Item 1. Subtask Number and Title: Radiation Effects in Man: Manifestations and Therapeutic Efforts NWER RMD 4.009

Item 2. Agency Having Technical Supervision: Defense Atomic Support Agency, Attn: STMD

Item 3. Agency Performing Work: Department of Radiology, University of Cincinnati College of Medicine: Contract No. DA49-146-XZ-315

	Principal Investigator - Name
FY (PRIOR)	Eugene L. Saenger, M.D.
FY (CURRENT)	Eugene L. Saenger, M.D.
FY (+1 Budget)	Eugene L. Saenger, M.D.

Item 4. Funding Data:

FY (total funding up to Prior FY)	$ 274,200
FY (Prior)	61,356
FY (Current)	71,326
FY (+1 Budget)	71,369
FY (+2 Planning)	85,054
FY + 3	85,000
FY + 4	90,000

Item 5. Estimated completion date: 1973

Item 6. Requirement and/or Justification

As in previous years there is no decrease in world tensions from the possibility of nuclear warfare on any scale. In spite of disarmament discussions tensions may be increasing as noted in current discussions concerning ABM defenses.

In this present and continuing situation of crisis it is necessary to pursue with increased diligence the scientific investigations of acute radiation effects and the attendant treatment possibilities in the human being. The changes to be investigated continue to be (1) those of the critical organ systems such as the bone marrow and gastro-enteric tract and (2) decision making processes. The time span of interest continues to be the early period of about 3 days but with the emergence of some improved therapeutic considerations a time of about 6 weeks need be considered.

This study continues its emphasis on investigation of the human being. In order to evaluate these early changes one can only utilize human data although helpful concepts may be contributed by animal research. Data obtained from these studies will continue to be correlated with information obtained from human radiation accidents.

The proposed studies continue the investigation of changes in metabolism of DNA and RNA, and add evaluation of bone marrow reserve and immunological competency. The possibility of

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estimating effects of combined injury by comparison of urinary excretion of amino acids and certain nucleosides in burned vs. irradiated individuals becomes a possibility. The studies of psychological effects and cognitive functions will continue.

These studies are performed on patients who are given total or partial body radiation as treatment for metastatic malignancy. This therapy is being used in place of systemic chemotherapy. In the patients where radiation of this type is used our data suggests that it may be equal or superior to current chemotherapeutic measures. The study design has been approved by the Research Committee of the College of Medicine in regard to its therapeutic value and informed consent of the subjects under study.

A reassessment of our earlier work suggests that studies of "biological indicators" may well offer more promise than previously suspected. Since most human exposures are non uniform both in regard to distribution of radiation and also in a military situation, non uniform in regard to types of radiation (gamma and neutron) and energy, an expression of net biological effect is an important goal. Possible indicators might be amino acids, nucleoside fragments, enzyme changes or chromosome aberrations. Since the excretion levels of some of these compounds are affected by burns, comparison of excretion levels under varying circumstances of injury will be of interest in endeavoring to evaluate relative effects.

Comparison of whole and various types of partial body exposure will continue to provide useful estimates of weapons effects.

The use of marrow transfusion, initially autologous, will be used both for support of the irradiated subject and as a possible important future method of treatment. With the rapid increase of understanding of tissue compatibility and techniques for analysis of these factors, the possibility of the use of homologous marrow even only as a temporary support until regeneration of an individual's own tissue becomes of increased interest.

Item 7. <u>Research Work Units</u>:

A. **Identification**

1. a. DA-49-146-XZ-315. Radiation Effects in Man: Manifestations and Therapeutic Efforts

2. Department of Radiology

3. Principal Investigator: Eugene L. Saenger, M.D.

Collaborators: Harry Horwitz, M.D.
James Kereiakes, Ph.D.
Edward B. Silberstein, M.D.

Consultants: Louis Gottschalk, M.D.
Evelyn Hess, M.D.
Allen Litwin, M.D.
Robert Kunkel, M.D.
John Varady, Ph.D.

4. Continuation of Existing Work Unit: Yes

5. Estimated Interim Report Date: 1970

6. Estimated Completion Date: 1973

7. Estimated Final Report Date: 1973

8. If R & D Contract Proposal:

Cost: $71,369
Start Date: 1969
Completion Date: 1970
Agency: University of Cincinnati College of Medicine, Cincinnati General Hospital, Cincinnati, Ohio 45229
Continuation of Existing Contract: Yes

Synopsis of Research Proposal:

These studies are designed to obtain data from whole and partial body radiation in the human being. The effects being studied are clinical, hematological, biochemical, immunological and behavioral. Evaluation of storage and reinfusion of autologous bone marrow is being carried out.

9. Approach:

a. Selection of Patients

Patients selected for study will be those who are to receive partial or total body irradiation in the treatment of metastatic malignancy from various primary sites, excluding neoplasms which are treated by internal radiation, e.g. carcinoma of the thyroid. They will have stable hematologic values and may have received local radiation previously.

b. Experimental Design

The design of the study is such that the patient serves as his own control. For this contract period there will be two groups. In the first, pre-therapy studies will be completed within one week and immunological studies will be omitted. It has been found that too many subjects were lost either for personal or medical reasons because of the 21 day pre-irradiation study period. A second group for patients who can tolerate the 21 day pre-irradiation will be continued whenever possible. The post-irradiation period studies continue as long as the clinical course of the patient allows. Because of the

careful design of the study it is possible to make between patient comparisons.

Three to five observations are made in the pre-irradiation period. Post-irradiation specimens are then obtained at three day intervals or oftener until clinical and laboratory findings become stable.

Some of the patients will be hospitalized on the Tumor and Surgical Wards of the hospital. Other patients will be in the enlarged Clinical Research Center within the new Cincinnati General Hospital. The new hospital building will begin receiving patients in mid 1969. In some situations the irradiated individual will be followed on an out-patient basis.

During the pre-irradiation period, the patient's records are reviewed by the physicians to be certain that the contribution of the underlying disease can be evaluated. Two or more sham irradiations are given to permit accurate dosimetry, obtain cooperation by the patient and evaluate psychic factors. The sham treatments will be randomized between the actual radiation. There is no discussion of possible subjective reactions resulting from the treatment. Other physicians, nurses, technicians and ward personnel are instructed not to discuss symptoms or reactions with the patient.

c. Parameters to be Investigated

1. Clinical Findings

   (a) Complete history and physical examination
   (b) Temperature, pulse and respiration
   (c) Body weight at standard test times

2. Hematology and other Laboratory Tests

   (a) Hgb., RBC, WBC, Differential, Hematocrit, Platelets, Reticulocytes, Erythrocyte Sedimentation Rate, Etiocholanolone for marrow reserve.
   (b) Bone marrow--smear and block for microscopic pathological analysis at regular intervals.
   (c) Urinalysis
   (d) Other clinical laboratory tests, e.g. Serum urea Nitrogen, electrolytes, etc., will be obtained if needed.
   (e) Pre- and post-radiation karyotyping for biologic dosimetry.

3. Biochemical studies including tracer studies of isotopically tagged nucleosides. Additional enzyme studies. Comparison with patients suffering burns and other trauma.

4. Bone marrow storage and reinfusion

5. Immunology

6. Psychiatric evaluation and testing

   (a) Five minute verbal samples
   (b) Clinical psychiatric interviews and rating scales

Work Units:

This program is based on the concept of obtaining all possible useful information from each subject studied. Although this statement may seem to be a truism, one should understand that appropriate subjects are somewhat difficult to obtain as compared to non-human studies and that once a given subject is started it is desirable to derive all possible data for the effort required.

There are two major closely related work units:

A) Radiation exposure, clinical and laboratory evaluation and biochemical and immunological studies

B) Psychiatric and psychological studies

Work Unit A:

The techniques of administration of radiation will be as follows:

1. Bidirectional radiation. Half of the dose is given from each side as before.

   a. Whole body
   b. Partial body using the xiphoid as the boundary
   c. Trunk and thorax radiation using the suprasternal notch and symphisis pubis as the boundary

2. Unidirectional radiation. In selected instances the total dose will be given from an anterior, posterior or single lateral field.

Dosimetry

In previous studies the radiation beam has been directed horizontally at a wall 338 cm away with the patient midline at 282 cm from the source. Under these circumstances the beam area for the 50% isodose curve at the patient's midline has been a square field 75 x 75 cm. The patient is placed in a sitting position with legs raised and head tilted slightly forward. Each lateral portal receives half the dose.

A new Cobalt 60 teletherapy unit (Theratron Model 8, Atomic Energy of Canada, Ltd) was installed. The dose rates as used in the past of 3-6 R/min will continue. The source to midline-trunk distance for this unit is 286 cm. The field size at 286 cm for this unit is 100 cm (90% isodose line) compared to 75 cm (50% isodose line) for previous Eldorado 8 Unit, thus providing a larger and a more homogeneous radiation field.

Dosimetry studies are in progress to determine experimentally "active" bone marrow dose under simulated whole-body and half-body Co-60 exposure conditions. Thermoluminescence dosimeters (LiF) are being placed in selected bone spaces of an Alderson Rando phantom and the phantom then irradiated under simulated patient exposure conditions. These "active" bone marrow doses will be related to the hematologic findings observed for whole-body irradiation and for other conditions of partial body irradiation. These data will aid in interpretations of the effects of shielding portions of "active" bone marrow.

Clinical and laboratory observations will continue as indicated above. There will be 3-5 observations made before radiation, daily observations afterwards for 3 days and then every 3 days as long as deemed necessary.

Comparisons will be made for partial vs. whole body, partial upper vs. partial lower and trunk vs. partial irradiation. The frequency of prodromal symptoms, hematological changes and biochemical changes will be followed. Whenever possible unidirectional radiation will be attempted since this type of exposure is of military interest.

As indicated above, the doses for partial body radiation will be increased so as to determine the effect of dose on the severity of prodromal symptoms. In previous studies (10) it has been noted that clinical symptoms with partial body radiation are proportional to the dose received although hematological changes are either minimal or absent. In one patient receiving 300 rad of partial body radiation, a significant drop in white cell elements was noted. These changes will be evaluated in reference to bone marrow reserves by etiocholanolone. Since some of these patients experience therapeutic benefit from the radiation, the use of higher doses of partial body irradiation is both justified and desirable. This effort will seek to identify the dose range causing hematological changes similar to those observed with previously observed levels of whole body radiation.

Hematology

Etiocholanolone, a naturally occurring steroid metabolite of testosterone, is a potent stimulus to leukocytosis in man. It produces an elevation in the white blood cell count by mobilizing granulocyte reserves. At a dose of 0.10 milligram of etiocholanolone per kilogram of body weight the average maximum change in granulocyte count in men is 5850 ± 770 per cu mm. and in women 6700 ± 1400 per cu mm.

The immediate effect of whole body radiation on the kinetic of bone marrow granulocyte reserves are not known. It is proposed to investigate etiocholanolone-produced granulocytosis both before, and at daily intervals after, patients with metastatic tumors have received therapeutic whole body radiation. The sequential measurement of the radiation-induced change in granulocyte reserves will not only yield basic quantitative data on radiation effects but may provide a biologic dosimeter when the exact time of radiation is known.

The granulocytosis induced by etiocholanolone may also be of value in the early evaluation of the effectiveness of bone marrow transplants after radiation, before the peripheral granulocyte count has actually risen as a result of the transplant.

Radiation-induced chromosome aberrations both in vivo and in vitro have been employed as dosimeters of radiation damage but the specificity of these changes has never been questioned. Since victims of nuclear weapons will be exposed to blast and thermal injury as well as radiation, we also plan to perform karyotypes on patients who have sustained severe burns and/or trauma.

Reference:

Vogel, J.H., et.al. The effect of Etiocholanolone on Granulocyte Kinetics. Blood 30: 474, 1967.

Biochemical Studies

The investigations of DNA metabolism have been pursued both in man and in the rat. Some results and plans for the forthcoming contract period follow:

I. Animal Studies

It is desirable to carry out some animal studies in support of human studies. (These will be of limited cost to the contract).

The results obtained from previous rat experiments indicate that radiation can cause a considerable increase in the amount of deoxycytidine (CdR) in the blood and urine. However, studies on irradiated patients with various types of cancer reveal that CdR-uria is not sensitive and specific to radiation (1).

The difference in radiosensitivity of CdR-uria in man and rats is of interest because understanding of the cause of this difference may provide further insight into the metabolic origin of radiation induced urinary CdR and may well lead to obtain more sensitive biological indicators of radiation injury in man. Our comparative study of CdR deaminase activity in rat and human serums suggest that CdR is metabolized differently in these two species (2). Recently, we used CdR specifically

labeled with ^3H on the carbon-5 of the cytosine to study the effect of radiation on the catabolism of CdR by rats. It was found that irradiated rats (200R) excreted about 21% of total radioactivity injected whereas unirradiated rats excreted only 13% of radioactivity. The radioactive compounds excreted in urines were analyzed by the use of anion and cation exchange columns, charcoal absorption and paper chromatography. Only about 1% of the total CdR-^3H injected into the rats was excreted as CdR whether or not the rat was irradiated. The remainder of the radioactive substances excreted in the irradiated and unirradiated were not absorbed on either cation or anion exchange columns. They were absorbed on charcoal and were analyzed by paper-chromatography after elution from charcoal. The radioactive tracing of the paper chromatogram of ^3H-labeled compounds excreted in the urine of unirradiated rats showed two peaks corresponding to uracil and deoxycytidine; whereas, that of ^3H labeled compound from irradiated rats gave an additional peak migrating slower than uracil and uridine (3). Further identification of the excreted radioactive compounds is underway at present, but the preliminary results indicate that CdR in the irradiated rat is catabolized differently and excreted into urine as different end-products other than CdR as compared to the pattern in the unirradiated rat. The unknown compound behaves chromatographically as cytosine but is not absorbed on ion exchange columns.

It seems that CdR is not an end-product of pyrimidine metabolism in man. If CdR is further metabolized via deoxyuridine by the action of CdR deaminase, one might expect an increase of uracil level in urine by irradiation provided that the pattern of CdR catabolism is not altered by irradiation because uracil has been shown to be a specific end-product of pyrimidine metabolism in man (4). On the other hand, it has been reported that β-alanine and β-aminoisobutyric acids are the major end-products of cytosine-uracil or thymine catabolism (5).

II. Studies with labeled nucleosides in human beings

Studies will be done using ^3H labeled deoxycytidine given intravenously before and after therapy to determine changes in elimination as an effect of irradiation as compared to similar studies in the rat. Earlier work in this laboratory done in unirradiated subjects showed that about 40% of CdR radioactivity was eliminated in breath as $^{14}CO_2$ within 2 hours and about 20% in urine over 48 hours. In that work the biochemical nature of the ^{14}C in the urine was not determined. This aspect of the investigation will aid in the evaluation of possible new specific urinary components. The excreted compounds will be analyzed by column and paper-chromatography.

Doses of 5-10 uCi of ^3H CdR will be given intravenously before and after irradiation. These dose levels are below MPD levels for the population at large and have been approved by the Radiation Safety Officer.

III. Serum Enzymes

Recent work under this contract has shown elevation of CdR deaminase in the serum of three cancer patients after irradiation (3). It has been demonstrated that many enzyme activities, especially the activities of lysosomal hydrolases, are elevated by X-ray irradiation. Increases of DNase I and DNase II a few hours after irradiation in the serum and in the urine of animals have been reported (6). We intend to study the radiation effect on the serum enzymatic activities involved in the catabolism of DNA such as DNase, nucleotidase, phosphorylase and phosphatase, since these enzymes could be responsible for the radiation induced degradation of DNA. Furthermore, the assay of serum enzyme activities is usually simpler and more sensitive than that of urinary metabolites.

These studies will be of value in providing better understanding of the nature of the biochemical lesion in man and perhaps in suggesting ways to provide protective or therapeutic agents for the acute radiation syndrome. They may also be helpful in identifying biological indicators of radiation damage.

Various enzyme activities will be measured by the conventional methods with the exception of CdR deaminase and DNases. Radioactive CdR has been used as a substrate for CdR deaminase (2). For the assay of DNase, labeled DNA will be prepared from Escherichia coli strain T^- grown in a medium containing labeled ^3H thymine (7). These radioactive substrates provide increased sensitivities as compared to conventional methods.

IV. An attempt to evaluate the effects of combined injury

Our previous studies of aminoaciduria (DASA-1844) indicated increased excretion of BAIBA and taurine under conditions which seemed indicative of non-specific "stress" rather than due to radiation per se. Similarly the urinary excretion of CdR in several patients suffering from thermal burns has been elevated and prolonged. Thus it seems possible that comparisons of these substances in burned vs. radiated patients might provide a beginning of insight into the mechanism of combined injury.

We plan to assay 24 hour urines on a number of patients with burns of varying extent and degree, patients with severe trauma and those with irradiation as noted above. These findings will be compared with those of chromosome studies (See Hematology). Although the exact form of analysis is undefined, hopefully some comparisons of relative metabolic effect at a human level may provide an insight into this obscure problem.

Bone Marrow Storage and Reinfusion

All patients to be given 150 rad or more of total body radiation will have autologous marrow stored under sterile conditions at 4 degrees C. on the day prior to irradiation or just prior to irradiation. Reinfusion will be done beginning 6 hours after irradiation.

Three groups of patients will receive or will have received 150 - 200 rad total body irradiation as treatment for metastatic malignancy. The first group (Group I) will include patients who have already been irradiated at the 150-200 rad dose level and did not receive bone marrow infusion. A second group (Group II) will be given filtered autologous bone marrow two weeks after irradiation. The third group of patients (Group III) will be treated with 150-200 rad total body irradiation, followed by infusion through filters of their previously stored marrow on the second day after irradiation. In view of the life threatening hematologic abnormalities we have encountered in patients receiving 150-200 rad (226 to 336 R) total body radiation, marrow storage is felt to be mandatory.

The Group III patients will test the hypothesis that bone marrow "take" is best obtained early after radiation when presumably the marrow space is relatively empty and can accept viable cells more readily.

In our previous transfusions of 1.1×10^9 - 4×10^9 apparently viable nucleated marrow cells infused at various times after irradiation, it has not been possible to establish clear evidence of a hematological response. The recent experience of Wald et.al. in the Pittsburgh accelerator episode of October 1967 showed a marrow response after the infusion of 9×10^9 cells given without storage from an identical twin to the patient. The success of this therapy could have been due wholly or in part to the several factors -the volume of cells, the lack of storage, state of health of donor and recipient and the level of irradiation. It will be possible to evaluate these factors in this and succeeding study periods.

Immunology

These studies are designed to study the effect of irradiation on the primary immune response in man.

There are few data on the effect of irradiation alone on the mechanism of the immune response in man. Most of the data has been obtained from total and partial body irradiation in animals. Two phenomena have been described. (1) Enhancement of the primary immune response. This occurs when the antigen is given at varying times prior to irradiation. (2) Depression of the primary immune response. This occurs when the animal is exposed to the

antigen after irradiation. Other experimental data shows that the response is also dependent upon the type of antigen. For instance, a particulate antigen gives rise to enhancement, the closer it is given to the exposure than a soluble antigen which requires a longer induction time.

Autologous bone marrow transfusion will be given to some of the patients in the study. The evidence from experimental data is that bone marrow cells given 2 to 6 days post-irradiation will not interfere with the fixed pattern of the immune response.

The immunological studies require the use of two phages. If only one phage is used to measure the immune response both before and after irradiation the second injection would produce an anamnestic (secondary) response. Thus it would not be possible to evaluate the radiation effect. Hence the use of the crossover design as described below becomes essential.

Work over the past years in Dr. Hess's laboratory has resulted in the development of safe phages which have been tested repeatedly in human beings and animals. The use of these agents and this experimental design has been approved by the Research Committee of the College of Medicine.

In order to study the primary response, the patient will receive an injection of T2 phage 22 days prior to irradiation. Antibody titers will be obtained at 2, 5, 7, 10, 14 and 21 days. On the day of irradiation ΦX 174 phage will be injected either 12 hours before irradiation or 24 hours post irradiation. Antibody titers to ΦX 174 will be obtained on days 2, 5, 7, 10, 14, 21, 28, 35 and 42.

Both phages are potent antigens and antibodies can be measured easily. The order of use will be varied in matched patients as follows:

Experimental group 1 -	T2 phage	21 days pre-treatment
	ΦX 174 phage	12 hrs. pre-treatment
Experimental group 2 -	ΦX phage	21 days pre-treatment
	T2 phage	12 hrs. pre-treatment

Along with antibody titers the patterns of immune response will be measured in terms of 7S and 19S antibodies using 2-mercaptoethanol testing and sucrose gradient ultracentrifugation and column chromatography in selected sera.

Previous work done under this contract has indicated alteration in gamma globulin of irradiated patients (Luzzio, A.J., Friedman, B.I., Kereiakes, J.G. and Saenger, E.L., Specific Proteins in Serum of Total-Body Irradiated Humans, Jour. Immunology Vol. 96:64-67, 1966). Preliminary data from earlier studies here suggest that various serological

factors appear after irradiation. These substances will be evaluated further.

B. Psychiatric Evaluation

Following exposure to acute whole or partial body radiation it is possible that there will be significant impairment of the decision making capability of key personnel who have major command responsibilities. This concern has become more important in recent years since the findings that complex electronic systems can be rendered inoperative by very high doses of radiation. Thus it is necessary to maintain dependence on the human being. It is quite possible that even moderately high doses or dose rates could produce impairment of cognitive processes either of an obvious or of a subtle nature which in moments of stress would impair or defeat a military operation. In order to gain understanding of such possible changes it is necessary to seek changes in cognitive processes and decrease in the capability to perform highly technical processes.

These problems are difficult to solve. The studies can only be carried out using human subjects. There are relatively few tests which seem capable of yielding useful information.

In cooperation with the Department of Psychiatry a program has been started which may yield some of these answers. The tests are administered in the same way as in Work Unit A, i.e. in the pre- and post-radiation periods. During the pre-radiation period the tests are done in conjunction with the episodes of sham irradiation.

Certain psychological tests are performed in order to obtain an estimate of the subject's intelligence and personality structure. These include the Reitan Trail Making Test, Wechsler-Bellevue Intelligence Scale, the PAT and Par test.

Changes in cognitive though processes are being studied by a method of verbal sampling. This technique is particularly useful since it requires no training or adaptation by the subject. At each interview the subject merely talks for five minutes about anything of interest or concern and the material is recorded on tape for subsequent analysis. These interviews are then analyzed for depression, hope, anxiety and clinical impression.

Two such interviews are obtained prior to any irradiation event. They are obtained immediately before and after each sham irradiation and similarly at the time of actual exposure. The tests are administered again two weeks after radiation.

These studies will then be analyzed to determine changes with dose and with total vs. partial body radiation and for differences between upper and lower body radiation.

Bibliography

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4. Adams, W.S., Davis, F. and Nakatani, H. Purin and Pyrimidine Excretion in Normal and Leukemic Subjects. Amer. J. Med., 28:726, 1960.

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BUDGETS

Personnel	% total effort		Amount
Internist	30%		4,500
Radiation therapist	5%		1,500
Physicist	3%		600
Biochemist	90%		14,008
Technician	100%		5,000
Technician	50%		3,000
Laboratory aide	50%		1,836
Medical illustrator			650
Secretary	66%		4,504
Psychiatrist	8%		1,000
Research Psychologist	37%		3,600
Research Technician	50%		3,000
		$	43,198
	13% Staff benefits		5,616
		$	48,814
Equipment			1,000
Consumable supplies			4,300
Consultant			1,000
Travel			2,000
	Total Direct Costs	$	57,114
Overhead	33% Salaries		14,255
	TOTAL	$	71,369