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APPLICATION FOR AID IN THE INVESTIGATION OF THE BIOLOGICAL
EFFECTS OF RADIOACTIVE SULFUR

Med 624

I. GENERAL OBJECTIVES

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Dr. Jaffe and I began some studies with radioactive sulfur several months ago. However, the cost of the isotope, its synthesis into organic form, and the equipment necessary for the studies are so expensive that we must have financial aid to pursue our plans. We believe that highly important information may be obtained by studying S 35 with reference to (a) its irradiational effects in the body, (b) its usefulness in the treatment of hyperadrenocorticism and hypertension, and (c) its aid in studying fundamental aspects of sulfur metabolism.

II. OUTLINE OF PROCEDURES

(General Procedures)

- A. The demonstration that RaS will concentrate, if not localize completely, in a specific form in the adrenal gland.

Accordingly, it will be necessary to test various forms of sulfur and its compounds and thus determine if there is a specific structural type which will preferentially localize in the adrenal gland. Two types of compounds are suggested by the physiological character of the adrenals: (a) S-amino acids and (b) S-lipids. (A possible modification may be the use of a substance preferentially localizing in the gland and which further possesses a high affinity for sulfur, e.g. heavy metal derivatives.)

- B. The demonstration that a compound fulfilling the requirement of preferential concentration and containing the radioisotope is capable of supplying an adequate dosage of radiation to affect physiological activity.

(Specific Procedures)

- C. General Distribution (Tissue) Studies: Degradative digestions of various tissues, organs and glands and radio-assay of the RaS. These data will allow the evaluation of the relative concentration of the test compounds or their derivative forms in the tissues and degree of preferential localization in the adrenals.
- D. Histological examination of the various tissues and gross findings will allow evaluation of the radiation effects on the physiological processes.

III. POSSIBLE EXTENSIONS OF THE PRINCIPAL PROBLEM

- A. Detailed studies of the correlation of sulfur metabolism and endocrine functions.

III. (Cont'd)

B. Clinical evaluation

IV. ESSENTIAL CRITERIA WHICH MUST BE SATISFIED FOR THE UTILIZATION OF RaS IN TISSUE RADIATION THERAPY

- A. The compound selected must possess a high specific "affinity" for the tissue either in a chemical sense or in a sense of greater susceptibility of the tissue for the compound.
- B. The therapeutic efficiency must be high
 - 1. A sufficiently rapid uptake of the compound by the tissue should exist and its retention should be high.
 - 2. Sufficient radiation energy must be available to effect the therapy at or below the level of saturation of the compound in the tissue.
 - 3. The compound must be "non-toxic" at the effective radiation dosage level except for specific damaging effect desired.

V. EXPECTED DURATION

- A. Development of techniques and organic synthesis: 1 year
- B. Outlined investigations, extensions and possible modifications in plan of attack: 1 to 3 years.

VI. PRESENT FACILITIES

- A. Controlled radioactive research unit with standard equipment for radio-assay.
- B. Consultation facilities with Harvard, M.I.T., and Tracerlab on equipment, techniques and control.

VII. ADDITIONAL FACILITIES NEEDED

- A. Contracting for organic syntheses
- B. Improved equipment for the assay of S 35.

VIII. QUALIFICATIONS FOR PERFORMING THE PROPOSED INVESTIGATIONS

I am an Assistant Professor of Medicine at the Harvard Medical School. After graduating from Johns Hopkins Medical School in 1934, I interned for one year in Pathology and then for four years in Medicine. I then was a research fellow in Medicine at the Massachusetts General Hospital for one year and during the subsequent seven years I have had a laboratory at the Thorndike Memorial Laboratory, engaged, full time, in the investigation of metabolic diseases. The results of these studies have appeared in approximately 60 publications.

My first experience with isotopes began in 1940 when I began a series of studies on the distribution of radioactive potassium in a variety of endocrine disorders. More recently, Dr. Jaffe and I have conducted intensive studies with I 131. We have used it as an indicator of thyroid function when rats and human beings are exposed

to a great variety of severe forms of stress. We have also used it to study the effect of a series of antithyroid compounds. Moreover, we have used it in the treatment of more than 100 patients with thyrotoxicosis and a few patients with cancer of the thyroid. The results of these studies will be published soon.

Dr. Jaffe received a B.S. degree from the Massachusetts Institute of Technology in 1939 and a Ph.D. degree in Biochemistry in 1943. As a student he published two papers in enzyme chemistry, with Dr. I. W. Sizer and Dr. E. S. Gould. He served in the Armed Forces from 1943-46, having charge of the chemistry laboratory of a general hospital. In 1946 he came to work with me at the Thorndike, having been highly recommended by Drs. Francis Schmidt, Irwin Sizer and Bernard Gould. He is one of the best chemists that we have had at the Thorndike Laboratory.

In addition to Dr. Jaffe and me, a well-qualified technician will be working on the project. It will require all of her time, about one-half of Dr. Jaffe's time and about one third of mine.

IX. COST OF INVESTIGATIONS

We estimate the cost of the investigations for the first year to be as follows:

A. Salary of Dr. H. Jaffe	\$ 2,000
Salary of Dr. R. H. Williams	2,000
Salary of technician	1,900
Pensions for above	236
B. Capital equipment	
Automatic sample changer (less the SC 9a sample changer and preamplifier)	1,250
Printing timer	450
4 S.M. tubes	150
C. Materials, such as planchettes, isotopes, synthesis of sulfur into organic form	1,800
D. Other expenses	
Express	50
Telephone and telegraph	25
Travel	75
E. Provisional overhead (computed at 8 1/2 per cent of total estimated cost)	820
F. Additional overhead (computed at 6 3/4 per cent of total estimated cost)	
<u>Total estimated cost</u>	<u>671</u> <u>\$11,427</u>