MEDICAL MODIFICATION OF HUMAN ACUTE RADIATION INJURY

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In weighing the benefits and risks of utilizing nuclear energy, there must be a continuing reassessment as nuclear technology develops and changes. The health effects of radiation accidents, a most important part of the risk, must also be reevaluated as our medical ability grows to modify and ameliorate the consequences.

As part of a recent reactor safety study (1), we reviewed the pertinent human experience (including atomic bomb victims, radiation accident cases and radiation therapy cases) associated with useable exposure, effect and treatment information. Some large animal experimental data were used where important gaps in information required it.

The acute somatic effects of human exposure to ionizing radiation occur in a relationship to the magnitude of exposure which is non-linear. That is, the responses which can be recognized as manifestations of clinical injury do not appear unless the absorbed radiation dose is above a certain level. Beyond that level a variety of malfunctions become apparent, the most characteristic of which will be described below. This apparent "threshold" is a result of the end point chosen, i.e., clinically manifest injury, and does not mean that damage detectable by other criteria has not occurred at lower levels of exposure.

When man is exposed to a large single short-term (seconds to a few hours) whole body exposure to ionizing radiation, the resultant injury is expressed as a complex of clinical symptoms, signs and laboratory findings which are collectively termed the acute radiation syndrome. The exposure is almost invariably to external penetrating radiation. Accidental external and/or internal radionuclide contamination alone does not usually occur at high enough radiation levels for a long enough time to produce this kind of clinically apparent response. Acute clinical effects of a combination of external penetrating exposure with radionuclide contamination have been seen in one nuclear weapons test and in a few industrial "criticality" accidents in reactor research and fuel processing operations.

Dose-Mortality Curves for Whole Body Short Term Exposure

The production of nuclear weapons during World War II was the major stimulus for the development of quantitative information about the mortality to be expected in humans exposed to brief bursts of high dose radiation. Both information concerning the effects of various forms of radiation therapy on patients and the results of the growing body of animal experimentation were utilized for this purpose. Subsequently information became available concerning radiation effects on otherwise normal individuals from the Hiroshima and Nagasaki populations exposed to nuclear weapons in 1945 and relatively small number of individuals involved in radiation accidents in the growing nuclear industry.

General agreement developed that the most useful single piece of radiobiological information was the quantity of radiation exposure which would be lethal to 50% of an untreated human population within 60 days. This information was generally extrapolated from animal dose-response experiments and some human data as it became available. There was a general consensus that the $LD_{50/60}$ was 450 R, as reported by Warren and Bowers in 1950 (2). (This corresponds roughly to 300 rads midline absorbed dose). Both the

concept and the quantitative data have undergone many refinements and reevaluations since that time. Since direct experimental information on normal humans cannot be obtained for ethical reasons, the subject remains incompletely resolved, with continuing attempts to infer the most likely answers from new data made available by radiation accident or therapy cases. This paper represents one such attempt.

Over the years there have been several definitive reviews of the subject such as that of UNSCEAR in 1962 (3) and NCRP Committee 42 in 1974 (4). The advent of human space travel led to a new effort at risk assessment for crew members who might inadvertently encounter radiation exposure from solar storms. This was evaluated by a National Academy of Sciences space radiation study panel chaired by Langham (5), and more recently reviewed by Lushbaugh (6).

Two newer studies of radiation therapy patients have also been used in arriving at human dose-response information for lethality. These are the leukemia patients treated by Thomas et al at the University of Washington, Seattle (7), and the Ewing's sarcoma patients given radiation therapy by Rider and colleagues at the Ontario Cancer Institute, Princess Margaret Hospital in Toronto (8).

In the analysis of the lethality data it was considered that a dose-response relationship based on the absence of any treatment would be somewhat unrealistic and less than useful in evaluating the health hazards of radiation accidents. For this reason dose-response relationships were developed for three levels of treatment: minimal, supportive and heroic.

"Supportive" treatment has been used to indicate inclusion of "reverse" isolation (measures to protect patient from pathogenic bacteria and viruses in his environment, such as the use of sterile garments and masks by entering personnel, sterilization of all objects in patient's room, use of portable or permanent laminar air-flow systems, etc.), copious antibiotics and transfusions of whole blood packed cells, or platelets. "Minimal" therapy was used to indicate the absence of any of these measures. "Heroic" therapy was used to indicate extraordinary procedures such as bone marrow transplantation or lung lavage.

The mortality curves shown in Figure 1 are drawn from the fortunately limited amount of pertinent human experience. The $LD_{50/60}$ doses for the three levels of treatment are 340, 510 and 1050 rads, respectively. The curves developed for these three levels of clinical management obviously are not based on large numbers of cases studied under ideal conditions. Rather, they are the best interpretations we can make of the various clues obtained from the available human data. The reasoning for the specific features of each curve are given below.

Curve A ("Minimal" treatment): It is considered that lethality might occur in rare instances beginning at about 150 rads, in spite of the absence of any fatalities in the Marshall Islanders (9) who supply the first actual data point at about 175 rads. This conservative approach was based on the recognition that the exposure in the Marshallese was protracted to approximately 50 hours which may have ameliorated some of its effects. The selection of 250 rads as an LD_{10} is based largely on the clinical observations in Rider's series of Ewing's sarcoma patients (8). In the absence of the supportive therapy that they received, it appeared likely that several more fatalities would have occurred and therefore, that somewhat lower exposures would also be lethal to some. When LD_{10} and LD_{100} points were connected to form Curve A, an LD_{50} or 340 rads resulted. Accepting the uncertainty of $\pm$ 10% suggested by NCRP Report 42 (4), this provides a range of 314-374 rads, which overlaps the best estimate figure of the Biomedical

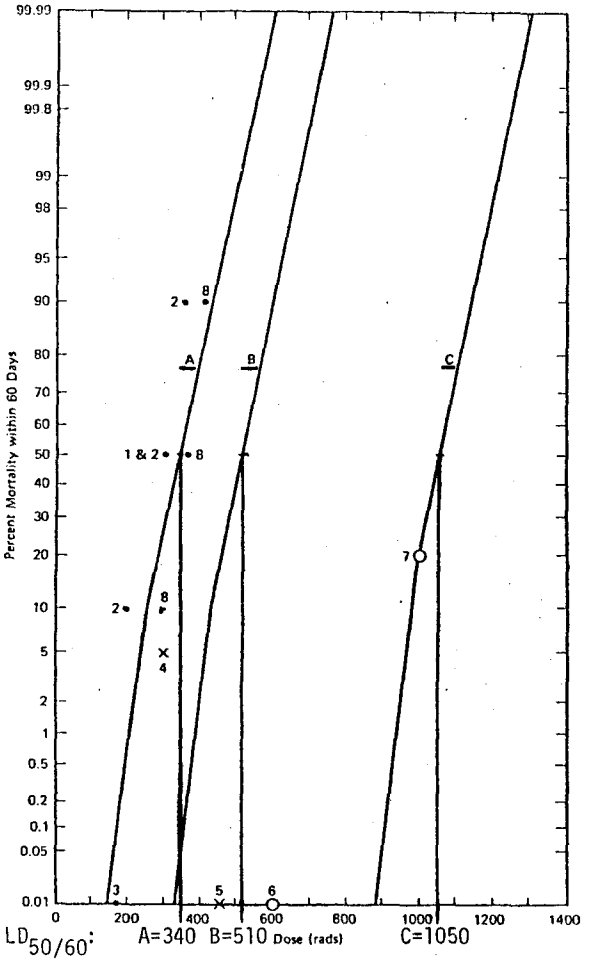

Figure 1

Estimated dose response curves which provide the basis for predicting the exposure levels that would produce 50% mortality in 60 days with minimal treatment (curve A), supportive treatment (curve B), and heroic treatment (curve C). Origin of data points: 1: NCRP Report 42 (4) (converted to rads using factor given in report); 2: Langham (5) (Table 12, estimate for "normal man?"); 3: Marshall Islanders (9) (protracted exposure); 4: radiation therapy series, 22 patients (8); 5: clinical group III accident patients (12) (with newer cases added); 6: Pittsburgh accelerator accident patient (13,14); 7: 37 leukemia patients (7); 8: "best estimate" of the Biomedical and Environmental Assessment Group, BNL (10).

and Environmental Assessment group at Brookhaven National Laboratory (10) and the UNSCEAR Report of 1962 (3) at 360 rad, and is close to the 300 rad suggested in NCRP Report 42 (4) and NAS document 1487 (5). In addition, it provides a span of 230 rads from LD_{50} to LD_{95} which is in fairly close agreement with the span of about 200 rads found experimentally in dogs (11) and other animals. Finally, it is in keeping with the analysis of statistical features of radiation injury in NCRP Report 42 (4) which suggests that the LD_5 in large animals and man is about half the LD_{50}.

Curve B ("Supportive" treatment): Assumptions used in the development of this curve included that the shape would be likely to be approximately the same as Curve A and that the effect of therapy in the experimental dog studies cited above suggest that a factor of approximately 1.5 increase in the LD_{50} exposure is obtainable by supportive theory. In addition, evaluation of Rider's patients (8) (data point 4) showed only one fatality in the post-irradiation period in 22 cases, and that was related to an accidental fall complicated by radiation effects. Another supportive therapy data point, (data point 5) was located on the basis of the lack of mortality in Group III accident patients (12) having a mean exposure of at least 450 rads but less than 600 (4). Curve B gave an $LD_{50/60}$ of 510 rads.

Curve C ("Heroic" treatment): The same curve shape was used for Curve C as in the preceding ones. The main data points were the 600 rad Pittsburgh accelerator accident patient (data point 6) who survived following syngeneic bone marrow transplantation (13,14) and the therapy series of Thomas, et al. (7) (data point 7) which showed a post-irradiation period mortality of only 20% in the 37 leukemic patients treated with 1000 rads of whole body irradiation followed by allogeneic bone marrow transplantation in the past two years. The severe illness which justified this form of therapy suggests that the latter data point is conservative for normal individuals. An $LD_{50/60}$ of 1050 rads was derived from Curve C.

Specific Organ Involvement

Because of the possibility of external exposure to part but not all of the body, or the inhalation or ingestion of radionuclide contamination, the potential for fatal effects of localized radiation injury of certain key organs requires some consideration. The bone marrow, lungs and gastrointestinal tract are organs of particular importance.

Bone Marrow: Damage to the bone marrow is, of course, the predominating event in the production of the hematologic form of the acute radiation syndrome. The sequence of events has been reviewed in detail in many publications (15-17).

When bone marrow damage is produced by external sources of irradiation, the lymphoid tissue is also severely damaged, resulting in a further enhancement of the reduction of defenses against infection. Also, the vascular system is damaged under such circumstances, enhancing the hazard of bleeding. In the event of bone marrow irradiation by the incorporation of radioactive isotopes of elements with predilection for the bone or marrow cells, e.g. ^{90}Sr, ^{198}Au or ^{32}P, the additional damage accompanying external irradiation may be relatively reduced. However, if the dose is sufficiently high, the marrow aplasia alone may produce the characteristic radiation-induced pancytopenia with its clinical consequences.

Lungs: Radiation injury to the lungs may result from intense irradiation from external sources and/or from internally deposited radionuclides. The injury is evidence by an early stage of radiation pneumonitis and a late stage of pulmonary fibrosis. The magnitude of the injury and its time course are related to the total radiation dose, dose rate, fraction of the lung

irradiated, and the condition of the lung before exposure. The effects of lung irradiation have been reviewed recently by Hahn (18).

There are virtually no data concerning the acute effects of inhaled radionuclides in man; however, dogs show qualitatively similar pulmonary effects and the doses required to produce them are consistent in many species, probably including man. Canine studies suggest that the rate of dose accumulation is the critical parameter for lethality and morbidity (18). Dogs show 100% morbidity after cumulative doses of 5000 rads or more from internally deposited radionuclides, and mortality following doses three to four times greater. The resultant dose response relationship is in reasonably good agreement with the available human experience. It suggests that pulmonary morbidity can reasonably be estimated by assuming a 100% incidence after 6000 rads and a 5% incidence after 3000 rads.

Gastrointestinal Tract: Fatal radiation-induced gastrointestinal injury and its clinical evidences result from the disruption of the normal proliferation of the intestinal epithelial lining. Reduction of the relatively radiosensitive stem-cell population results in a diminished flow of new cells required to line this high turnover system. However, lethal damage is produced only by radiation doses in the kilorad range (16) because there are a number of protective mechanisms enhancing the tolerance of the intestine to acute radiation damate (19).

Internal radionuclide contamination of gastrointestinal tract occurs after ingestion or inhalation. The dose to any particular segment of the tract is a function of the residence time of the contaminant in that segment, and the lower large intestine is therefore a region of major concern. No acute gastrointestinal injury from internal radionuclide contamination has been reported in humans so animal studies are the basis for current information.

Studies of Sullivan and Cross (1) indicated that internal irradiation from ingested beta emitting radionuclides can produce acute injury to the lower large intestine in dogs. An acute dose on the order of 3500-5000 rads at a critical depth in intestinal tissue is required for early lethality. Lower doses on the order of 2500-4000 rads cause significant morbidity and delayed death.

Modification of Radiation Injury by Medical Intervention

Bone Marrow: The most dramatic evidence of the effect of medical intervention is provided by the work on bone-marrow transplantation of Thomas and co-workers (7). In preparing leukemic patients for grafting, a 1000 rad midline tissue dose of total body ^{60}Co irradiation was administered in less than four hours. In the majority of the 70 cases reviewed, bone marrow from an identical twin or closely matching sibling, administered immediately subsequent to the irradiation, grew successfully in the recipient. Although there were many subsequent fatalities due to recurrent leukemia, graft vs. host syndrome and infections, the evidences of the classical gastrointestinal syndrome did not occur in these individuals. Also, the classical changes associated with the hematologic form of the acute radiation syndrome did not materialize.

Another significant series is that of Rider who treated at least 22 Ewing's sarcoma patients with 300 rads whole body ^{60}Co exposure delivered in a 15 minute period (18). Clinical management of these patients included a pre-treatment anti emetic, hospitalization through the 48 hour prodromal symptom period and subsequent discharge for outpatient observation until about 3 weeks postexposure when the signs of pancytopenia resulted in readmission. In the management of the pancytopenia, the general approach was

to utilize barrier nursing; antibiotics for infections on their recognition, not prophylactically; and transfusions of red cells, platelets and, rarely, white cells when indicated. As previously noted, only one accident-related fatality occurred post-irradiation in 22 cases.

In view of the paucity of human data regarding treatment effectiveness, reliance has been placed, in particular, in dog studies (11,20) designed at evaluating the extent of improvement in mortality which active treatment can make possible. They suggest that supportive therapy can raise the LD_{50} by a factor of about 1.5. The utilization of more heroic treatment techniques such as bone marrow transplantation may increase the LD_{50} even further, by a factor of 3 or more.

Lungs: Another heroic treatment measure, lung lavage, has been proposed and utilized as a treatment technique for individuals accidentally exposed to relatively insoluble radionuclides. The initial canine studies (21) led to the use of the method of Kylstra et al. (22) in a human ^{239}Pu inhalation accident patient (23).

A possible mortality incidence of approximately 0.5% can be inferred from the series in which this treatment was applied to patients with various types of severe obstructive lung disease (22). This must of course, be weighed against the risk of the potential presence of internal radioactive emitters in the lung in the intermediate or long term. Although there is little human data with which to judge the efficacy of the treatment, it has been suggested that it may reduce lung radioactivity by as much as 50 percent. In high level exposure this could be an effective and worthwhile result. For its optimal usage one would have to call on one of the few chest physicians who has had active experience with the technique.

Gastrointestinal Tract: Since the development of the classical GI syndrome requires that the functional efficiency of both the gastrointestinal and hematopoietic systems be altered (16), heroic treatment of the bone marrow injury may reduce mortality from the intestinal changes produced by total body external irradiation. When ingested radionuclides are the source of gastrointestinal radiation exposure, the gradual dose buildup in the intestinal tract provides adequate time to initiate the use of mild laxatives to accelerate excretion of contaminated ingesta. Such supportive treatment, which reduces the average intestinal dose by a factor of from 2 to 4 (24), is suggested for individuals receiving significant inhalation and/or ingestion exposure.

Availability of Medical Intervention

In considering the availability of medical modification for human acute radiation injury, we concentrated on the possible accidental exposures arising from nuclear industry operations rather than the catastrophic affects of the use of nuclear weapons. It was considered inconceivable that a serious industrial or reactor accident in the United States would not result in the mobilization of medical resources throughout the country to aid the exposed population. In view of the relatively slow tempo of the development of the manifestations of acute radiation injury in individuals whose exposure is within the range where treatment may increase survival, transportation to appropriate medical facilities within seven to ten days post-exposure is considered feasible. On this basis the availability of facilities for both supportive and heroic treatment was investigated.

Supportive measures including strict reverse isolation procedures, adequately managed major antibiotic therapy with appropriate microbiological laboratory support, and the ready availability of blood and blood products or transfusion can be found in most large acute medical and surgical hospitals.

One index of the availability of such services is an ongoing program in renal transplantation. Another index about which more quantitative information was obtainable was the approval program for the residency training of internal medicine residents (25). In 1975 there were 433 such approved programs, 90% of which were in hospitals affiliated with teaching institutions. These are generally large hospitals with an aggregate average daily census of 92,373 patients, so we estimated that each hospital could care for at least 5 to 10 severely irradiated people. On this basis, it was estimated that 2,500 to 5,000 people could receive adequate supportive treatment.

For the category of heroic treatment, the major demand would probably be for bone marrow transplantation. Our investigation showed that in 1975 there were 8 medical centers in the United States performing such transplantations on a regular basis while an additional 12 hospitals had newly started programs. It was estimated that each center might handle 5 such patients, providing a total of 50 to 150 people with such heroic treatment.

It is of interest to put the availability of these medical services into perspective in relation to the potential need. In the worst nuclear power reactor accident postulated in the Reactor Safety Study (1), corresponding to a probability of about 10^{-9} per/reactor-year, the number of people receiving an exposure in the range of 350 to 550 rads and requiring active supportive treatment would be about 5,000. The number of exposures above this magnitude, where the need for heroic treatment would be anticipated, turned out to be zero in the study computations. Thus, it would appear that the facilities available for medical modification of acute radiation injury resulting from nuclear reactor accidents in the United States should be adequate to provide the necessary care for the exposed population.

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