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To

THE DEPARTMENT OF DEFENSE

Armed Forces Special Weapons Project

Contract No. DA-49-007-MD-533

A PROPOSAL FOR THE CONTINUATION OF THE STUDY OF THE POST-IRRADIATION SYNDROME IN HUMANS

Period: April 1, 1955 - March 31, 1956

Submitted by

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Renewal Proposal

RESEARCH PLAN

A. Specific Aim:

To study the post-irradiation syndrome in man: 1) To establish the natural history of the syndrome by clinical observation, hematologic measurements, and biochemical determinations, 2) To define the mechanisms of the changes with the view of devising possible therapeutic modalities, 3) In certain situations, to extend the study to dogs, where high doses may be given.

B. Method of Procedure:

Patients at the Memorial Center with widespread cancer will be selected for study. No patient showing marked biochemical evidence of hepatic or renal malfunction nor with evidence of bone marrow impairment will be included in the series. The 1000 Kw, G. E. resonant generator will be used for all exposures. After appropriate base line studies, patients will be irradiated and then followed for a minimum of three weeks. If clinical or objective evidence of severe damage occurs the patients will be followed until the situation is corrected.

1. Hematological, coproporphyrin and radioactive iron studies.

Daily measurement of the formed elements of the blood will be done for several days prior to irradiation and for at least four weeks thereafter. A few patients will be studied with particular reference to prior courses of "radiomimetic" drug therapy. (Details of the significance of this study are given in the Annual Report.) Bone marrows will be done prior to chemotherapy, at the maximum reaction as judged by peripheral

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counts, when recovery is complete, and prior to total body irradiation. Bone marrows will be done post-irradiation at intervals as indicated by the clinical situation and the peripheral counts.

Coproporphyrin studies will be continued at somewhat lower priority. Though increased coproporphyrin excretion has not been a consistent finding, certain facets are worthy of further investigation. The dependence on previous therapy, such as systemic chemotherapeutic agents, and endocrine status will be examined. It is hoped that adrenalectomized patients may be obtained for investigation so that stress reactions may be eliminated. Urinary 17-ketosteroid determinations will be done on all patients in an effort to correlate coproporphyrin excretion with stress reaction.

Radioactive iron uptake has been shown to be an indicator of radiation damage(1) and may be used as indication of heme synthesis(2). Radioactive iron uptake studies will be done in the control period and at intervals post-irradiation. A correlation will be made with the urinary coproporphyrin.

2. Lipoprotein studies.

Prior to the experiments of the last year, it was not known whether the serum lipoprotein would be altered by radiation or on which day any change might occur. Therefore, detailed analysis did not seem justified. Almost every patient who received a total body dose greater than 120 r showed changes on the third day post-irradiation. Moreover, patients developing a severe thrombocytopenia and hemorrhagic tendencies showed changes in the serum lipoprotein pattern at that time

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indicative of increased "clearing factor" activity. More detailed studies seem to be indicated at these periods and prior to irradiation. Two procedures are suggested:

a. The alpha and beta lipoproteins will be separated by cold ethanol fractionation (Method 10 of Cohn, et al). The lipoproteins of density less than 1.063, which are in the beta fraction, will be separated and studied in the ultracentrifuge, and all fractions will be analyzed for cholesterol and phospholipids. Detailed procedures have been published(3).

b. The clearing of the plasma lipoproteins after the ingestion of a standard fat meal will be determined.

3. Electrolyte studies.

Alterations in electrolyte and water transport mechanisms in the dog bowel following irradiation will be studied further, using the techniques developed during the past year.

The acute 3 - 5 day death occurring in mice, rats and dogs given doses of 1,000 to 2,000 r is thought to be due to fluid and electrolyte imbalance(4); however, no systematic attempt to define this syndrome has been reported. If the early death is due to fluid and electrolyte imbalance, therapeutic modalities are available to prevent the early "gastro-intestinal" death.

After control studies dogs will be given doses of x-rays in the range of 1,500 r. In the control period and at 12-hour intervals following irradiation, blood samples will be analyzed for pH, Na, K, Cl,

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CO_2, and PO_4. Blood urea nitrogen and the hematocrit will be determined to establish the degree of hydration and an estimate of the glomerular filtration rate. Once the nature of the syndrome has been established, appropriate studies will be performed to measure the total body water, Na, and K, and the distribution of electrolytes in the intracellular and extracellular spaces as measured by para-aminohypurate and inulin. Should it appear that elevated NH_4 from tissue breakdown should play a role in this mechanism of death, methods for measuring plasma NH_4 are available.

Survival studies utilizing energetic fluid and electrolyte replacement will be carried out.

Fine structure of electrolyte alterations in humans during and immediately following irradiation will be measured.

REFERENCES

(1) Hennessy, T. G., and Huff, R. L.; PROCEEDINGS SOC. EXPT. BIO. MED.; 73, 436, 1950.

(2) Walsh, R. S., Thomas, E. D., Chow, S. K., Fluharty, R. G., and Finch, C. A.; SCIENCE 110, 396, 1949.

(3) Barclay, M., Cogin, G. E., Escher, G. C., Kaufman, R. J., Kidder, E. D., and Petermann, M. L.; CANCER 8:253, 1955.

(4) Brecher, G. and Smith, W. W.; RADIATION RESEARCH SOC., May 1955 (Abst.)

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A Proposal for the Study of the Post-Irradiation Syndrome in Humans

Dr. J. J. Nickson

Budget for the Year Beginning April 1, 1955 $19,977

		Cost per Item	Category Totals	Study Totals
I. General				
Personnel:	Secretary (1/2 time)	$1,500	$1,500	
Equipment:	Jig for holding patients during irradiation.	400	400	$ 1,900
II. Hematology, Coproporphyrin, Radio Iron Studies				
Personnel:	Technician	3,000	3,000	
Supplies :	30 lbs. ether/wk.	140		
	Glassware	150		
	Radioactive Iron	200		
			490	$ 3,490
III. Lipoprotein Studies				
Personnel:	Technician	3,180	3,180	
Supplies :	2 ultracentrifuge cells	240		
	1/2 Maintenance Contract, Ultracentrifuge repair	60		
	Photography and Illustration.	25		
	Temperature Regulator	50		
			375	$ 3,555
IV. Electrolyte Studies				
Personnel:	Research Assistant	3,763	3,763	
Supplies :	20 dogs at $15 each	300		
	Animal Maintenance (Indefinite period)	400		
	Chemicals and glassware	200		
	Na^{24} , K^{42} (20 shipments)	800		
			1,700	$ 5,463
V. Patient Care				
For 10 patients:	Hospitalization, $17/patient/day for 12 days	2,040	2,040	
	Additional Biochemical determinations	1,400	1,400	$ 3,440
VI. Travel to Meetings of Importance to This Investigation				650
		SUBTOTAL		$18,498
		OVERHEAD, 8% of subtotal		1,479
		GRAND TOTAL		$19,977

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JUSTIFICATION OF INCREASED BUDGETARY REQUEST

The budget submitted for the coming year is slightly increased over the budget for the period of 1954-55. This increase is accounted for primarily by the following:

1. Personnel - The need for a part-time secretary, and salary increases in certain technical categories in keeping with institutional policy.

Institution-wide increases in salaries of technical supporting personnel was effected in December 1954 in order to bring salaries in line with those currently offered for similar work elsewhere.

For technicians, the starting salary was raised from $2,500 to $2,820 and the maximum for the category from $3,120 to $3,180. For senior technicians, the starting salary was raised from $2,860 to $3,180 and the maximum for the category from $3,660 to $3,900.

2. Supplies -

a. The additional use of radioactive Na, K and Fe in the various studies.

b. Additional biochemical determinations to define objectively the stress reaction.

3. Equipment - A jig is needed in order to establish better control of the experimental conditions under which patients are irradiated, especially position which, in the past, may have varied from patient to patient.

It is felt that these are natural outgrowths of the study of the past year and are useful additions to defining the post-irradiation syndrome in humans.

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