EFFECTS OF IONIZING RADIATION ON HEMOPOIESIS*

by

Eugene P. Cronkite, M.D.

Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

Presented at: University of Minnesota; Pathobiology of Trauma
June 4-6, 1973

NOTICE

This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Atomic Energy Commission, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

MASTER

*This research supported by the United States Atomic Energy Commission.

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

Pen

INTRODUCTION

Radiation affects most remarkably those tissues of the body that are in a steady state of renewal, such as hemopoietic tissues, gastrointestinal tract, skin and testes. Radiation effects may be subtle and not expressed for many years, or they may be acute coming on promptly and producing severe symptomatology related to the central nervous system, the gastrointestinal tract or the hematopoietic system. All radiation effects have distinct dose-effect relationships which are reasonably well established. The symptomatology will also vary, depending upon whether the entire body is exposed or whether only a portion of the body has been exposed. Dose rate, the type of radiation, the distribution of absorbed dose within the body, fractionation and oxygen tension of tissues are all factors that influence the intensity and the type of

radiation effect that may be observed at various time intervals after the exposure.

DOSIMETRY

Prior to mid 1930's there was no satisfactory unit for the quantitative measurement of radiation to correlate with biological or chemical effects. Accordingly observations prior to late 1930's are qualitative. The basic principle of the scientific toxicology is quantitative measurement of the causative agent and the biological effect produced. In pharmacology, standardization of drugs becomes scientific only when the structure is known and one can measure the drug in appropriate units such as the milligram or some other quantitative reference. With ionizing radiation one is concerned not with the mass of the agent administered, but with the amount and distribution of energy that has been absorbed by tissue at the point of interest, such as the hemopoietic tissue or gonads.

Two dose units are commonly used. The roentgen (R) is a measure of total dose in air of ionizing radiation, and is that quantity of x-ray or gamma radiation such that the associated corpuscular emission per 0.001293 g. of air at standard conditions produces in air ions carrying one electrostatic unit of either sign. For energy to be deposited, there must be an interaction with matter. Hence, with x rays passing through a vacuum, no radiation dose is delivered. In practice one is interested in the energy imparted to various tissues from a number of different types of radiation, and it is therefore essential to have a second unit of radiation which overcomes the limitation of the roentgen. The second unit, the rad, is the unit of absorbed dose, equal to 100 ergs/g. of

absorbed energy, which applies to any type of radiation in any tissue. For practical purposes in small pieces of tissue, one R is close to one rad. However, as irradiated objects become larger and change in composition, one must consider the diminution in intensity due to the interaction of radiation with matter (buildup and then exponential attenuation) and the changing types of interaction (photoelectric effect, Compton effect, etc.). In tissue this leads to a decreasing absorbed dose at successive levels after equilibrium is attained. However, at interfaces such as soft tissue and bone, the absorbed dose may sharply increase. Thus, in addition to the exposure dose in roentgens and the absorbed dose in rads, one must be concerned with the distribution of the absorbed dose in the areas of interest. For example, if there is sufficient protection of bone marrow by shielding from one's own tissue to permit marrow regeneration and survival from what is considered an otherwise fatal exposure dose, this may lead one to erroneous conclusions about effects or therapy.

THE INFLUENCE OF DENSITY IONIZATION

The density of ionization or the number of ion pairs per unit track length or electron volts deposited per unit track length varies depending upon the type of radiation. For example, with alpha particles and high energy neutrons the number of ion pairs per unit path length per erg absorbed is significantly greater. In general with more ion pairs per unit path length there is a higher relative biological effectiveness (RBE) of the radiation per ergs deposited.

THE DOSE RATE

In general, the lower the dose rate, the less will be the acute

somatic effect. Dose rates in excess of approximately 5 rads/min give essentially the same result. However, as the dose rate falls below 5 rads/min, the effect per unit of radiation becomes less. As the dose rates fall substantially, biological repair processes become significant, both for somatic and genetic effects.¹

LEVELS OF EXPOSURE FROM NATURAL AND MANMADE SOURCES OF RADIATION

Living things have been exposed to radiation throughout the entire evolutionary process. Natural radiation sources consist of cosmic radiation that is partly galactic in origin with the major part coming from the sun. Cosmic radiation consists primarily of protons with energies up to 10^7 MeV, alpha particles and heavier charged atomic nuclei (mainly C, N, O, Mg, Ca and Fe). The preceding primary cosmic radiations interact with the atmosphere of the air and produce secondary cosmic radiation. According to Libby², cosmic radiation results in exposure of human beings to about 30-50 mrad/year at sea level and about 5 times this at about 9000 feet.

Terrestrial radiation comes from natural radioactive materials in the earth's crust, such as radium, radon, polonium, bismuth, lead, potassium and thallium. In addition, carbon-14 and tritium are created in the atmosphere due to cosmic radiation. In addition to cosmic and terrestrial radiation at sea level, there are certain building materials which contain higher concentration of radioactive materials such as bricks and granite so that individuals living in structures made of these materials have a further increment of radiation exposure. There are also small amounts of radioactivity that are in the diet and water, and become incorporated into the tissues of the body; for example,

potassium-40, tritium, and carbon-14. In some areas of the world radium produces a further increment in exposure.

To increase the sum total, there is also radioactive fallout produced by explosion of nuclear bombs.

Natural radiation from all sources delivers an average of 125 mrem per year to the gonads and 122 mrem/year to the bone marrow. Fallout radioactivity from nuclear bombs adds a few more mrem/year.

The sum of the exposure from natural radioactivity and fallout radioactivity, although delivered to essentially the entire world's population, is small compared to the recommendations of The International Commission on Radiological Protection for occupationally exposed individuals in which the average exposure shall not exceed 5 rem in a year or about 50 times the natural radiation exposure. In actuality those exposed in radiation industries receive only about 0.5 rem/year.

At the present time radiation exposure of man is about half from manmade sources and half from natural unavoidable background radiation. Of the manmade sources, about 20% is through the medical use of radiation for diagnosis. The preceding doses of radiation from unavoidable background and manmade sources have not been shown to have any detectible effect. These annual doses are to be contrasted with a single dose of 25 rads to the entire body, the smallest dose that will produce just detectible effects on hemopoiesis. As the dose is further increased, the magnitude of the effect on hemopoiesis, gastrointestinal tract, and other tissues increases proportionately. Again however one must contrast the effect of thousands of rads to a finger which will produce only local damage, to such doses to the entire body which would be fatal within a short period of time. The median lethal dose of ionizing radiation measured in the midline of the human body is about 300 rads³.

MECHANISM OF ACTION OF IONIZING RADIATION

There is a classic discussion on mechanism of action by Lea⁴. The concepts of direct hits on the target molecules versus the indirect action mediated through products of reaction with the protoplasmic solvent water are all important. Today the most acceptable current view to account for a major part of the biologic effects of radiation may be divided into three interlinked steps. First, photons or particles, penetrate the protoplasm, interacting to produce ion pairs. This reaction takes of the order of 10^{-13} seconds. The second step is a primary radiochemical reaction of these ions primarily with water, producing free radicals such as H and OH. These reactions take about 10^{-9} seconds. These free radicals produce a further chain of reactions with themselves, tissue water and oxygen to produce further reactive forms such as H_2O_2 and HO_2 . These products persist for microseconds or in part a few seconds at the most. The last reaction is between these products and critical protoplasmic molecules. The nature of this last reaction is not known with certainty. Since the actual amount of energy imparted to the system is small, it is generally believed that the damage must involve substances of low concentration but major importance to the living system; for example, nucleic acids or possibly some enzymes. The average cell nucleus can be considered to have a mass of 270×10^{-12} gram. The DNA content of the average diploid cell is 6×10^{-12} g. Or about 2% of the average nuclear mass. Of the average cellular mass it would be less than 1%. It is of interest that the amount of energy deposited to produce 100% mortality in animals would raise the body temperature by only $0.001^{\circ}C$. Whatever the mechanism may be, it sets into motion a series of observable histological

or chemical lesions that unfold with time. In addition to the effects observable within days, "bad, invisible genetic information" may be stored not only in the gonads, but also in somatic proliferative or nonproliferative cells, presumably in DNA, that may not be manifested as a disease process for several years.

BIOLOGICAL EFFECTS AT THE CELL LEVEL⁵

Dose rate effect was mentioned earlier in a general sense. If dose rate is sufficiently low as with background, it is believed there is little or no effect. At least one cannot with certainty prove an effect at levels of background or a few times higher. However if dose rate is sufficiently high, depositing doses of the order of several thousands of rads in a short period of time, actual death of any living cell can be observed promptly in terms of classical pathologic criteria of cell necrosis. However after lower doses of radiation (25 to several hundred rads - precise values vary with the tissue), only disturbances in cell proliferation are seen. The rate at which cells divide is decreased. DNA synthesis is impaired in two manners: (1) The rate of DNA synthesis is somewhat slower generally, (2) cells may continue DNA synthesis and become polyploid. It is reasonably certain that radiation has effects other than the outright killing of cells and the interference with mitosis and DNA synthesis.

The diminution in the production of new cells in tissues that are undergoing continual renewal, such as the gastrointestinal mucosa, the blood cell lines, the gonads, etc., results in a progressive hypoplasia to total atrophy, depending upon dose. Some cells still capable of mitosis that are not killed outright may be so injured that they will go through 1 or 2 generative cycles, producing abnormal progeny, such as giant metamyelocytes and hypersegmented neutrophils, before dying. The atrophy of these steady state cell renewal systems and direct injury of other

tissues produce clearly defined clinical syndromes which simplistically can be divided into three categories.

For teaching purposes these acute radiation syndromes may be classified generally as cerebral, gastrointestinal, and hematopoietic.

The cerebral syndrome is produced by extremely high doses of radiation, order of several thousands of rads, either directly to the brain or to the entire body. It is always fatal, whether the radiation is delivered to the brain alone or to the whole body.

The gastrointestinal syndrome occurs when the dose of radiation is lower in the range of 600-1500 rads. It is characterized by intractable nausea, vomiting, and diarrhea; these lead to severe dehydration, diminished plasma volume, vascular collapse and death. The symptomatology is caused by diffuse necrosis of the proliferating cells in the crypts of the gastrointestinal tract followed by the usual orderly migration of the mature cells off of the villus, leaving denuded villi which is followed by extensive loss of blood and plasma into the gastrointestinal tract which will result in death unless there is massive fluid replacement promptly. After doses below roughly 1300 r, regeneration of the gastrointestinal tract will commence around the 6th day with complete restoration by 2 weeks. However, the individuals are yet to experience the sequelae of bone marrow aplasia.

To understand the effects of radiation on hematopoiesis, it is necessary to describe the essential characteristics of the hematopoietic system. (1) The bone marrow is distributed in the child throughout the body and in the adult limited to vertebrae, ribs, sternum, pelvis, upper parts of the femur, and to a lesser extent, the calvarium. (2) Continuous cell division in the bone marrow provides steady supply of mature elements to the peripheral blood constituting a steady-state cell renewal system.

(3) The mature cells produced by each cytologic subunit of the bone marrow find their way into the common pool, the blood. (4) The marrow is subdivided into 4 cellular systems producing granulocytes, erythrocytes, platelets and lymphocytes. The system is regulated by feedback loops from the periphery that regulate the cell production within the bone marrow. On an average in the hematopoietic cell renewal system, the production of cells in the bone marrow is compensated by the death or disappearance of cells in the peripheral blood.

A most important radiobiological principle in understanding radiation damage to the hematopoietic system is the law enunciated by Bergonie and Tribondeau in 1906. They stated that cells which divide frequently are radiosensitive and cells that do not divide are radioresistant. This law holds remarkably well for most cell systems. There are two notable exceptions - the exquisite radiosensitivity of the nondividing oocyte and small lymphocyte.

There are degrees of radiation injury in all proliferating systems. With dose sufficiently high, cells can be killed outright and evidence of severe damage can be seen within minutes to hours following exposure even before the cells commence to divide. This is described as "direct cell death". In most cell systems the cell appears to function normally until it attempts to enter division. At this time damage may be seen, consisting of chromosome damage and nuclear fragmentation. The nucleus may divide, the absence of cell division leading to polynucleated cells. In some instances the cells do not divide but continue to grow, producing giant cells. The radiation sensitivity of the hematopoietic stem cell has been determined by Till and McCullough⁶ to be of the order of 100 rads. From the

nature of the stem cell dose-survival curve in the mouse, it can be shown that about 2-3 stem cells/thousand remain capable of proliferation after exposure to an LD₅₀. If human stem cells have the same dose-survival curve as the mouse, then about 5 in 100 stem cells survive after the human estimated LD₅₀ of 300 rads.

The bone marrow cell renewal compartment consists of: a) a stem cell pool, b) a proliferating differentiated pool for each cell line, and c) a nonproliferating maturing compartment. A as mentioned earlier, is very radiosensitive. B being more mature is somewhat more radioresistant and C is very radioresistant. Therefore after exposure to radiation, a dose-dependent fraction of the stem cells are killed and the surviving fraction remains to reconstitute hematopoiesis in all cell lines. However there is a dose-dependent time before the remaining stem cell fraction commences to replete itself prior to differentiation. In this interval, the cells in the dividing maturing compartment are very rapidly reduced to small numbers resulting from their continued maturation and release into the storage compartment and ultimately into the blood. As the stem cell compartment repletes itself, differentiation into each of the cell lines again commences at various time intervals depending upon the intensity of the stimulus from the peripheral feedback loops for differentiation of the common stem cell into the particular cell line.

Another phenomenon that is observed is called the "abortive rise". Although the abortive rise is not completely understood, it is believed that the most probable explanation lies in stem cells that are not grossly damaged, although they are incapable of sustained proliferation. When they divide they produce a short-lived progeny of cells that can be seen as

the abortive rise in neutrophils in the peripheral blood.

THE HEMOPOIETIC SYNDROME

With due consideration to the general principles of radiobiology and characteristics of hematopoiesis, one can consider the sequence of events in different cell lines. The hematopoietic syndrome consists of the sequelae of bone marrow suppression. It is produced by partial or complete aplasia of the hematopoietic tissues. The aplasia results from two phenomena. First, the more radiosensitive cells are killed directly. For example, lymphocytes, erythroblasts and other cells within the marrow and lymphocytic tissues can be found undergoing pyknosis, karyorrhexis and karyolysis. In addition, those cells that are not killed outright may suffer severe injury to their chromosomal material resulting in aberrations of mitosis characterized by tripolar mitoses, chromosomal bridges, fragmentation, micronuclei and other well-known cytologic abnormalities. The result is a decreased production of new cells that upsets the normal steady-state equilibrium between production, utilization and senescence. When production ceases, as with total aplasia of the marrow, the diminution in concentration of the various elements in the peripheral blood is a function of the normal lifespan of the cells involved. Thus, for example, the red cell with a lifespan of approximately 120 days shows a diminution in the red cell mass of about 0.83%/day unless accelerated by hemorrhage. Platelets with lifespans estimated in the vicinity of 10 days diminish slowly as long as megakaryocytes still remain in the marrow. Upon disappearance of the last megakaryocyte, the diminution in the platelet count is more abrupt and approaches zero within about 10 days after the disappearance of the last megakaryocyte. Granulocytes have a half-life in the

bloodstream of about 6-12 hours with a random disappearance from the bloodstream. Thus after high doses of radiation, which eradicate the progenitor cells for granulocytes, there is a very sharp diminution in the granulocyte count in the peripheral blood as the preformed pool of cells in the marrow are extruded into the bloodstream and utilized. Granulocytes attain minimum values in about 5 days under these conditions. After lower doses of radiation that do not totally eradicate granulocytopoiesis, there is a slower diminution in the granulocyte count as production is impaired and the peripheral level decreases and fluctuates with "abortive rises". It may take as long as 30-40 days for the minimum granulocyte levels to be reached. During this period of time, abnormal granulocytes characterized by hypersegmentation and, at times, nuclear satellites are observed in the blood and marrow.

The destruction of lymphocytes is dose-dependent up to about 300 rad. Further increases in dose decrease the peripheral level of lymphocytes no further. The diminution in peripheral concentration of lymphocytes develops rapidly and is maximal by about 48-72 hours after exposure with the bulk of the diminution occurring within 24 hours after exposure. Concomitant with the atrophy of the lymphocytic tissues and the developing lymphopenia, there is severe diminution in the capability of new antibody production and suppression of the anamnestic response.

As a result of the progressive granulocytopenia, thrombopenia and lymphopenia, a typical symptomatology develops. The individual becomes susceptible to infection as a result of the severe granulocytopenia and the impairment of antibody production. Within about 7 days, infections from commensal or exogenous pathogens may develop. Ulcerations of the

oral mucosa are characteristic and may be scattered throughout the gastrointestinal tract to the anus, producing a second bout of gastrointestinal signs and symptoms. When the platelet count falls below $25,000/\text{mm}^3$, a tendency to bleed develops. If the thrombopenia becomes worse with platelets falling below $10,000/\text{mm}^3$, the purpura will be severe, and fatal hemorrhage into the brain or myocardium may develop. Hemorrhages into the bowel will accentuate GI dysfunction and may act as a focus for intussusception. The bleeding greatly accelerates the onset of anemia which may be fatal unless treated with adequate blood transfusions. The clinical picture is similar to that seen from aplasia of the marrow due to any cause and its treatment is identical.

In the real world the probability of having totally homogeneous whole body radiation which results in a uniform pattern as described above, is very unlikely. Several human radiation casualties have been observed from radiation accidents in industry or in the laboratory. These have all been marked by inhomogeneities of the absorbed dose ⁷. In some of the individuals, many thousands of rads were received by the hands with almost total destruction of the epithelium. Superficial skin over the abdomen and the face also received tremendous amounts of radiation with the absorbed dose grading off toward the back and down to the legs which had some shielding. Very severe gastrointestinal injury was observed in two of these individuals. In the fatal cases, there was severe injury to the gastrointestinal tract and marked necrosis of the skin of the hands and the face, with prominent edema and erythema of the side of the body facing the criticality event. Of course in addition there was severe hematopoietic depression, as described above.

In another criticality accident ⁸, the dose to the head and the thorax was measured in the thousands of roentgens. Immediately after the exposure, the individual was disoriented, amnesic and shortly thereafter went into collapse and was prevented from immediate death by extensive fluid and electrolyte replacement. He died within a short period of time and at autopsy there was serious injury to the myocardium in addition to the brain.

In another incident, a group of individuals were exposed to x rays being emitted from an unshielded Klystron tube that was not functioning properly. The technicians trying to adjust the radiofrequency output received serious radiation exposure from unfiltered 200 kV x rays. The dose to the face and upper part of the body was severe. The details of this incident are of considerable interest ⁹. The dose distribution to the head of one individual showed marked inhomogeneities in the absorbed dose. The initial neurological symptoms were minimal but later severe neurological symptoms developed, demonstrating that neurologic injury per se is not necessarily fatal unless the absorbed dose is uniform throughout the head and greater than the minimum necessary to produce a neurologic syndrome in animals.

Lastly, in the event of nuclear warfare and widescale radioactive fallout, there will be marked inhomogeneities in the absorbed dose as observed in the one fallout accident ¹⁰. In this case fallout material was deposited directly upon the skin in some individuals. In these people, the dose to the first few mm was greatly in excess to the whole-body dose. These individuals developed severe beta burns. On the day of exposure, they experienced severe itching and burning of the skin which

subsided within a period of 24-36 hours. Thereafter, for a period of about 10 days, there were no symptoms referable to the skin. After the 10-day latent period, itching and burning of the skin returned with spotty pigmentation that increased in size and coalesced to form large plaques. This was followed by either dry desquamation, comparable to sunburn in some individuals, or to ulceration of the exposed areas in others. It is difficult to assign a meaningful number for the dose to the superficial layers that were contaminated by fallout. However, it is most likely in excess of 2,000 rads at the level of the Malpighian layer of the skin.

The above incidents clearly demonstrate that in accidents involving ionizing radiation, one should expect marked inhomogeneities in the absorbed dose. Accordingly, the symptom complex observed may not necessarily follow the oversimplification presented under the three classic symptom complexes induced in animals by uniform whole-body irradiation exposure. After radiation accidents one should be on the alert for the unusual and should, after the health physicists work out the exposure conditions and distribution to the body, be alert for signs and symptoms to develop in the organ systems most heavily exposed.

THERAPY OF RADIATION INJURY

Therapy of all disease processes is based on proved clinical principles that apply to the signs and symptoms that are present in the course of the disorder. Accordingly, there is no mystery about the management of radiation injury. Standard principles are involved and one treats the nausea, vomiting with standard therapy. Similarly electrolyte balance is also managed in the established way. Granulocytopenia

and thrombopenia per se need no therapy. Severe granulopenia will dictate reverse isolation and possible administration of prophylactic wide spectrum antibiotics in addition to nonabsorbable intestinal antibiotics. Hemorrhage and infection are treatable by fresh platelet transfusions and antibiotics respectively.

Very high exposure groups in which the probability of survival is very low require consideration of bone marrow transplantation from HLA compatible individuals. Discussions of this are beyond the purview of this chapter.

LATE EFFECTS OF RADIATION

All types of leukemia with the exception of chronic lymphocytic leukemia, cancer of the female breast, lung cancer, thyroid cancer, cancer of the bowel, and possibly other cancers have been observed following exposure to high doses and high dose rates. Admittedly there are few data. However the data are sufficient to allow reasonable predictions of what would happen in an irradiated population exposed to high doses at high dose rates. The data on which the following statements are based is published by The United Nations¹¹, and The National Academy of Science¹². These data lead one to the conclusion that there will be one to two excess leukemias per 10^6 people per year per rem exposure for at least a period of 20-25 years after the exposure. The incidence of other types of cancer is of the order of 7 or 8 times that of leukemia alone. Accordingly, one can say that there will be approximately 10 excess cases of cancer per 10^6 people per year per rem exposure. Whether the incidence will be less with chronic exposure is not known, however, it is very likely that it will be.

In concluding a discussion on radiation injury in a conference on pathobiology of trauma, it is worthwhile contrasting radiation with

other traumatic events in modern life. Bond¹³ has collated information on probability of serious injury or death from numerous factors in modern life. These are listed in Table 1 as probability per year. The probability of injury in an automobile accident is 1 in 100 per year. Example from table show the probability decreases 1 in 4,000 deaths from autos, 1 in 25,000 deaths from the "Pill", 1 in 50,000 from firearms, and 1 in 200,000 from electrocution. Radiation from existing possible sources is the least hazardous. For example, if each person in the United States took one round trip transcontinental jet flight per year, the additional exposure of 1 millirem per year assuming linearity and no threshold at equilibrium for the 200,000,000 population would increase the probability of cancer by less than 1 in 1,000,000. This is not to say that radiation can be ignored. The hazard potential is present. The study, caution, surveillance and regulation that has characterized development of nuclear industries and power production are commendable. They are models for application for control of other hazardous factors of modern life and in new industrial processes.

Table 1

Chance of Serious Injury or Death - Per Year*

Auto accident (disability)	1	chance in	100
Mortality attributable to smoking	1	" "	175
Cancer, all types and causes	1	" "	700
Auto death	1	" "	4,000
Air pollution	1	" "	10,000
Fire death	1	" "	25,000
The "Pill" death	1	" "	25,000
Drowning	1	" "	30,000
Firearms	1	" "	50,000
Electrocution	1	" "	200,000
Airplane round trip, New York City-San Francisco and return. Radiation cancer risk	Less than 1	" "	1,000,000
Reactor emanations; site boundary (5 to 10 mrem/yr)	Less than 1	" "	1,000,000
Average for population within 50 miles of reactor	Less than 1	" "	10,000,000

*From Bond 13.

REFERENCES

1. Russell, W. L., The effect of radiation dose rate and fractionation on mutation in mice. In: Repair From Genetic Radiation Damage. Ed. F. Sobels, Pergamon Press (Oxford) 1963, pp. 205-217, 231-235.
2. Libby, W. F., Proc. National Acad. Sci. 45, 959-976, 1959.
3. Cronkite, E. P., Radiation injury in man. Chap. V in The Biological Basis of Radiation Therapy. Ed. by E. E. Schwartz, M. D., J. B. Lippincott Co., Philadelphia and Toronto, 1966.
4. Lea, D. E., Action of Radiation on Living Cells. MacMillan Co. New York, 1947.
5. Bond, V. P., T. M. Fliedner, and J. O. Archambeau, Mammalian Radiation Lethality. Academic Press, New York and London, 1965.
6. Till, J. E. and E. A. McCulloch, A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Rad. Res. 14, 213-222, 1961.
7. Hempelmann, L. H., H. Lisco, and J. C. Hoffman, The acute radiation syndrome: a study of nine cases and a review of the problem. Ann. Int. Med. 36, 279-510, 1952.
8. Shipman, T. L., A radiation fatality resulting from massive overexposure to neutrons and gamma rays in Diagnosis and Treatment of Radiation Injury. pp. 113-133, WHO, Geneva, 1961.
9. Howland, J. W., M. Ingram and H. Mermagen, The Lockport incident: Accidental partial body exposure of humans to large doses of x-irradiation in Diagnosis and Treatment of Radiation Injury. pp. 11-26, WHO, Geneva, 1961.

10. Cronkite, E. P., V. P. Bond and C. L. Dunham, Some Effects of Ionizing Radiation on Human Beings. U. S. Atomic Energy Com. TID 5358, Supt. of Documents, U. S. Gov't Printing Office, Wash. D. C., 1956.
11. Ionizing Radiation: Levels and Effects. A report of the U. N. Scientific Committee on the Effects of Atomic Radiation to the General Assembly. Vol. II, 1972, New York and Geneva.
12. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Report of the Advisory Committee on the Biological Effects of Ionizing Radiations. (BEIR report), Division of Medical Sciences, National Acad. of Sci., NRC, Wash. D. C. 1972.
13. Bond, V. P., Radiation effects data and their interpretation. Presented: American Bar Association, National Institute/Environmental Litigation, Dallas, Texas, 12-14 April 1973.