

AN APPRAISAL OF HUMAN STUDIES IN  
RADIOBIOLOGICAL ASPECTS OF WEAPONS EFFECTS

Eugene L. Saenger, M. D.  
Ben L. Friedman, M. D.

Radioisotope Laboratory University of Cincinnati  
College of Medicine

Prepared for DASA under Contract DA-49-146-KZ-029

November 14, 1962

AN APPRAISAL OF HUMAN STUDIES IN  
RADIOBIOLOGICAL ASPECTS OF WEAPONS EFFECTS

A. Introduction

This memorandum considers the significance of utilizing human data to determine radiation effects and to develop appropriate countermeasures in relation to weapons effects. There are two broad categories of study which require elucidation. One concerns itself with effects on humans, the second with effects on the environment in which human beings exist.

In the initial consideration of these two categories one can reasonably assign effects on the eco-systems to groups other than the Defense Atomic Support Agency. These studies of effects on all types of flora and fauna are of great importance and little consideration has been given to the long term effects of high doses of radiation.

The primary problem of human effects of high doses - both acute and chronic - requires considerable further analysis in regard to proper allotment of research time and effort. The obvious concern is the division of support between animal and human investigation.

B. Philosophy of Approach

In any problem in radiobiology one is interested in two aspects. The first is the discovery of general laws or principles which are essentially the same for all animals, all mammals, all large animals, etc. The second aspect is the documentation of specific information concerning man. If a general principle can be demonstrated in several types of animals, one may then assume that it is probably true for humans. For example, repeated studies have shown that if an animal is placed under severe stress, e.g., exercise to exhaustion or thermal burns, its tolerance to a given dose of radiation is less than an animal lacking the same stress. It is reasonable to assume that human beings under stress tolerate radiation less well than a healthy individual. Qualitatively such a concept is of great value; quantitatively it is of less help since one is not able to extrapolate the specific stress effects to different species of animals or to people. Nor is one able to predict the effect of a given stress in a human being after observing it in an animal. Anderson (1) states that the use of laboratory animals in radiation research programmes is necessary in order to obtain a better understanding of a number of the basic changes resulting from radiation injury. Extrapolation from animal to man is different if not impossible.

It is, however, quite apparent that many high dose effects simply cannot be studied in humans because of obvious humanitarian considerations. One cannot subject people to whole body doses of 800 rad although such a study would be

entirely feasible in an animal. Thus many experiments of radiobiological interest will continue to be done in animals.

Nevertheless, it is essential to consider further well planned studies in patients so long as the following criteria are fulfilled:

1. There is a reasonable chance of therapeutic benefit to the patient.
2. The likelihood of damage to the patient is no greater than that encountered from comparable therapy of another type.
3. The facilities for support of the patient and complications of treatment offer all possible medical services for successful maintenance of the patient's well being.

The type of patient usually selected for whole body radiation exposure is an individual with cancer which is far enough advanced either by direct extension of tumor or by metastatic spread so as to eliminate consideration of attempts at curative therapy. Usually these patients receive nonspecific supportive treatment or palliative treatment by surgery, radiation or chemicals. The consequence of these forms of therapy are usually helpful but sometimes the sequelae or complications of the various treatments are in themselves life threatening and constitute a hazard to the patient. Hence, whole body radiation therapy is no more likely to produce untoward sequelae than many other currently accepted treatments of other types.

Animal studies (2) have suggested that small doses of whole body radiation actually potentiate the effect of subsequent radiation given locally to tumor areas. In acute radiation injury of humans interesting contributions have been made by a number of workers. Hempelmann et al (3) have described the salient features of acute radiation injury and these observations have been amplified by Andrews et al (4) Shipman (5), Howland et al (6) and others. An excellent review adding certain new diagnostic criteria was presented by Thoma and Wald. (7)

Observations following therapeutic whole body radiation have been made by Collins (8), King (9) and Muller et al (10).

Although too few patients have been treated by whole body radiation at the University of Cincinnati College to be valid statistically, we have made several interesting observations. In general, these studies have demonstrated the relative innocuous nature of doses at or below 100 rad and have continued to confirm the well known hematological changes. At 150 and at 200 rad we have had responses to radiation of the type seen in group II of the acute radiation syndrome. We have had two cases, one at 150 and one at 200 rad, expire while

manifesting the hematologic abnormalities of group III of the acute radiation syndrome. These responses are in cancer patients suggesting that the more serious response may not be due solely to radiation. These findings also suggest that patients with various illnesses may be unusually susceptible to radiation doses whereas "healthy" patients may be less affected. One wonders whether the effect of prolonged stress as found in fatigue would produce similar effects. Searches for biological indicators other than blood changes have to date been unrewarding primarily because very few biochemical systems have been carefully studied in humans. Certain indicators such as urinary beta amino isobutyric acid which have appeared to be useful in accident victims, seem in cancer patients to be much less predictive than one would have anticipated.

### C. Role of Future Human Research in Relation to Remainder of Radiobiology Program

When one considers the nature of the total problem of weapons effects it is surprising to see the paucity of human studies. This problem is probably the single most important area of biological weapons investigation to be pursued in the next decade. Much valuable diagnostic, prognostic, behavioral and therapeutic information can be gleaned from well planned and executed studies in this area.

Continuing and future studies of acute external whole body radiation fall logically into the following categories:

1. Clinical evaluation - effect of various doses on signs, symptoms routine laboratory tests or new tests (newer biological indicators).
2. Metabolic effects - Effects of various doses on nutrition, fluids and electrolytes and biochemical systems of interest (including changes in the immune system). Use of labeled precursors.
3. Behavioral effects - Effects of radiation at various dose levels on human performance.
4. Dose rate response - Changes in effects with very high, very low and mixed dose rates, together with evaluation of single and multiple doses should be made. The concept of equivalent residual dose (ERD) (Rept. #29) should be investigated.
5. Partial body irradiation - Comparison of effects of shielding of various parts of the body.
6. Prognosis - Development of criteria for patient care based on the observations from these studies.
7. Therapeutic methods - Adequate supportive care of patient receiving radiation. Development of new methods of prevention and treatment of radiation injury.
8. Use of healthy volunteers - Limited use of normal volunteers based on preceding careful investigation of therapy and accident patients.

D. Specific Areas of Endeavor:

1. Clinical Evaluation - All patients who receive whole body radiation for any purposes should be evaluated carefully utilizing all clinical and laboratory observations which can be reasonably obtained. Clinical patterns related to dose, coexisting disease, nutrition and other parameters may thus be identified.

It would seem important to carry these observations further at various dose levels as most planning for capabilities of humans after exposure depend on a knowledge of their expected performance.

2. Metabolic Effects - Continuing metabolic studies are needed. Little is known of nutritional requirements and fluid and electrolyte changes in humans. Some investigators state that these aspects are not important in radiation injury on the basis of animal studies. There has not been enough human research in this area to provide convincing data at any dose level. Such information is essential in planning patient care.

Changes in DNA-RNA systems in so complex a mammal as man may be difficult to find. Some preliminary observations in our laboratory indicate that further studies in this general area may be fruitful. Many other systems might be suggested as shown by the observations of Cerber et al (11) regarding creatinuria, beta aminoisobutyric acid and hydroxy proline. The use of labeled precursors is suggested since at some time it will be necessary to determine whether certain changes following irradiation are due to specific biochemical alterations or are due to nonspecific stress.

Changes in the immune system have to date eluded most observers who have sought them. With the renewed interest in immunology centering both about the lymphocyte and thymus, new techniques of study should be sought.

3. Behavioral Effects - One of the questions most frequently asked by individuals responsible for planning for nuclear warfare concerns the effect of a given dose of radiation on subsequent capability and performance of an individual or group. It is apparently not easy to find a suitable test or battery of tests which measure the important human functions of performance or decision making such that one or more tests could be used before and after exposure to radiation.

Appropriate performance tests should be developed or adapted. These tests should be given to subjects before and after exposure to ascertain changes in the capability of the individual.

4. Dose Response Studies - Most studies have been carried out with rates such that the dose is delivered within 30-300 minutes. If a dose of 200 rad is delivered in approximately 90 minutes and produces a given effect it becomes

important to determine the change in effects if this dose is given in 0.5 - 5 minutes. There is much speculation about this problem at a human level based on animal studies but no precise data has been obtained in humans. Similarly the effect of low dose rates should be studied particularly in relation to performance testing. The effects of high doses (100 - 200 rad) followed by daily doses to test the concepts of equivalent residual dose (12) would be of importance. Fractionation studies should be continued.

3. Partial Body Studies - Patients in whom various parts of the body have been shielded would be compared to patients who have received whole body radiation using a variety of indices.

6. Prognosis - The vast amount of data which could be generated by the studies described herein should be collected, tabulated and prepared for computer analysis so as to make these data easily available for physicians, commanders et al. This function might well be assigned to the office of the Surgeon of DASA or other representatives of the respective Surgeons General to insure presentation of the data in its most useful form.

7. Therapeutic Methods - In view of the hazards involved in this form of therapy, before increasing the dose beyond 200 rad all measures to protect the patient must be available and ready for immediate use. The patient should be in a clean area with an aseptic treatment room available. Autologous marrow should be stored and ready for reinfusion before therapy. Optimum time for reinfusion will have to be determined.

In general one might consider studying antiradiation drugs in humans. In spite of the great volume of animal work in this area, most drugs have various drawbacks for human use. One such drawback is that it is not possible to do drug testing at an LD<sub>50</sub> level in humans. With the development of additional biological indicators, however, such drugs might be studied at lower dose levels.

8. Use of Healthy Volunteers - Once patients from the therapy group are being managed so that their hematologic consequences of radiation have been controlled then it will be advisable to utilize a less ill, more normal group of individuals for study.

Consideration should be given to the use of volunteers because of the possible biases introduced, and perhaps unrecognized, in patients receiving therapeutic radiation. Similarly in accident victims complete pre exposure data is usually not available.

E. FUTURE PLANS REGARDING FUNDING: The studies described above will require the participation of a number of research centers and the development of at least a limited number of special facilities such as radiation units capable of very high and very low dose rates and appropriate clean and aseptic rooms as

as well as other laboratory facilities.

If one assumes that the ratio of funds for all human radiation research is about 5% of the total funding of biomedical research one might also assume that present "high dose" or acute studies represent no more than 0.5 - 1% of this total budget.

Therefore, a three to fourfold increase in research funds in the above areas is recommended for the next three to five years. After that time the total funds should again be doubled.

At such a time as there is no threat of thermonuclear war, these programs could be greatly reduced or even eliminated.

## REFERENCES

1. Anderson, D. R. Experimental Treatment of Radiation Injury in Monkeys... in *Diagnosis and Treatment of Acute Radiation Injury* p. 363 World Health Organization, 1961.
2. Hollcroft, J. W. and Matthews, M. Effect of Ionizing Irradiation Treatments on Tumor Regression. *J. Nat. Cancer Inst.* 14: 527-535, 1953.
3. Hempelmann, L. H., Lisco, H. and Hoffman, J. G. The Acute Radiation Syndrome. *Ann. Int. Med.* 36: 279-510, 1952.
4. Andrews, G. A., Sitterson, B. W., Kretschmar, A. L., and Brucer, M. Criticality Accident at the Y-12 Plant in *Diagnosis and Treatment of Acute Radiation Injury*. 27-48. WHO New York 1961.
5. Shipman, T. L. A Radiation Fatality Resulting From Massive Overexposure to Neutrons and Gamma Rays. *ibid* p. 113-133.
6. Howland, J. W., Ingram, M., Mermagen, H. and Hansen, C. L. The Lockport Incident: Accidental Partial Body Exposure of Humans to Large Doses of X-irradiation. *ibid* p. 11-26.
7. Thoma, G. E., Jr., and Wald, N. The Diagnosis and Management of Accidental Radiation Injury. *J. Occup. Med.* 1: 421-447, 1959.
8. Collins, V. P. Therapeutic Use of Single Doses of Total Body Radiation. *Am. J. Roentg., Rad. Therap. & Nuc. Med.* 75: 542, 1956.
9. King, E. R. Use of Total Body Radiation in the Treatment of Far-advanced Malignancies. *J.A.M.A.* 177: 610-613, 1961.
10. Muller, L. S., Fletcher, G. E., and Gerstner, H. B. Systemic and Clinical Effects Induced in 263 Cancer Patients by whole-Body X-irradiation with Nominal Doses of 15-200r. Report 57-92 School of Aviation Medicine, Randolph AFB, Texas 1957.
11. Gerber, G. H. Gertler, P., Altman, K. I., and Hempelmann, L. H. Dose Dependency of Radiation Induced Creatine.
12. Exposure to Radiation. Report No. 29. National Committee on Radiation Protection and Measurements. Univ. Chicago 1962.