Nuclear Weapons Effects Research No. 03.011

Sub-task Title: The Effect of Total Body Irradiation on Immunologic Tolerance of Bone Marrow and Homografts of Other Living Tissue

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Report Period: Feb. 1, 1963 - Jan. 31, 1964
Final Report

Investigations in the effect of total body irradiation have been carried out in this department for more than 10 years and this final report is based on data collected during this time. The project was initiated when comparison of response of patients receiving therapeutic total body irradiation with that of patients receiving chemotherapy indicated that, in the dose range used, total body raidation was well tolerated and could be used as as adjunct to treatment of disseminated cancer (1, 2). Intensive studies on response of erythropoiesis were undertaken (3) and findings gave new directions for further study so that, in the final years, the protocol included a large series of clinical, hematologic, biochemical and physiological tests (4) as well as studies in protection. The investigation includes observations on 112 patients receiving therapeutic total body irradiation; pilot and parallel studies were carried out on experimental animals.

The fundamental problem has been to define effect of irradiation and quantitate effect with amount of radiation exposure. Since quantitation is possible only to the degree that measurement of both effect and amount of radiation is possible, it was necessary to consider all the variables that would influence measurement.

Comprehension of the problem begins with the recognition that a simple numerical expression cannot define dose of irradiation. The physical characteristics of irradiation require that dose be described not only by the number of units (roentgens, rads, etc.) but also by distribution and intensity in a given volume of tissue, and time or duration of exposure. For each irradiation procedure planned, dosimetry studies were carried out so that uniform distribution of irradiation could be achieved. Several methods, and types of dosimeters, were used for comparison, and for accurate measurement of dose to specific anatomical sites. These methods assured even distribution of radiation and produced comparable data on radiation exposure throughout the entire study.

Similar dosimetry studies were carried out for animal experiments. Protocols required animals of similar age, weight and physical structure so that volume irradiated and response could be compared. All animals received immunization vaccine, were quarantined for two weeks, and all were well nourished and in good health prior to experimental work.

Although variables associated with patients requiring therapeutic total body irradiation are present, certain aspects were comparable. All patients were adults suffering from disseminated cancer, all received evenly distributed exposures of irradiation and, except when reaction was severe, none received supportive treatment that would mask effect of irradiation. Since prediction of effect is the basis of radiotherapy, experience in this field is helpful in evaluating response to treatment and in estimating response to heavy exposures by extrapolation of data obtained with therapeutic exposures.

A PREDICTION OF THE EFFECT OF TOTAL BODY IRRADIATION BASED ON CLINICAL OBSERVATIONS

The essential problem posed by the possibility of massive irradiation of the human is to predict the lethal dose, the dose at which immediate but temporary incapacity will occur, and the dose at which delayed but significant injury will occur. The possible answers proliferate as probable qualifying factors are introduced, e.g.,

1. Unless there is a uniform concept of dose and dosimetric procedures, gross discrepancies in estimates of dose-effect are to be expected.
2. The effects of irradiation are not specific and are apt to be confused with other types of injury,--mental, physical or biochemical.
3. The effect of the accidental or catastrophic irradiation exposure will vary with the geographic, geometric and anatomic relations that may be unsuspected or, at least, difficult to reconstruct.
4. Age, general health and competing disease will modify the response of the individual. Prediction of dose-effect is possible for individuals or for uniform groups of individuals but a very wide rante of dose-effects is to be expected in the general population.
5. Prediction of dose-effect in humans must be based upon the controlled circumstances of clinical use of radiotherapy where uniformity of radiation throughout the body may be sought although this is unlikely ever to be achieved in accidental or catastrophic exposure.
6. Morbidity and mortality will clearly depend upon medical assistance whether this be merely supportive or actually specific.

Nevertheless, some simple expression of the hazard of radiation is necessary and a prediction can be offered if an allowance of ± 3 d B is granted.

The following predictions are based on a hypothetical group of adult males between 30 and 50 years of age, with training or education to permit a basic understanding of radiation and biology, physically and mentally conditioned to work in the field of radiation hazards and free of any previous physical or chemical trauma likely to impair tolerance to radiation. The dose is expressed as the amount of radiation measured in air at the site where the individual is exposed. The geometry of exposure and quality of irradiation is assumed to be such as to produce a uniform distribution through the entire body.

"Acute incapacity" means uncertain ability to carry out crucial mental or physical tasks.

"Partial disability" means ability to carry out mental tasks and sedentary work but vulnerable to stress, e.g., severe physical exertion, infection or further irradiation.

The problems of single brief exposure and of protracted exposures are dealt with separately.

Table 15
Predicted Effect
of
Single Exposures of Total Body Irradiation

Amount of Irradiation	Acute Incapacitation	Partial Disability	Blood Counts (% of normal)	Time t Recover
50r	0	0		
100r	0	0	75%	60 day
200r	0	0	50%	60 day
300r	1 - 6 hrs. (minor)	0	25%	60 day
500r (no deaths anticipated below this level)	1 - 12 hrs.	2 - 3 mos.	5%	90 day
700r (LD-50 range)	1 - 72 hrs.	6 mos.	1%	120 day
900r (LD-100 range)	2 mos.	12 mos. (if any survivors)	<1%	1 year (if any surv

The prediction of the effects of protracted total body irradiation is less readily described in simple numerical values for dose and time.

The rule to be anticipate is that, taking values for single exposures of the order of one hour as a standard, the effect of protraction will be (A) to obscure the time of onset of signs or symptoms due to delayed and insidious development , and (B) to prolong the recovery period due to: 1) increased time required for accumulation of an effective amount of irradiation, 2) inhibition of the repairative response, 3) vulnerability to infection and other forms of stress during the period when repairative response is impaired.

It is evident that at some low level of protracted exposure, no detectable effect will occur and at some high level of protraction falling short of lethality, the above description will be clearly applicable. Intermediate exposures will be difficult to define with precision.

Table 16

Predicted Effect
of
Protracted Total Body Irradiation

Amount of Radiation and Duration of Exposure	Symptoms: Acute Incapacitation	Symptoms: Partial Disability	Blood Counts: % of normal	Blood Counts: Recovery time
100r in 1 wk.	0	0	90%	
in 1 mo.	0	0	90%	
in 1 yr.	0	0	0	
200r in 1 wk.	0	0	75%	
in 1 mo.	0	0	50%	
in 1 yr.	0	0	0	
300r in 1 wk.	0	Day 15-50	50%	3 mos.
in 1 mo.	0	Day 30-90	25%	4 mos.
in 1 yr.	0	0	0	
500r in 1 wk.	Day 7-10	Day 10-90	20%	4 mos.
(MLD range) in 1 mo.	Day 25-35	Day 35-150	1%	6 mos.
in 1 yr.	0	Mos. 10-24	50%	4 mos.
700r in 1 wk.	Day 5-30	Day 30-150	1%	6 mos.
(LD-50 range) in 1 mo.	Day 15-50	Day 50-200	<1%	12 mos.
in 1 yr.	0	Mos. 10-24	25%	4 mos.
900r in 1 wk.	Day 4-30	Mos. 1-6	1%	1 yr.
(LD-90 range) in 1 mo.	Day 10-50	Mos. 2-12	<1%	2 yrs.
in 1 yr.	0	Mos. 8-24	10%	1 yr.

The above values are predictions, not conclusions.

They are offered as "best answers" to current conjecture based on total experience in clinical radiotherapy.

The values below 300r are firm estimates.

The values below 500r are safe estimates.

The reason for continued clinical investigation is to accumulate further observations and develop more reliable tests to confirm or alter the impressions in high dose ranges.

The effect of Total Body Irradiation on Immunologic Tolerance of Bone Marrow and Homografts of Other Living Tissue

Location:
Baylor University College of Medicine
Texas Medical Center
Houston, Texas.
approximately 1953 - 1964.

Researchers:
Vincent P. Collins, M.D., Baylor University, Principal Investigator
R. Kenneth Loeffler, M.D., Baylor University

Organization:
This research was conducted by the Baylor University College of Medicine. The work was initially supported under Armed Forces Special Weapons Project (AFSWP) contract DA-49-007-MD-428 and then supported by the Defense Atomic Support Agency (DASA) contract DA-49-146-XZ-032.

Subjects:
The subjects were patients at the Texas Medical Center. The majority had generalized neoplastic conditions. There were 112 patients treated in the study. Exposures ranged from 25r-250r in 1 day to 25r-545r over periods of time from 4 days to 3.5 years.

Purpose:
The goal of treatment by total body irradiations for patients with disseminated cancer is relief of symptoms. Despite the fact that many patients were approaching the terminal stage when referred for treatment, therapeutic response was evident in many by decrease in size of nodes, relief of impending obstruction and by decreased narcotic requirements subsequent to relief of pain. In some instances, response was dramatic; a few completely bedridden patients became ambulatory and several experienced long term remissions. Among the 112 patients there were more than 30 different types of cancer; since total body irradiation was given only for generalized disease, a survival of one year or even temporary remission was gratifying. Extensive data from clinical observations and laboratory tests were reported in series of reports to AFSWP and DASA throughout the period of the study.

Value to DoD: In his summary report, Dr. Collins included a set of tables predicting the effect of total body irradiation based on clinical observations. He also included detailed and extensive tables of biochemical effects and hematological data. All of this can and probaly was used to support predictive analysis of radiation effects on troops in a wartime environment.

Records:
Currently identified records are the reports submitted to AFSWP and DASA by the University of Baylor. The titles and dates

of the reports indicate that certain reports are missing; the missing reports are being sought for review.

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