few result from the exposure of some other organ. The outstanding exceptions to this statement are (1) the changes in numbers of circulating blood cells since these reflect total (or average) lymphocytic and bone marrow damage, and the consequences of radiation-induced failure of these organs to replenish the constant loss of blood cells; (2) the symptoms and signs of the gastrointestinal prodromal responses that appear to reflect irradiation of an autonomic nervous system diffusely distributed in the middle of the body, and (3) radiation death that reflects many different lesions that are determined by whether the whole body or a particular part of the body was exposed, by the radiation dose

given, and by the rate or number of fractions of the total exposure. Considering all these reservations complicated by unpredictable variations in the radiosensitivity of individuals, a physician can make clinically meaningful dose approximations from the course of clinically observable events and the changes that occur in numbers of peripheral blood cells and in radiation-exposed tissues.

Historically, this clinical ability to appraise dose was developed first for the skin and its component parts (Strandquist, 1944). The production of erythema was so constant a postirradiation event that in the absence of physical dosimetry and any international agreement on the definition of a physical unit, radiologists coined their own unit of measurement—the S.E.D., or skin erythema dose. It is now well known that the slow appearance of erythema within 4 weeks after exposure to a single radiation dose indicates that 400–750 rads were deposited in the skin. In half of the cases, the dose will have been less than 575 rads (Langham, 1967, Chapter 5). Most radiologists consider an S.E.D. approximately equal to 600 rads. A more rapid appearance of erythema followed by blisters, moist desquamation, and ulceration follows dermal doses between 1660 and 2000 rads. In half of the patients, skin exposed to 2000 rads or less will heal in 4–6 weeks with only moist dressings for treatment—defining the so-called skin tolerance dose for man ($TD_{50} \simeq 2000$ rads). This effect is dependent on the area of skin irradiated only if the area is less than 400 cm^2. It is also dependent on the energy and quality of the radiation and upon the dose rate and number of fractions in which the dose is given. The knowledge that man can *repair* radiation damage was also learned first from studying the skin responses clinically after fractionated exposures. Strandquist showed in a now classical study (1944) that the skin-tolerated dose was increased as a power of number of daily dosage fractions (t) it was administered in, according to the formula

$$TD_{50} = 2000\ t_{(\text{days})}^{0.32}$$

Among the oddities of medicine practice that are no longer being practiced universally was the exposure of the scalps of children suffering from "ringworm" to 300 r of 80–100 kvp X-rays. Since the fungus grows in the hair follicle and 300 r stops dermal mitosis, the disease is cured by X-ray causing hair growth to stop and epilation to occur. Such *temporary* loss of hair is another well-known biological dosimeter that says the dose in the skin at the level of the hair follicle was about 300 rads. The permanence of the resulting baldness is a clinical measurement of either an excessive epilating dose or an excessively

sensitive patient. Permanent baldness and skin damage cannot always be avoided when a deep seated resistant tumor must be irradiated through the skin. Another radiation telltale can be found microscopically in the atrophic skin lesions caused by radiation exposure. This clue to the nature of the kind of energy causing the dermatitis rests on the small smooth muscle bundles that erect the hair during fright being spared (like the myocardial muscle and the striated muscle of the extremities) by radiation dose of about 20,000 rads that causes destruction of all other dermal appendages. If surgical biopsy fails to demonstrate the selective survival of these muscle bundles in the ultimate scar, ionizing radiation can be ruled out as being involved in the production of a dermal lesion whose etiology is being questioned (Lushbaugh and Spaulding, 1957).

Vomiting has been used as a human radiation dose indicator for years as it is one of the most characteristic responses of man to a serious level of exposure to ionizing radiation. About 2 hours after acute exposure of all or a major portion of the body to more than 10 but less than 1000 rads of penetrating ionizing radiation, most men begin showing signs and symptoms of acute gastrointestinal effects (anorexia, nausea, vomiting) called collectively the prodromal syndrome. Because such acute gastrointestinal distress usually interferes with man's ability to function, these prodromal responses are the earliest symptoms that accompany radiation-induced decrements in man's performance after acute radiation exposure in accidents or nuclear war. During acute attacks of radiation-induced nausea and vomiting, few people can be expected to maintain maximum levels of performance.

III. The Human Radiation Prodrome

The initial or prodromal radiation syndrome has had many labels since being described originally in 1897 as a severe prostrating sunstrokelike illness due to "deep tissue traumatism" (Walsh, 1897). Some names for it like "radiation sickness" have caused it to be confused with the acute radiation syndrome, of which it is only the initial symptom complex. Prodromal radiation reaction or syndrome seems at present to be the most widely used and appropriate designations for it (Gerstner, 1960). Other names, however, among its many other synonyms are descriptive of characteristic aspects of this reaction. "Premonitory phase" was preferred by Warren and Bowers (1950) to emphasize that the severity and duration of these early symptoms seem to predict the subsequent course and severity of the acute radia-

tion syndrome. Its German designation, "Strahlenkater," is compounded from "radiation" and "hangover," which its symptoms mimic to a large extent. While "radiation sickness" might seem generally appropriate, this term seems best avoided in reference to the prodromal syndrome because it has been and still is used loosely to designate any and all stages of acute or chronic radiation effects.

The various symptoms making up the human prodromal syndrome vary with respect to time of onset, time of maximum severity, severity itself, rate of recovery, and duration depending upon the size of the dose, protraction of the dose, and nondeterminable individual sensitivity of the exposed person. With a sufficiently large single acute dose (i.e., above the lethal range) of deeply penetrating ionizing radiation, individual variability conceivably would be minimized and practically all individuals exposed would develop all phases of the prodromal response. With doses of a few thousand rads all individuals can be expected to show all phases of the syndrome within 5–15 minutes of exposure (Langham *et al.*, 1965). Reaction would be maximally severe, reaching its most fulminating stage within 30 minutes and might persist for several days, gradually diminishing in intensity until the prodrome merged with the universally fatal vascular syndrome (Shipman *et al.*, 1961; Fanger and Lushbaugh, 1967) or, after doses of ~1000 rads, with the fatal dysenteric gastrointestinal syndrome. With smaller doses the interplay of multiple determinant factors makes dose-response predictions clinically difficult. Although it is not always so, a severe fulminating prodromal response has a poor clinical prognosis and predicts at least a prolonged period of acute hematological aplasia accompanied by potentially fatal infection, anemia, and hemorrhage.

At doses near or less than those estimated to be the median lethal range for man, see below, the interaction of the multiple variables affecting the quantal and quantitative aspects of the prodromal reaction prevents prediction of the level of response for a single exposed individual and restricts such predictions to statistical probabilities. This restriction is fortified by ignorance of the mechanisms by which the prodromal responses are induced. There is little agreement as to whether they are direct or indirect effects, although there is abundant evidence that the prodromal responses can be produced by irradiation specifically of the abdomen, thorax, or head (Conard, 1956). Apparently the autonomic nervous system is intimately involved in production of the reactions and can be activated directly or indirectly. Irradiation of the epigastrium elicits the responses with the least dose, while any irradiation of the extremities is ineffectual.

In total-body irradiation, shielding the abdomen with a sheet of lead can prevent the response (Walsh, 1897) unless large doses are delivered simultaneously to the head.

The signs and symptoms of the human postirradiation prodromal syndrome can be divided into two main groups: gastrointestinal and neuromuscular. The gastrointestinal ones are anorexia (loss of appetite), nausea, vomiting, diarrhea, intestinal cramps, salivation, fluid loss, dehydration, and weight loss. The neuromuscular symptoms include easy fatigability, apathy, or listlessness, sweating, fever, headache, and hypertension followed after high doses by hypotensive shock. All these signs and symptoms are not seen unless the exposure is in the supralethal range or the observation period is prolonged beyond the 48-hours postirradiation period, usually used to delineate the duration of the acute prodromal syndrome. At median lethal doses (? 300 rads ± 100, see below), the principal symptoms of the prodromal reaction are anorexia, nausea, vomiting, and easy fatigability. Immediate diarrhea, fever, and hypotension seem to be signs of supralethal exposure.

In recent retrospective studies (Gerstner, 1960; Langham, 1967; Lushbaugh *et al.*, 1967), the temporal distribution of onset of vomiting in 100 men exposed to single acute doses at or in excess of the assumed $LD_{50/60}$ (300 rads) for man was found to be 144 ± 66 minutes. For lower doses, Gerstner (1960) predicted that peak incidence of nausea and/or vomiting, if these symptoms occur at all, will be approximately 6 hours after exposure.

With doses of total-body irradiation that are less than lethal, the incidence of the various responses in the prodromal syndrome seem to have a positive correlation with the size of the dose (Lushbaugh *et al.*, 1967). This dose-response relation is expressed best as the effective dose for producing the response in 50% of the population, the ED_{50} for a particular response. A typical regression line relating the probability of the response occurring as a function of dose may be expressed by the probit equation, $Y = a + b(x)$, where Y is the probability in probit units, x is the dose, b is the slope, and a the intercept. Such a dose-response relation once established can be used to predict a dose that will elicit some percentage of responses in the exposed population, providing the fiducial and clinical limitations of the data are known. As explained above, the clinician intuitively has used his experience to establish such a relation as a useful diagnostic threshold. True radiation dose-response relationships, however, are not known for normal man, although in the past there have been a number of attempts to capitalize upon information contained in

the histories of the atomic bomb casualties (Oughterson and Warren, 1956; Warren and Bowers, 1950), the 240 nuclear accident victims,[2] and the 30-year experience with therapeutic trial of total-body irradiation for cancer to establish correlations (Medinger and Craver, 1942; Miller *et al.*, 1958; Saenger *et al.*, 1966; Lushbaugh *et al.*, 1967). Most of the early correlative studies of the atom bomb experience and radiation accidents were not truly quantitative because the dosimetry was largely conjectural or determined only retrospectively. In the clinical studies dose measurements in radiotherapy have been adequately precise during the last 20 years, but there has always been uncertainty about the etiology of the response. Patients being treated always have a concurrent incidence of signs and symptoms caused by disease that cannot be separated, for example, from the prodromal responses. Furthermore, their probability of dying from their disease was high and was in itself often the reason why in many cases there was a therapeutic trial with total-body irradiation which in some instances was life saving. All postirradiation responses in patients cannot for these reasons be attributed solely to radiation exposure. Relating the entire incidence of such response to the dose produces a lower ED_{50} than that expected for normal men with no natural incidence of the response. Extrapolation from the effects of irradiation upon sick man to those "expected" in *well man* seems permissible, therefore, only if the biased nature of the responses of *sick man* is kept in mind. Such a procedure seems more acceptable than extrapolation to man from experience with lower animals, although some animal radiobiologists may not agree.

A retrospective study of the effects of intentional therapeutic total-body irradiation of patients has been in process by the author and his colleagues (G. A. Andrews, R. M. Kniseley, F. Comas, and C. L. Edwards) for several years with AEC/NASA support. The purpose of this study is to determine as best we can the apparent dose-response relationships for the various phases of the prodromal syndrome from all available case histories. The details of cases, case selection, dose evaluation, and evaluation and processing of data are not given here but may be found in an earlier report of the progressing study (Lushbaugh *et al.*, 1965, 1967). This preliminary study comprising 100 cases was later expanded to include the data from 165 cases (Langham, 1967) and finally from 504 cases where all radiation exposure factors (corrected for natural incidence of nonradiological in-

[2] For the convenience of the reader, at the end of the alphabetized reference list is an abbreviated list of articles that first described the accident or clinical courses of the victims.

duced symptoms) and quality of clinical records were known (Lushbaugh *et al.*, 1968b). Our best and most recent estimates are shown in Tables II and III. The figures representing the computed ED_{50} and ED_{10} in rads absorbed in the upper abdominal body compartment were obtained by probit regression analysis of the incidence of gastrointestinal responses in various numbers of persons exposed to the same number of roentgens at hospitals throughout the United States and Canada. The ED_{10} (Table III) is the dose estimate at which one patient among ten is expected to respond. The ED_{50} estimates (Table II) show a logical internal agreement in that the list

TABLE II

ED_{50} ESTIMATES FOR PRODROMAL SYMPTOMS OF GASTROINTESTINAL DISTRESS FOR IRRADIATED PATIENTS

Response	Previous[a] estimates, N[c] = 163	ORAU,[b] N = 104	Other hospitals, N = 400	All hospitals, N = 504	All, 6 nursing notes required[d]
Anorexia	97^{+31}_{-26}	63^{+13}_{-12}	129^{+56}_{-31}	92^{+33}_{-20}	59^{+14}_{-10}
Nausea	139^{+72}_{-33}	128	172^{+83}_{-43}	154^{+47}_{-29}	118^{+154}_{-50}
Vomiting	183^{+178}_{-63}	165	276^{+217}_{-87}	230^{+104}_{-53}	176^{+76}_{-41}
Diarrhea	238^{+122}_{-55}	$370^{+\ ?}_{-172}$	$294^{+\ ?}_{-166}$	302^{+162}_{-76}	286^{+230}_{-86}

[a] Space Radiation Study Panel Report (Langham, 1967).

[b] ORAU—Oak Ridge Associated Universities, Medical Division.

[c] N = number of patients.

[d] Clinical histories not having this minimum number of consecutive post-irradiation notes were discarded.

of symptoms of distress (shown in ascending order of severity) corresponds to an increasing dosage requirement. This internal agreement of the data supports the concept that the acute hematological radiation syndrome in man is composed of a close-knit series of progressive dose-response relationships which, for single doses, range from the least serious symptom (anorexia) of the prodromal response toward the most serious effect (hematopoietic death). In Table III, the results of the various analyses have been summarized for the expected 10% response (ED_{10}) level for the various symptoms from a recent study done to test the reliability of the estimates by making more restrictive quantal definitions for the responses. The slight increase in the doses required to produce these responses sooner than 48 hours (within 12 hours) lends credence to the clinical and statistical observations that the majority of the observed gastrointestinal effects occur within

12 hours after exposure (a mean induction time of 144 minutes at supralethal doses; see above). Because an unknown incidence of these responses from causes other than radiation is present, statistical programs used here were designed to adjust the regression lines for the presence of an unknown natural incidence of the symptom but in addition, patients that according to the history, showed signs of

TABLE III
ED_{10} ESTIMATES (RADS)

Response	Previous estimate,[a] N[b] = 163	ORAU, N = 104	Other hospitals, N = 400	All hospitals, N = 504
(A) All patients, no restrictions				
Anorexia	39^{+17}_{-20}	26	22	20
Nausea	51^{+17}_{-20}	39	32	33
Vomiting	62^{+20}_{-20}	54	42	54
Diarrhea	$102^{+?}_{-44}$	45	79	66
(B) No predose responders; response within 48 hours				
Anorexia		29	29	26
Nausea		40	35	35
Vomiting		54	48	47
Diarrhea in 6 weeks		54	84	72
(C) All patients, response within 12 hours				
Anorexia		39	39	36
Nausea		62	52	54
Vomiting		74	68	67
(D) No predose responders; response within 12 hours				
Anorexia		43	54	47
Nausea		64	57	57
Vomiting		74	79	72

[a] Space Radiation Study Panel Report (Langham, 1967).
[b] N = number of patients.

illness before radiation exposures were deleted as "predose responders." This restriction upon the data, however, did not affect the estimates significantly. Acceptance of these figures as those for normal man has to be conditioned upon the premise that a well man is not significantly more radioresistant than a sick one. Although this premise is probably false, the number of completely "normal men" among potential radiation victims throughout the world is, on the other hand, significantly less than 100% (~30%?).

These clinically and statistically derived dose-response relations for the gastrointestinal symptoms of human radiation-induced prodromal response can only be used as a biological dosimetry system when a single radiation exposure is involved. They define well the lowest observable bound of the acute hematological syndrome for man. Langham *et al.* (1965), and Langham and the Space Radiation Study Panel (see Langham, 1967) predicted on the basis of past clinical observations by others during radiotherapy trials in cancer that fractionation of radiation exposure over 1–2 weeks might decrease the

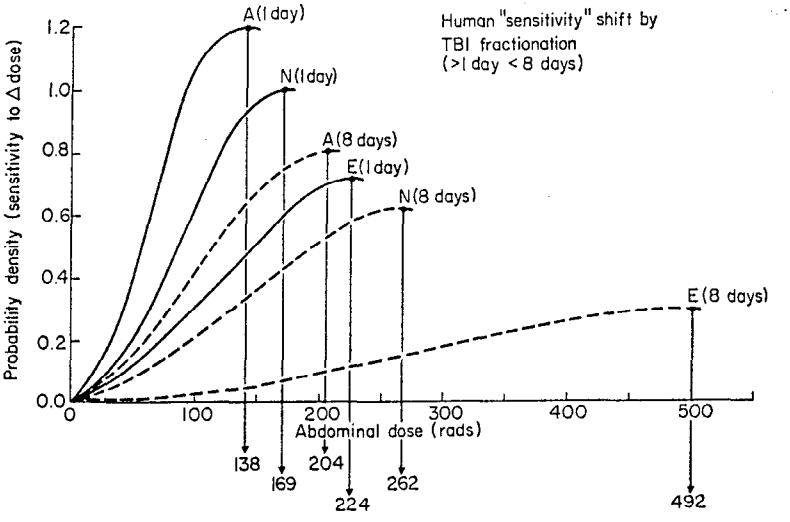

FIG. 1. Fractionation of total body dose over 8 days increases the doses required to produce the same incidence of various prodromal symptoms in the exposed population of patients, by 1.5 for anorexia (A), 1.6 for nausea (N), and 2.2 for emesis (E).

incidence of these radiation-induced prodromal responses by about a factor of 2.5 times. Lushbaugh *et al.* (1968b) tested this conjecture and found that such dose fractionation in patients reduced dose effectiveness 1.5 times for anorexia; 1.6 times for nausea; and 2.2 times for emesis as shown in Fig. 1. In the figure, the probability densities for incidence of prodromal responses in respect to dose are shown for single and fractionated exposures made over a period of time, less than 8 days in length. The graph shows an obvious shift in "sensitivity" caused by a reduction in effectiveness of the fractionated radiation exposures that was less pronounced for the milder symptoms. The larger change in the dose-response relation for vomiting supports

the clinical observation that decreased dose rate or increased number of fractions decreases the incidence of untoward gastrointestinal responses and gives evidence of the presence of radiation-damage repair mechanisms in this human physiological system.

IV. Human Hematological Responses

Among all the morphologically based, response versus dose relations none is considered more quantitative and clinically useful than the well-known changes in the peripheral lymphocyte count after total-body irradiation. In a radiation accident the decrease in absolute lymphocyte count during the first 48 postexposure hours has many times the prognostic value of the first film badge reading or serum sodium-24 estimate. Clinicians, well acquainted with the medical radiation-accident literature, cannot forget that in the past, when they have been made, the initial exposure estimates accompanying the victims to the hospital have sometimes been erroneous by factors of 2 to 3 and occasionally by a factor of 10. For the clinician, during this early period of hospitalization, the progressive changes in the patients' symptoms and signs must be used as his measure of the seriousness of the exposure in order to plan therapy. Knowingly or not, however, the clinician assumes that the blood of all normal men exposed to 300 r, for example, will follow the same temporal-course pattern. He concludes, therefore, when he observes such a pattern that the victim has received this exposure and not that reported by the health physicist if this estimate is not the same as his. Working against these odds has been a major stimulus to the development of rapid, accurate dosimetric methods and practices by physicists working in occupational health for the AEC in this and other countries. Precision in dosimetry and improved personal radiation exposure monitors may help clinicians in the future define man's hematological variability in response to the same dose. Because of the invariable way that lymphocyte death begins at about 50 rads and virtually none escape damage from doses above 1000 rads after single, prompt exposures the relation of the lowest lymphocyte count within 48 hours will, even then, prove to be the most reliable and easily interpreted biological dosimeter. Changes in platelet and granulocyte count are not as reliable as lymphocyte counts, but have been used similarly to appraise clinical dose. Individual responses, however, have been much more variable in respect to imagined dose as might be expected in diffusely located cellular systems, where rate of change can also depend upon loss of cells in repairing damage to other tissues (viz.,

blood vessels and epithelial linings) besides damage to its own stem cell replicating mechanisms.

Unlike the clinical studies of radiation effects on skin and tumors (Strandquist, 1944; and others) there is little evidence that man repairs radiation damage to his bone marrow as lower animals seem to be able to do. Although the incidence of vomiting, for example, was less than expected in the Marshallese natives exposed to about 175 r protracted over 50 hours (Cronkite *et al.*, 1955) their hematological responses showed such little evidence for reduced radiation effectiveness due to low dose rate that Cronkite and Bond (1960) concluded that man was significantly more radiosensitive than had previously been estimated by Warren and Bowers (1950), or that he is extremely slow to repair the bone marrow lesion of the acute hematopoietic syndrome. Recently Lushbaugh *et al.* (1968b) found that fractionation of total-body dose into two or more fractions over an 8-day overall treatment interval, does not alter the temporal course or degree of the subsequent changes in total leukocyte count from irradiation damage in patients. The exquisite radiosensitivity of patients with chronic lymphatic leukemia (Andrews *et al.*, 1966) was found in this study to be about twice that expected from study of the changes in white cell count in normal persons after radiation accidents. Doses of 100–200 rads appeared to produce the hematological changes found only after 300–400 rads in normal men, and 8-day fractionation failed to alter this sensitivity or to allow repair in this interval.

Langham and the NAS Space Radiation Study Panel (see Langham, 1967) recently reviewed the hematological medical literature and constructed time course templates of the changes expected in total white blood cell count, platelets, and lymphocytes after exposure to various assumed doses of radiation. They predicted that dose fractionation might reduce radiation effectiveness in producing hematological damage by a factor of 2.5. The failure to obtain evidence to support this opinion from the study of patients (Lushbaugh *et al.*, 1968b) exposed over a week, suggests that man may not repair radiation-induced bone marrow damage significantly during the first week after exposure. There are, however, many observations that man like other animals can repair such damage effectively in time. In the now famous Mexican accident (Martinez *et al.*, 1964), for example, the single survivor of the five persons exposed to cobalt-60 was exposed at the lowest daily dose increment for about 116 days during which time he accrued a total exposure estimated to be between ~960 and 1200 rads. When seen medically he was symptom-

less but had a severe aplastic anemia from which he subsequently recovered. In radiation accident victims with presumably normal bone marrow kinetics, a phenomenon in peripheral white blood cells occurs that is peculiar to man and some other large animals. Shortly after exposure to a single dose, an "abortive rise" in leukocytes begins to occur, reaching peak incidence in about 12 days (Bond *et al.*, 1965). These abnormal granulocytes (Fliedner, 1969) disappear during the next 2 weeks and contribute to the 2-week long displacement of the WBC nadir in man to 30 days postexposure instead of 12–15 as seen in most small mammals. The occurrence of this abortive rise is not found in leukemic patients. It is considered evidence of an early but ineffectual attempt at bone marrow repair. Usually bone marrow repair after a single whole-body dose (about the estimated $LD_{50/60}$) requires 50–60 days to be completed in man. Lymphopenia is amazingly prolonged even in persons exposed accidentally to less than 150 rads (Shipman *et al.*, 1961).

V. Dosimetric and Other Conceptual Problems in Human Radiobiology

Dosimetry in radiation accidents has improved beyond simple description in the last 10 years (1958–1968). Improvements have been made in dosimetric methods such as in the use of thermoluminescence and tissue equivalent humanoid phantoms containing actual bones and air-containing pulmonary spaces. Health physics safety practices have met with increased acceptance and compliance, so that the old saying that "accident victims never wear film badges" no longer borders on the truth. These pressures have resulted in more realistic exposure and dosage estimates in recent radiation accidents that strengthen our confidence in man's dose-response relationships and give hope that we will be able in time to resolve some of the divergent opinions about what actually happened in past accidents. We are probably not yet being realistic about the target volume as Rossi has pointed out (1968).

An accident occurred at Vinca, Yugoslavia, in 1958 where the human dosimetry problem is well illustrated. The Yugoslavian and French physicians (Mathe *et al.*, 1964) argue here that bone marrow infusions given to these men and women were life saving because the doses were so high (350–640 rem), but their American physician counterparts consider the bone marrow infusions unnecessary as well as unsuccessful, because the "true" doses were so low. In Table IV, the Vinca dosage estimates of Hurst *et al.* (1961), have been manipu-

lated to demonstrate the complicating dosimetric problem of the large animal: The rationale for depth dose attenuation of the free-field exposure dose and use of a radiobiological efficiency (RBE) factor for neutrons for total-body irradiation dosage estimates in all large animals. In Table IV, the first column shows the original individual dose estimates in rem as made by Pendic (1961), and the second column shows the free-field radiation estimates made of the first collision "air-dose" in rads by a team of health physicists from the Oak Ridge National Laboratory (Hurst *et al.*, 1961; Auxier, 1961). Although the latter estimates have always been accepted as absorbed dose, they are truly "exposure" measurements of the free-field and need to be reduced by at least 30% to approximate the dose absorbed

TABLE IV
VINCA DOSE ESTIMATES

Patient	Pendic (1961) (rem)	Hurst-Auxier (1961) rad exposure field (rads)	Depth dose estimate rem if $RBE_n = 1$ (rem)	Gamma: neutron dose fraction 3.8:1 (rads)	Neutron dose if $RBE_n = 3$ (rem)	Resulting total depth dose (rem)
H	420	323	226	179 47	141	320
V	640	436	305	241 64	192	433
G	600	414	290	230 60	180	410
M	580	426	298	236 62	186	422
D	500	419	293	232 61	183	415
B	350	207	145	115 30	90	205

in the vital central portions of the body (column 3; see also Fig. 2). Although it is widely accepted at this time by most radiobiologists, led by Alpen and Bond and their groups (Bond *et al.*, 1956; Alpen *et al.*, 1958; Alpen and Baum, 1959), that the RBE = 1 for all high LET radiation for lethality in all large animals including man (Langham, 1967), there is some evidence in man that radiation from atom bombs and other devices require the assumption of an RBE for fission neutrons in man of from 2 to 3. This modern radiobiological heresy, discussed more fully below, has been used in Table IV along with the gamma neutron ratio in the accident of 3.8:1.0 to derive additional individual depth doses for these victims in "corrected rem" where RBE = 3 (columns 4–7). These arithmetic shenanigans result in approximately the same numbers for depth dose as the free-field exposure estimates of Hurst *et al.* (1961), creating the philosophical

dilemma of the loop where a scientific or medical evaluator may find reason to choose an estimate to strengthen or destroy his preconceived concepts about dose-response and RBE relations in this or other accidents. Obviously the "true doses" in this accident were lower than Pendic's original estimates in 1961 and the effective doses were larger than those derived here using a depth dose attenuation factor without an RBE factor for neutrons.

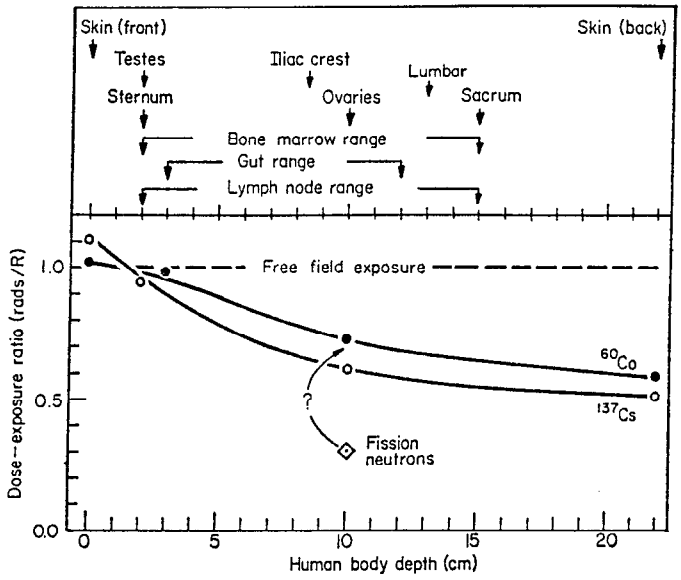

FIG. 2. A large animal like man is an effective shield to centrally located organs, reducing the free-field radiation level up to 50% when the exposure is unidirectional. The widely dispersed hematopoietic organs of man have unit doses that vary by a factor of 2. First collision fission neutron dose to the center of the body is only 30% of the free-field, but secondary photon production increases the local dose by a factor of 2 or more (as indicated by the question marked arrow). (Drawn from Jones, 1966; Piesch, 1968.)

Obviously a reliable physical means of neutron dosimetry (that a worker can wear) is needed in conjunction with a precise means of measuring the victim's absorbed dose before we can avoid such a dilemma as is still posed by the dosimetry in the Vinca accident. Hopefully, the use of chromosome analysis (see Bender, this volume) will ultimatey obtain sufficient substantiation in irradiated man to help resolve these dosimetric problems.

Although it is assumed that a dosimeter reading can be converted

from surface exposure (roentgens) to another site of interest (an organ dose, in rads) this is possible only when the energy, nature, and direction of the radiation are known (Piesch, 1968). In addition, the volume and bodily distribution of the organ must be known in relation to a three-dimensional array of previously determined isodose lines for the radiation involved. Most dosimeters are neither small enough nor sufficiently energy independent for this purpose. In addition, the spatial distribution of the four most important tissues of the body; lymphopoietic tissue, bone marrow, alimentary canal epithelia, and blood vessels are relatively ubiquitous so that no single small volume of tissue contains a significant fraction of functional units for which a radiation dose can be expressed by one number. For such tissues, the average dose absorbed by the whole body would seem to be most appropriate, but this view is patently fallacious in regard to the bone marrow (Bond and Robinson, 1967a,b). In Fig. 2, the dosimetry problem for all large animals is diagrammed using human dimensions as an example. Bone marrow, lymphatic system, and intestine can be seen here to have a depth dose that varies from almost 50 to 100% of the free-field exposure. Maximum dose to the bone marrow is approximated by the dose to the testes, and minimum bone marrow dose is about half of that. Although it is true, as pointed out by Hurst *et al.* (1961), that the $^{24}NA:^{23}Na$ ratio in nuclear accidents is an excellent way to obtain the whole body average dose (WBAD), the WBAD has little radiobiological value if the irradiation is not omnidirectional and it has none if less than half of the body is irradiated while the other portion is shielded. A recent review of this problem (Cloutier *et al.*, 1967) concluded that the average whole-body dose was the best dose expression for therapeutic total body irradiation, but that in studies of specific organ responses the dose to that site of interest was more appropriate. Bond and Robinson (1967a,b) have made an interesting attempt to obtain the average bone marrow dose in total body irradiation, but our biology at present is too poor to help us decide whether this dose expression is better than any other for use in determining hematopoietic dose-response relations. It is not as simple a choice as that in radiotherapy of a tumor where the dose given is expressed for obvious reasons as the least dose that the centrally located cancer cells were exposed to.

Rossi has recently pointed out (1968) the biological error in specifying irradiation conditions in terms of macroscopic quantities of energy densities per unit mass. The true biological targets receive doses distributed about this mean value. Depending on the volume of the irradiated organelles and the complex way that many radiation

particles dissipate their energy, the real doses to microscopic sites of interest can vary widely, and biological results be unpredictable. Measurable biological end points assume great importance here as they afford a means of relating dose and effect in volumes that have greater mechanistic information than such end points as 30–60-day lethality, mean after survival time, etc., that are necessarily expressed in terms of the average dose to the whole body, or the extrapolated dose to an imaginary midline, midplane point. But in human radiobiology, we are not yet ready to apply such fine sophisticated dosimetry to our retrospective evaluations.

The recent development and study of *in vitro* and *in vivo* cellular systems that employ human as well as animal cells in tissue culture indicate that we are making some progress in this direction by introducing the application of precise mathematics and physical principles to this field of clinical radiobiology. But more important than that, these techniques have shown without doubt that many of our assumptions for man about the underlying cellular mechanisms of radiation effects are correct; that radiation-induced death of the stem cells of replicating systems underlies the various types of human as well as animal hematopoietic death; that decreasing dose rate decreases the efficiency of the cell-sterilizing effect of radiation; that tissue oxygenation enhances the damaging efficiency of radiation and that cellular radiosensitivity of all animals depends upon the stage of the mitotic cycle that the cell is existing in at the time of the radiation event. The rough agreement of the various $LD_{50/30}$ for mice and rats at various exposure rates with those for HeLa cells irradiated at these rates *in vitro* has recently been used to imply a one to one correlation with the LD_{50} of the whole animal and his stem cells (Hall *et al.*, 1968). The implication that this correlation can be made in man may not be intended but would not appear to hold true, since the cancerous cells (HeLa) of human origin used in these studies have an LD_{50} that is from three to four times greater than the best estimates of man's $LD_{50/60}$ ($\sim$300 rads, see below).

VI. Human and Large Animal Radiation Sensitivity

The phenomenon of the greater hypersensitivity of the whole large animal relative to small laboratory animals and to *in vitro* as well as *in vivo* cellular systems is far from explained. The work of Cole *et al.* (1967), for example, shows that the dog can be protected from hematopoietic death after supralethal radiation exposure by transplantation of less than 2% of his bone marrow stem cells. This observa-

tion cannot be reconciled with the hypothesis that whole-body LD_{50} corresponds to the D_0 (37% survival) of *in vitro* cellular systems. It is much more likely that rates and mechanisms of cellular repair and organ reconstitution are responsible for the wide differences observed in mammalian species radiosensitivity. While conveniently measured in animals by 30-day lethality as the end point, the radiosensitivity of man obviously cannot be equated experimentally by this technique. Nonetheless, numerous attempts have been made to appraise man's radiosensitivity in these terms by studying the incidence and temporal pattern of human deaths after radiation exposure, by using statistical methods that permit the possibility that an unknown number of such deaths were not purely radiation induced.

VII. Evaluation of Human Radiation Lethality

As shown in Table I, there have been about 27 serious radiation accidents where 384 normal men and women have been partially or totally irradiated. In radiation accidents in the United States only 4 persons have died directly from radiation damage, and 14 others have survived dangerous levels of irradiation that have required prolonged hospitalization. Among the 384 worldwide accident victims, 14 have died and 161 were seriously injured. As small as this clinican experience is, it still serves as our only study material for comparing *normal* man's radiation-induced responses with those of various experimental animals in the vast experimental radiobiological literature. This knowledge is augmented by the now voluminous investigations of the Hiroshima and Nagasaki atom bomb casualties and of the effects of therapeutic irradiation in patients (see above). In these studies of patients, deductive information about lethal radiation syndromes is questionable because of their complicating diseases and the relatively small doses that have been used therapeutically to avoid inducing death. In the Japanese victims early radiation death syndromes were, unfortunately for radiobiology, often obscured by simultaneous injuries caused by blast and fire; many deaths were prevented by highly variable but effective shielding conditions. Hematopoietic death syndrome is, however, well documented by the medical observations made in Japan immediately after cessation of hostilities (Oughterson and Warren, 1956; and others). Attempts are still continuing to relate these clinical observations to dose estimates for the purpose of defining normal man's radiosensitivity in the quantitative terms of animal radiolethality and after survival. These studies by the Atomic Bomb Casualty Commission and others are presently

focused chiefly on studying delayed radiation effects in the surviving exposed population.

The lethal radiation dose (LD_{50}) of man has never been established in fact. Several attempts to do so indirectly and in retrospect have been reported and recently summarized by Langham (1967) (see Table V, part A). The earliest attempt to make an educated

TABLE V
SOME GUESTIMATES OF HUMAN $LD_{50/60}$

	Exposure	Dose	Reference
A. *Previous estimates*	r	Rads	
Hiroshima/Nagasaki Atomic-bomb casualties	~450	(~300)[a]	Warren and Bowers (1950)
Marshallese casualties and extrapolation from large animals	~350	(~300)	Cronkite and Bond (1960)
Total-body radiotherapy	400	(300)	Mathe *et al.* (1964)
Total-body radiotherapy	370	243 ± 22	Lushbaugh *et al.* (1967)
Total-body radiotherapy	(380)	251 ± 28	Langham (1967), p. 81.
Space Radiation Study Panel evaluation	(430)	285 ± 25	Langham (1967), p. 114.
B. *Recent estimates*	Rem		
T_{65} ORNL/Dikewood shielding study	$RBE_n = 1$	$RBE_n = 2$	
Hiroshima	180	258 ± 39	Lushbaugh-Axier,
Nagasaki	255	265 ± 27	This chapter

[a] Exposure and doses in parentheses are converted from air-dose to body depth dose or vice versa.

guess of man's total body radiosensitivity was made by a committee composed of 10 senior staff members of the U.S. Armed Forces studying the casualties of the atom bombs in Japan (L. Taylor, 1967). This estimate rests heavily upon 1947 and 1948 estimates for free-exposure fields (Wilson, 1951) at various distances from the epicenters of the bursts. Some of these free-field dose estimates, now known to have been based on an overestimate of the yield of the Hiroshima bomb (Auxier *et al.*, 1966) led in 1948 (Warren and Bowers, 1950) to an LD_{50} estimate for man of 450 r. The roentgen unit used then has been freely translated by many persons since to mean dose in rads. In modern terms of dosimetry, however, this exposure should be translated into an absorbed dose equivalent of 325 rads in the center of the human body. This number is presently widely accepted as

normal man's $LD_{50/60}$, since it has been incorporated into all USAF medical training manuals. In those early observations it was first noted that man seems to develop signs of hematological damage and to recover from it much more slowly than all other mammals. The peak incidence of human deaths from hematological damage was about 30 days after exposure, but deaths occurred up to 60 days. The LD_{50} estimates for hematopoietic death for man is expressed, therefore, as $LD_{50/60}$ days instead of $LD_{50/30}$ days as in animals, where peak incidence of death occurs 10–15 days after exposure. Since 1948, other committees, radiotherapists, and radiobiologists have tested this estimate by trying to determine man's $LD_{50/60}$ using other study material and more modern statistical methods. For example, Mathe *et al.* (1964), found that incidence of death from bone marrow aplasia occurring in 110 therapeutically irradiated patients with various neoplasms and leukemia was 33% in the 52 that were exposed to more than 100 r but less than 400 r; 76% in the 21 who were exposed to more than 400 r but less than 500 r; 91% in the 23 who received more than 500 r but less than 1000 r; and 100% in the four who received exposure of greater than 1000 r (^{60}Co γ-radiation). He deducted from these observations that 400 r was the approximate $LD_{50/60}$ exposure for man. Dosimetry with humanoid phantoms in radiation fields produced by ^{137}Cs and ^{60}Co γ-radiation indicates that 65–70% of this radiation exposure is absorbed in the central core of the human body; converting this exposure estimate to a "dose" of about 280 rads (see Fig. 2). In spite of the shortcomings of clinical data, Lushbaugh *et al.* (1965, 1968b), and Langham and the Space Radiation Study Panel (see Langham, 1967) have also made predictions of man's lethal dose by statistical treatment of this material. The estimates of 243–251 rads (370–380 r) derived from sick patient studies ought to be too low to be acceptable as the $LD_{50/60}$ for normal man. In fact they may only be fortuitously derived numbers determined by the high death rate from nonradiation-induced diseases in these very ill patient populations, and not related to radiation exposure at all (Andrews *et al.*, 1965). Langham (1967) tried to "correct" the shallow slopes of the probit regression lines obtained in these studies by converting them to the steeper slope of the dose-lethal response relationship found by Cronkite and Bond (1960) in dogs and used by them to modernize the Warren estimate as well as to fortify the opinion that 300 rads was more likely the "human lethal dose" than the 800 rads dose suggested by Harris (1960, quoted by Cronkite and Bond, 1960). In doing this analysis, Langham obtained the upper abdominal compartment dose of 285 ± 25 rads as

the $LD_{50/60}$ for total-body irradiation in man. These historical educated guesses at man's $LD_{50/60}$ are shown in Table V, along with two new ones described here in detail in spite of the preliminary nature of the estimates.

Recently the free-field (air) dose distributions for the gamma and neutron radiations from the atom bombs in Hiroshima and Nagasaki have been redetermined (Auxier *et al.*, 1966). Early estimates were made by Wilson (1956). Ritchie and Hurst (1959) derived estimates from York's values that have become known and used as "T_{57} doses." The most recent ones of the Oak Ridge National Laboratory are known as "T_{65} doses" and will probably be the "best" estimates for some time to come since, with the atom bomb testing moratorium for air bursts, it is not possible to refine the experimental data further. According to Auxier (1968), the Hiroshima data are no longer considered interim in nature because existing uncertainties about the yield of this bomb have now been resolved to $\pm 10\%$. The Hiroshima data are considered, therefore, to contain no more than a probable error of $\pm 15\%$ as opposed to that of $\pm 10\%$ for Nagasaki. "Good" agreement with the T_{65} ORNL dose estimates has been obtained by Ichikawa *et al.* (1966) and Hashizume *et al.* (1967), using the thermoluminescence of roof tiles and the neutron-activated ^{60}Co in concrete in the two cities as dosimeters. While some divergence still exists, the data shown in Table VI for the air dose estimates at 1000 horizontal meters from ground zero in the two Japanese cities show that the three most modern dose estimates differ greatly from the one used to derive the original 450 r estimate $LD_{50/60}$ for man (Warren and Bowers, 1950). Considering the magnitude of the variables and the difficulties involved in making these extrapolations from field tests, the four estimates for Nagasaki appear to agree better than could be hoped for and to be sufficiently accurate for retrospective attempts to relate clinical response data to dose. The United States Atomic Energy Commission, Division of Biology and Medicine, has supported a study of these air doses by the Health Physics Division of the Oak Ridge National Laboratory in conjunction with the Atomic Bomb Casualty Commission of the U.S. National Academy of Sciences, and the National Institute of Health of the Ministry of Health and Welfare of the Japanese government. In addition, the Civil Effects Branch of the USAEC, DBM, has supported a study by Davis *et al.* of the Dikewood Corporation of the free-field weapon versus shielding effects upon mortality and casualties (1966). The data from both of these major studies are now being merged at ABCC in Hiroshima to relate dose and effect, but as yet no definitive studies

have been published. A preliminary but unpublished analysis by Fukishima and Beebe (1968) of the relation of various acute symptoms of systemic radiation damage in people in the two cities to the T_{65} doses shows that "the Hiroshima rad is about 1.6 to 1.8 times stronger than that of Nagasaki," suggesting that the RBE for neutron effects in man must be greater than 1.0. When the T_{57} doses were still in vogue, Heyssel and Brill (1960), and Brill *et al.* (1962), found that the "Nagasaki rad" was apparently "stronger" than the "Hiroshima rad," an observation also made by Beebe in his statistical studies (Beebe *et al.*, 1962) of dose-response relations with these data. The relative changes wrought by the "T_{65}" dose estimates (shown for 1000 meters in Table VI) avoid this apparent need to

TABLE VI
AIR DOSE (RADS) ESTIMATES FOR ATOM BOMBS 1000 METERS FROM GROUND ZERO

Hiroshima		Nagasaki		
η	γ	η	γ	T year (reference)
1140	680	80	680	1951 (Wilson, 1956)
380	680	56	820	1957 (Ritchie and Hurst, 1959)
192	260	37	903	1965 (Auxier, *et al.*, 1966)
150	280	60	900	1965 (Hashizume *et al.*, 1967)

proscribe an RBE of less than one for Hiroshima neutron rads as implied by Brill and others. The presently accepted dose estimates (Auxier *et al.*, 1966) for the two kinds of radiations in relation to horizontal distance from ground zero in the two cities, shown in Fig. 3, indicate that the "Nagasaki rad" has a relatively small neutron component while the "Hiroshima rad" has a significantly large one. The reduction in the relative neutron dose in Hiroshima greatly decreases the total air-dose in rads for any distance in Hiroshima below that in Nagasaki, as shown for example for 1000 meters in Table VI. And so the "weak Hiroshima rad" now becomes a "stronger than Nagasaki rad"! The dosimetric results of this change upon mortality were recently tested by Auxier and Lushbaugh (1968) by comparing the 60-day survival curves of the Dikewood Study (Davis *et al.*, 1966) with the clinical histories of the exposed Japanese people. In the Dikewood Study, mortality rate/distance in both cities was found to differ (as was expected) according to the type of shielding the

people had had at the time of the explosions. Among the twelve different exposure (shielding) conditions studied, we chose three that were common to both cities and seemed to us to define the "least, median, and most" shielding. The relative mortality curves were, respectively, those for "outside, unshielded (OU[3])," "inside light steel frame buildings (LSF[3])" and "inside seismic reinforced concrete buildings on the lower floor (SRC-L[3])." These two sets of three curves are redrawn from the Dikewood data in Fig. 4. Using probit regression

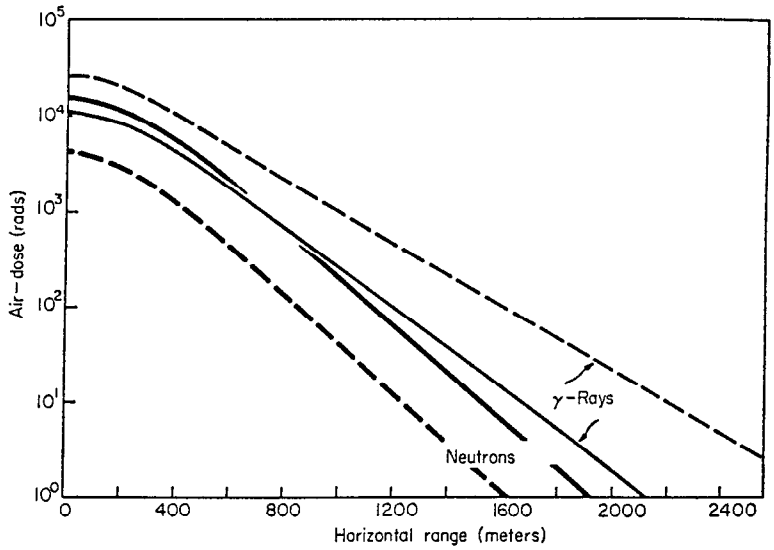

FIG. 3. Comparison of the approximate first-collision absorbed dose for neutrons and x-rays measured 3 feet above ground at variable distances from ground zero for the Hiroshima (——) and Nagasaki (----) bombs. Redrawn from Auxier *et al.* (1966).

analysis to define the distance where 50% survival is thought to have occurred in each city, we then converted these distances into gamma and first-collision neutron air-dose rads as shown in Table VII. Assuming that 50% lethality requires the same biological effective exposure (rads times some RBE = rem) we tried to obtain the same LD_{50} in rem in both cities for the three exposure (or shielding) conditions. The preliminary results (to be reported more extensively later) are shown in Table VIII (see also Table V). They seem to indicate that the fission neutrons from both bombs had a common

[3] Code used in Table VII.

RBE of at least 2.0 for human lethality, contrary to the extrapolation of Bond *et al.* (1956), and Alpen *et al.* (1958), from neutron exposure data in dogs. Using this RBE = 2 assumption, the $LD_{30/60}$ in rem for two of the three exposure conditions in both cities become approximately the same. Interestingly, in both cities light steel-frame buildings (LSF) from this analysis appear to have had a shielding factor of about 12 and seismic reinforced concrete seems to have been a very effective neutron shield, as is expected. If all neutrons can be

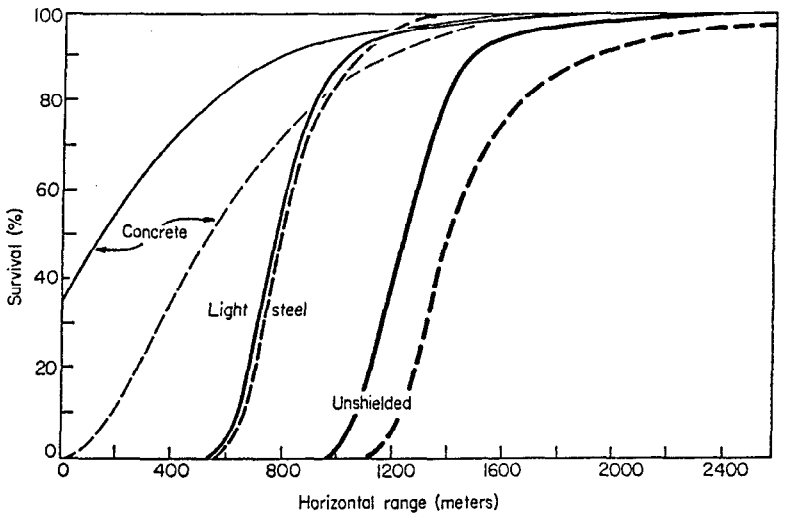

FIG. 4. Comparison of the 60-day survival curves of persons exposed to the Hiroshima (——) and Nagasaki (- - - -) bombs with and without the same kind of shielding at various distances from ground zero. Redrawn from Davis *et al.* (1966).

considered to have been shielded out completely by these concrete structures, radiation lethality under these conditions would have been from gamma photons. The exposure fields in gamma rads at the distances where 50% death occurred in the two cities for this type of shielding were found in close agreement also. Even though these lethal dose estimates for unshielded normal people under atomic attack appear to be lower than some of the previous estimates (Table V), many of these deaths in Japan are known to have been not from radiation exposure alone. These estimates, therefore, should probably be considered as being on the low side of the LD_{50} for "normal man." Experiences in many radiation accidents (the so-called Y-12 accident in Oak Ridge and that in Vinca, Yugoslavia, for example,

cited in Table I) have shown that normal men exposed accidentally in situations where first-collision free-field doses range from 300 to 400 rads will suffer severe hematopoietic damage from which most will recover under conservative care in a modern well-equipped hospital (Andrews, 1968). Although the upper limit of medical capabilities in treating such casualties was suggested by Brucer (1959) to be ~800 rads, observations from animal experimentation suggests that medical salvage at two to three times an LD_{50} exposure is not to be expected. Improvements in sterile precautionary facilities and

TABLE VII
AIR-DOSE ESTIMATES FOR 50% SURVIVAL FROM ATOMIC BOMB IRRADIATION UNDER VARIOUS SHIELDING CONDITIONS

Situation[a]	50% survival distance (km)	γ Rads	η Rads	REM RBE_n = 1	REM $RBE_{(n)}$ = 2.0	
			Hiroshima			
OU	1.18	102	78	180	258	± 39[b]
LSF	0.73	1000	1000	2000	3000	
SRC-L	0.13	9000	10,000	19,000	39,000	
			Nagasaki			
OU	1.35	250	5	255	265	± 27[b]
LSF	0.76	2900	250	3150	3400	
SRC-L	0.54	6500	600	7100	8300	

[a] OU = outside, unshielded; LSF = inside light steel frame buildings; SRC-L = inside seismic reinforced concrete buildings on the lower floor.
[b] Possible error in dose estimate (Auxier, 1968).

techniques together with modern blood bank and tissue transplant practices may, however, prove this prediction false.

In most radiation accidents the total body is not uniformly irradiated, and our best attempts to express the victim's most meaningful dose fail and predictions of outcome are almost baseless as well as medically useless. Experience has shown, for example, that twice the dose to half the body is not equally as effective in producing various biological effects as the whole dose to the whole body (Saenger, 1967). In regard to untoward gastrointestinal symptoms, the same dose confined to the epigastrium is as effective as when the whole body is irradiated and much more effective than when only the thorax or head is irradiated with the same dose. Any dose confined to the

lower extremities will reputedly not cause the prodromal symptoms of nausea and vomiting nor the acute hematopoietic syndrome.

Bond has suggested that the effect of nonuniform exposure might be quantified by the use of a "distribution effectiveness factor (DEF)." This factor would predict the decrease in response when the exposure is unidirectional and portions of such vital organs as bone marrow are shielded. It can be determined directly in animals but not man. The DEF can be considered analogous to RBE and used as a depth dose parameter to explain in comparison to X-radiation, the altered effectiveness of other kinds of radiation upon tissues, organs, and cells. DEF must by definition always be smaller than 1.0 and so cannot explain the increased susceptibility of large animals over that of small animals (like mice) to total-body irradiation. If uneven distribution of dose in depth results in increased stem cells survival and if hemoatopoietic death is related, as it seems to be, to how many stem cells survive, large animals should be more radioresistant instead of being more radiosensitive than the mouse. Alpen and his group have carefully documented, however, the remarkably great radiosensitivity of many large animals, but as yet there is no obvious explanation for this phenomenon in which man seems to share. The DEF concept, however, would seem to explain in part the great variation in response to the same dose that is seen commonly in accident victims as well as patients. These persons are most frequently irradiated unilaterally, and from different orientations to the source. The highest incident skin dose, therefore, rarely occurs in a common spot in victims said to have received the same absorbed dose. Bond's DEF concept emphasizes the obvious reason why clinical response and dosimetry in radiation accidents disagree more often than not so that hematologists have learned to disregard dosage estimates and base their therapeutic efforts upon the irradiated persons' total response over the course of the ensuing days. Using the DEF concept to resolve discrepancies in dose-response relations in previous radiation accidents, also, accentuates man's high rather than low radiosensitivity unless an RBE > 1 is assumed for high LET radiation, particularly for fission neutrons. Yet the best data have implied up to how many stem cells survive, large animals should be more radio- in studies of total-body irradiation of large animals. However, acute mortality curves for burros exposed to various kinds of radiation from critical assemblies, ^{95}Zr, ^{95}Nb, ^{182}Tu, and ^{60}Co sources show significant displacements of the dose-response curves that indicate at last a 2-fold increased efficiency of mixed neutron-gamma radiation (Brown and Cragle, 1968). These data necessarily lead to an assump-

tion of an RBE at least 2.0 for fission neutrons for the burro even using Page's recent conversion (1968) of the free-field gamma LD_{50} (784 r) to a depth dose LD_{50} of 280 rads, since an even greater attenuation factor reduces the midline neutron dose.

VIII. Repair

The explanation for the high radiosensitivity of man and other large animals seems to lie hidden at present in our ignorance of how these animals repair radiation damage. Little recent progress has been made in this field from studies of biological systems not involving the mouse or tissue culture.

In NCRP Report No. 29 on Exposure to Radiation in an Emergency (L. S. Taylor, 1961), the concept of equivalent residual dose (ERD) was suggested as a basis for regulating agencies to formulate permissible daily radiation doses for their workers, but it has since then been misused to predict whole-animal damage. It assumes on the basis of Blair's original (1952) and subsequently modified models of repair kinetics that 10% of the damage caused by a dose absorbed by man will remain irreparable while the other 90% will be repaired exponentially with a t_{50} of about 28 days. Although the concept is reputedly based on "best" extrapolations from animal experimentation and the case histories of irradiated men, it fits these data poorly and, of course, is untested in man. It is not universally accepted because as pointed out by Grahn and Langham (1965) and others (Storer, 1964), the ERD concept cannot predict realistically the amount of damage accumulated because it is based only on studies of lethality and not on studies of radiation-induced physiological or cellular injury. Further, other studies show that the amount of initial damage probably determines the rate of repair (Storer, 1961). Recently, Spalding *et al.* (1969) attempted to test this concept in monkeys (*M. speciosa*) and beagle dogs. They used the ERD formula to determine the size of the next exposure of 14 consecutive doses given to the animals over 360 days at time intervals of randomly chosen different lengths. Theoretically this schema should have allowed variable amounts of repair to take place before the next dose brought the damage (residual dose) level back to that of the 200 rads given initially. Even though rhesus-like monkeys all are estimated to have an $LD_{50/30}$ about 250 rads greater than that of dogs, all but one of the 8 monkeys were more radiosensitive than the dogs in this study and died with anemia and aplastic anemia before the end of the year. Only one of the dogs developed a significant drop

in RBC even though a total dose of 1048 rads was given. Both the monkeys and dogs recovered only partially from the initial decrease in WBC count produced by the initial dose of 200 rads, maintaining a count around 50% of normal. Although the results of this experiment are difficult to interpret and even more difficult to extrapolate confidently to man, their implications are clear in regard to the ERD concept and its shortcomings. Obviously the cellular kinetics peculiar to the animal species and to the tissues on whose replication he depends determine what constants are to be used in any ERD-like formula. If the cellular and repair kinetics of human hematopoietic organs were known, the present assumptions used in the ERD concept might then be corrected realistically and the concept itself modified to fit the data. The unexpectedly greater radiosensitivity of the relatively radioresistant monkeys in Spalding's study, however, questions the practical usefulness of the ERD concept as it now stands in human occupational medicine. A more cogent question seems to be whether the operational assumption of the ERD concept that 200 rads of damage can be accumulated safely by man is true. When single doses greater than 25 rads and fractional time intervals of less than one week are being considered, this assumption is most likely dangerously high for man.

Our hope for important progress in human radiobiological concepts rests on increasing emphasis being placed on comparative studies of repair rates and patterns. At present we know little about the complex interplay between stem cell survival, replication rates, and degrees of cellular differentiation that results in organ reconstitution and a functional capacity that allows survival of the animal. In this area of research, the most provocative pertinent observations for human radiobiology are being made at present by Ainsworth *et al.* (1968) in studies on the sensitivity of large animals to a second radiation exposure given days, weeks, or months later. They not only show that recovery from radiation injury is related to the rate at which the injury is produced (dose rate), but that in some large animals this relationship, the injury reversal rate, shows a 40-fold decrease from that of mice. In studies that are still incomplete, comparing recovery rates of sheep and swine from radiation damage, swine appear to "over-repair" and show an increase in radioresistance after a previous conditioning dose. According to Tubiana *et al.* (1961), just the opposite phenomenon occurs in man; a previous dose sensitizing him to a second one for an as yet undetermined time, but this has not been noted by Andrews *et al.* (1967). In sheep studied by Page (1968), this hypersensitive state lasts for about 2

weeks and is again related to the rate at which the injury is produced. These animals then show a transient period of radioresistance that lasts for about 2 weeks, after which the irradiated sheep appear to be permanently, slightly more radiosensitive than sheep not previously irradiated. It is not known whether transient periods of radioresistance in the large animal are related to over-repopulation of stem cell pools, but it is an attractive hypothesis.

Unfortunately, our clinical knowledge here is too incomplete to help us choose the large animal that could be used as an experimental animal/human model. Oakberg's studies (Oakberg, 1960, Oakberg and Clark, 1964) of the repair kinetics of the testicular germinative epithelium of irradiated mice and those of Heller *et al.* (1968) in man provide a point where the cellular kinetics of repair and differentiation of a common tissue of these two species can be compared. It has been previously shown that postirradiation "repair" of the human testis is remarkably slow in comparison with that of small animals. In one radiation accident victim, for example, where the testicular dose of neutrons and γ-rays was considered equivalent to less than 400 rads of 80 kvp X-rays, the return of the sperm count to borderline levels of fertility required about two mouse-lifetimes ($\sim$3 years) (Oakes and Lushbaugh, 1952). In mouse this level of repair after a comparable level of destruction is achieved in about 60 days (Oakberg, 1960). Heller *et al.* (1968) observed in 47 normal human volunteers whose testes were exposed to 8–600 r that the apparent rate of repair as measured by sperm count was related to exposure, being rapid after less than 50 r but prolonged after more than 400 r. Recovery rate depended, however, not only on the number of surviving spermatogonia, but also on the rate at which the surviving spermatogonial stem cells replaced themselves. Contrary to observations of Oakberg in the mouse, irradiated but surviving human spermatogonia continue to differentiate into spermatocytes and fail to replicate only themselves first. During the recovery period they do not refrain from differentiating until the stem cell pool is adequately repopulated as in the mouse. The rate of buildup of stem cell numbers, therefore, is retarded by their continuing to be lost in the pool of cells committed to the immediate production of sperm. As a result adequate sperm production for fertility is greatly delayed in man.

There is some evidence (however, not widely accepted) that man may differ also from mice in the manner by which he repairs radiation-induced hematopoietic damage. It is conceivable that man may fail to replenish his hematopoietic stem cells at an adequate rate

because of demands for differentiated functional granulocytes and megakaryocytes that are too great to allow cell replication to be confined to stem cell production. There is, however, little published evidence for this hematopoietic extrapolation from the comparative kinetics of spermatogonial repair. The evidence for the existence of a peculiarity in human marrow repair consists chiefly of morphological observations on human vertebral bone marrow where exposures had been fractionated over long periods of time. Years after irradiation large areas of marrow can be found that have not been repopulated as they would be expected to have been on the basis of our knowledge of mouse hematopoietic repair (Kurnick, 1961; Goswitz *et al.*, 1963). These irradiated vertebrae have areas of fatty, edematous, atrophic marrow in marked contrast to those of adjacent shielded or unirradiated vertebral marrow and require an explanation of their failure to repopulate. Some possible but untested explanations for this phenomenon are that man may not have a circulating multipotential stem cell as the mouse has, capable of repopulating marrow spaces destroyed by irradiation; that the surviving erythromyelopoietic system of man makes an integrated response to hormonal signals, so each surviving anatomical unit responds to its fractional level of hormonal signal and obviates the need for repopulation of depopulated areas; or that local radiation damage to marrow with doses in the greater than 1000 rad range produce vascular and reticular connective tissue damage that results in a tissue environment unable to support erythromyeloproliferation (Fliedner, 1969). Some of these explanations could be tested in patients with focal marrow aplasia by autotransfusion of bone marrow aspirated from nonirradiated sites.

IX. Summary

Human radiobiology has progressed slowly over the last 10 years, chiefly by the processes of extrapolation from animal experimentation and accretion of clinical observations now being based realistically on depth-dose measurements. As dosimetry for large animals has improved, the dose in critical human organs has been found to be lower than previously imagined, sharply underlining man's great radiosensitivity. Observations of accident victims and patients therapeutically irradiated have produced estimates of known statistical reliability of many of man's dose-response relations. Most recent attempts to estimate his level of radiation-induced lethality appear to agree well

and indicate at least that man is not a radioresistant species like mouse.

The greatest recent progress in our understanding of his ability to repair radiation-induced damage continues to be derived from generalizations based on animal experimentation, tissue culture, cytology, and cytokinetics. The increasingly excellent studies of this kind on radiation effects in large radiosensitive animals appear to offer the greatest potential for increasing man's understanding of his own radiobiology without putting too much strain on his imagination.

References

Ainsworth, E. J., Page, N. P., Taylor, J. F., Leong, C. F., and Still, E. T. (1968). *In* "Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology," UT-AEC CONF-680410, pp. 4.1–4.21.

Alpen, E. L., and Baum, S. J. (1959). *Radiation Res.* 11, 383.

Alpen, E. L., Shill, O., and Tochilin, E. (1958). *Radiation Res.* 9, 85.

Andrews, G. A. (1968). *In* "Proceedings of the International Conference on Leukemia-Lymphoma, Ann Arbor, 1967" (C. J. D. Zarafonetis, ed.), pp. 423–432. Lea & Febiger, Philadelphia, Pennsylvania.

Andrews, G. A., Auxier, J. A., and Lushbaugh, C. C. (1965). *Personnel Dosimetry for Radiation Accidents, Vienna, 1965,* pp. 3–16. IAEA, Vienna.

Andrews, G. A., Lushbaugh, C. C., Kniseley, R. M., White, D. A., and Friedman, B. I. (1967). *IAEA Panel on Effects of Various Types Ionizing Radiations from Different Sources on Haematopoietic Tissue, Vienna, Austria, 1966,* pp. 75–83.

Auxier, J. A. (1961). *In* "Diagnosis and Treatment of Acute Radiation Injury," U.S. ed., p. 141. IAEA, Columbia Univ. Press, New York.

Auxier, J. A. (1966). *Health Phys.* 12, 426.

Auxier, J. A. (1968). Personal communication.

Auxier, J. A., and Lushbaugh, C. C. (1968). Unpublished data.

Auxier, J. A., Cheka, J. S., Haywood, F. F., Jones, T. D., and Thorngate, J. H. (1966). *Health Phys.* 12, 425.

Becquerel, H., and Curie, P. (1901). *Compt. Rend.* 132, 1290.

Beebe, G. W., Ishida, M., and Jablon, S. (1962). *Radiation Res.* 16, 253.

Bender, M. A., and Gooch, P. C. (1962). *Radiation Res.* 16, 44.

Blair, H. A. (1952). USAEC Proj. Rept. UR-206. Univ. of Rochester, Rochester, New York.

Bond, V. P., and Robinson, C. V. (1967a). *Radiation Res.* Suppl. 7, 265.

Bond, V. P., and Robinson, C. V. (1967b). *Proc. 1st Intern. Symp. Biol. Interpretation Dose Accelerator-Produced Radiation, 1967,* USAEC CONF-670305.

Bond, V. P., Carter, J. S., Robertson, J. S., Seymour, P. H., and Hechter, H. H. (1956). *Radiation Res.* 4, 139.

Bond, V. P., Fliedner, T. M., and Archambeau, J. O. (1965). "Mammalian Radiation Lethality: A Disturbance in Cellular Kinetics," pp. 101–114. Academic Press, New York.

Brill, A. B., Tomonaga, M., and Heyssel, R. M. (1962). *Ann. Internal Med.* 56, 590.

Brown, D. G., and Cragle, R. G. (1968). *In* "Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology," UT-AEC CONF-680410, pp. 5.1–5.16.

Brucer, M. (1959). *U.S. At. Energy Comm. Rept., Oak Ridge Inst. Nucl. Studies* **ORINS-25.**

Cloutier, R. J., O'Foghludha, F., and Comas, F. V. (1967). *In* "Conference on Dosimetry of Total-Body Irradiation by External Photon Beams, Oak Ridge, Tennessee," USAEC-ORAU, CONF-670219.

Cole, L. J., Haire, H. M., and Alpen, E. L. (1967). *Radiation Res.* 32, 54.

Conard, R. A. (1956). *Radiation Res.* 5, 167.

Cronkite, E. P., and Bond, V. P. (1960). *U.S. Armed Forces Med. J.* 11, 249.

Cronkite, E. P., Bond, V. P., Conard, R. A., Shulman, N. R., Farr, R. S., Cohn, S. H., Dunham, C. L., and Browning, L. E. (1955). *J. Am. Med. Assoc.* 159, 430.

Davis, L. W., Baker, W. L., and Summers, D. L. (1966). "Analysis of Japanese Nuclear Casualty Data, Dikewood Corp., Albuquerque," DC-FR-1045, p. 60–61.

Fanger, H., and Lushbaugh, C. C. (1967). *Arch. Pathol.* 83, 446.

Fliedner, T. M., (1969). *Joint US/Japan Seminar on Comparative Cellular and Species Radio-sensitivity, Kyoto, Japan, 1968* (in press).

Friedman, M., and Pearlman, A. W. (1968). *In* "Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology," UT-AEC CONF-680410, pp. 19.1–19.40.

Fukushima, K., and Beebe, G. W. (1968). Personal communication.

Gerstner, H. B. (1960). *Ann. Rev. Med.* 11, 289.

Goswitz, F. A., Andrews, G. A., and Kniseley, R. M. (1963). *Blood* 21, 605.

Gerstner, H. B. (1960). *Ann. Rev. Med.* 11, 289.

Grahn, D., and Langham, W. H. (1965). *2nd Symp. Protect. Against Radiation Hazards in Space, Gatlinburg, Tennessee, 1964* NASA SP-71, pp. 59–63.

Hall, E. J., Berry, R. J., and Bedford, J. S. (1968). *In* "Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology," UT-AEC CONF-680410, pp. 15.1–15.20.

Harris, P. (1960). Quoted by Cronkite and Bond (1960).

Hashizume, T., Maruyama, T., Shiragai, A., Tanaka, E., Izawa, M., Kawamura, S., and Nagaoka, S. (1967). *Health Phys.* 13, 149.

Heller, C. G., Heller, G. V., Warner, G. A., and Rowley, J. J. (1968). *Radiation Res.* 35, 493.

Heyssel, R. M., Brill, A. G., Woodbury, L. A., Nishimura, E. T., Ghose, T., Hoshino, T., and Yamasaki, M. (1960). *Blood* 15, 313.

Hurst, G. S., Ritchie, R. H., Sanders, F. W., Reinhardt, P. W., Auxier, J. A., Wagner, E. B., Callihan, A. D., and Morgan, K. Z. (1961). *Health Phys.* 5, 179.

Ichikawa, Y., Higashimura, I., and Sidei, T. (1966). *Health Phys.* 12, 395.

Jones, A. R. (1966). *Health Phys.* 12, 663.

Kurnick, N. B. (1961). *In* "Diagnosis and Treatment of Acute Radiation Injury," U.S. ed., p. 309. IAEA, Columbia Univ. Press, New York.

Langham, W. H., ed. (1967). "Radiobiological Factors in Manned Space Flight," Report of the Space Radiation Study Panel of the Life Sciences Committee, Publ. No. 1487. Natl. Acad. Sci.-Natl. Res. Council, Washington, D.C.

Langham, W. H., Brooks, P., and Grahn, D. (1965). *Aerospace Med.* 2, 1.

Lushbaugh, C. C., and Spalding, J. F. (1957). *Am. J. Vet. Res.* 18, 345.

Lushbaugh, C. C., Comas, F. V., and Hofstra, R. (1965). "Workshop Conference on Space Radiation Biology." Univ. of California, Berkeley, California.
Lushbaugh, C. C., Comas, F., and Hofstra, R. (1967). *Radiation Res.* 30, Suppl. 7, 398.
Lushbaugh, C. C., Castaneda, G., Stokes, T., and Andrews, G. A. (1968a). Unpublished data.
Lushbaugh, C. C., Comas, F., Edwards, C. L., and Andrews, G. A. (1968b). *In* "Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology," UT-AEC CONF-680410, pp. 17.1–17.25.
Lushbaugh, C. C., Comas, F., Edwards, C. L., Kniseley, R. M., and Andrews, G. A. (1969). *Health Phys.* (in press).
Martinez, R. G., Cassab, G. H., Ganem, G. G., Guttman, E. K., Lieberman, M. L., LutzVater, F. L., Linares, M. M., and Rodriguez, H. M. (1964). *Rev. Med. Inst. Mex. Seguro Social* 3, 14.
Mathe, G., Amiel, J. L., and Schwarzenberg, L. (1964). *Ann. N.Y. Acad. Sci.* 114, 368.
Medinger, F. G., and Craver, L. F. (1942). *Am. J. Roentgenol., Radium Therapy* 48, 651.
Miller, L. S., Fletcher, G. H., and Gerstner, H. E. (1958). *Radiation Res.* 4, 150.
Oakberg, E. F. (1960). *Intern. J. Radiation Biol.* 2, 196.
Oakberg, E. F., and Clark, E. (1964). *Effects Ionizing Radiation Reprod. System, Proc. Inter. Symp. Colo. State Univ., 1962,* pp. 11–24. Pergamon Press, Oxford.
Oakes, W. R., and Lushbaugh, C. C. (1952). *Radiology* 59, 737.
Oughterson, A. W., and Warren, S. (1956). "Medical Effects of the Atomic Bomb in Japan." McGraw-Hill, New York.
Page, N. P. (1968). *In* "Proceedings of Symposium on Dose Rate in Mammalian Radiation Biology," UT-AEC CONF-680410, pp. 12.1–12.23.
Pendic, B. (1961). *In* "Diagnosis and Treatment of Acute Radiation Injury," U.S. ed., p. 67. IAEA, Columbia Univ. Press, New York.
Piesch, E. (1968). *Health Phys.* 15, 145.
Ritchie, R. H., and Hurst, G. S. (1959). *Health Phys.* 1, 390.
Rossi, H. H. (1968). *Radiation Res.* 35, 519.
Saenger, E. L. (1967). *Proc. 1st Intern. Symp. Biol. Interpretation Dose Accelerator-Produced Radiation, Berkeley, California, 1967,* USAEC CONF-670305, p. 114.
Saenger, E. L., Friedman, B. I., Kereiakes, J. G., and Perry, H. (1966) DASA-1844. Defense At. Support Agency. Dept. of Defense, Washington, D.C.
Shipmen, T. L., Lushbaugh, C. C., Petersen, D. F., Langham, W. H., Harris, P. S., and Lawrence, J. N. P. (1961). *J. Occupational Med.* 3 Suppl., 146.
Spalding, J. F., Holland, L. M., and Johnson, O. S. (1969). *Health Phys.* (in press).
Storer, J. B. (1961). *Radiation Res.* 14, 206.
Storer, J. B. (1964). *Ann. N.Y. Acad. Sci.* 114, 126.
Storer, J. B., Harris, P. S., Furchner, J. E., and Langham, W. H. (1957). *Radiation Res.* 6, 188.
Strandquist, M. (1944). *Acta Radiol.* 55, 300.
Taylor, L. (1967). Personal communication.

Taylor, L. S. (1961). "National Committee on Radiation Protection and Measurements, Exposure to Radiation in an Emergency," Rept. No. 29. Natl. Bur. Std., Washington, D.C.

Tubiana, M., Lalanne, C. M., and Surmont, J. (1961). *In* "Diagnosis and Treatment of Acute Radiation Injury," U.S. ed., p. 237. IAEA, Columbia Univ. Press, New York.

Walsh, P. (1897). *Brit. Med. J.* II, 272.

Warren, S., and Bowers, J. Z. (1950). *Ann. Internal Med.* 32, 207.

Wilson, R. R. (1951). Quoted by Auxier (1966).

Wilson, R. R. (1956). *Radiation Res.* 4, 349 (from York's values reported by Ritchie and Hurst, 1959).

Partial List of Initial References to Radiation Accidents Shown in Table I

Alekseyeva, O. G., and Bibikova, A. F. (1963). FTD-TT-63-558/1 and 2. U.S. Dept. of Commerce, Washington, D.C.

Bliss, S. P. (1962). *1st Colloque Intern. Protect. Grands Accelerateur, Orsay et Saclay, 1962* pp. 35–39. Presse Universitaires de France, Paris.

Brittian, R. O., Hasterlik, R. J., Marinelli, L. D., and Thalgott, F. W. (1957). ANL-4971.

Brucer, M. (1959). *U.S. At. Energy Comm. Rept., Oak Ridge Inst. Nucl. Studies* ORINS-25.

Cronkite, E. P., Bond, V. P., and Dunham, C. L. (1956). *U.S. At. Energy Comm. Rept.* TID-5358.

Fugua, P. A. (1962). Final Med. Rept. HW-81010. Hanford, Washington. Atomic Products Operation, General Electric Co., Richland, Washington.

Guskova, A. K., and Baisogolov, G. D. (1956). *Proc. Intern. Conf. Peaceful Uses At. Energy, Geneva, 1955* Vol. 11, pp. 35–44. Columbia Univ. Press (I.D.S.), New York.

Hayes, D. F. (1956). *U.S. At. Energy Comm. Rept.* TID-5360, pp. 10–12.

Hempelmann, L. H., Lisco, H., and Hoffman, J. G. (1952). *Ann. Internal Med.* 36, 279.

Hervin, R., Iriate, M., and Cobas, A. (1962). Investigation Committee Report on P.R.N.C. Gamma Facility Incident, Office of the Director, Puerto Rico Nuclear Center, San Juan, Puerto Rico.

Howland, J. W., Ingram, M., Mermagen, H., and Hansen, C. L. (1960). *In* "Diagnosis and Treatment of Acute Radiation Injury," p. 11. World Health Organ., IAEA, Geneva.

Jammet, H., Mathe, G., Pendic, B., Duplan, J. F., Maupin, B., Latarjet, R., Kalic, D., Schwarzenberg, L., Djukic, Z., and Vigne, J. (1959). *Rev. Franc. Études Clin. Biol.* 4, 210.

Karas, J. S., and Stanbury, J. B. (1965). *New Engl. J. Med.* 272, 755.

Knowlton, N. P., Leifner, E., Hogness, J. R., Hempelmann, L. H., Blaney, L. F., Gill, D. C., Oaks, W. R., and Shafer, C. L. (1949). *J. Am. Med. Assoc.* 141, 239.

Lanzl, L. H., Rozenfeld, M. D. and Tarlov, A. R. (1965). Proc. USAEC *1st Symp. Accelerator Radiation Dosimetry Experience, BNL, Upton, Long Island, New York, 1965.* USAEC Rept. CONF. 651109, pp. 574–598.

Martinez, R. G., Cassab, G., Ganem, G., Guttman, E. K., Lieberman, M. L. LutzVater, F. L., Linares, M., and Rodriguez, H. M. (1964). *Rev. Med.* 3, Suppl. I, 13–68.

Rossi, E., Thorngate, A. A., and Larson, F. C. (1962). *J. Lab. Clin. Med.* **59**, 655.

Safronov, Ye. I. (1964). *Studies Med. Radiol. (USSR-JPRS)* **24**, 452.

Shipman, T. L., Lushbaugh, C. C., Petersen, D., Langham, W. H., Harris, P. S., and Lawrence, J. N. (1961). *J. Occupational Med.* **3**, 146.

SL-1 Explosion Kills Three—Cause and Significance Still Unclear. (1961). *Nucleonics* **19**, 17.

Tsuzuki, M. (1956). "Research in the Effects and Influences of the Nuclear Bomb Test Explosions II," p. 1287. Japan Society for the Promotion of Science, Ueno, Tokyo.