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April 15, 1937

Research request for the year 1937-38 -- Dr. Joseph C. Hamilton.

Amount requested: \$250.00.

Problems to be studied:

1. Continuation of the present clinical studies with radio-sodium in the treatment of leukemia.
2. Determination of the rates of absorption and excretion, and concentration in the various body fluids of the following elements, or their compounds, in which radioactivity can be satisfactorily induced, such as: Na, K, Cu, Ag, Au, Mg, Ca, Sr, Zn, Mg, Pb, Bi, C, Hg, P, As, Sb, Bi, O<sub>2</sub>, S, Cl, Br, I, and Fe when administered orally, hypodermically, intravenously, and rectally to normal human subjects and to individuals suffering from pathological states for which certain of these substances are to be given for therapeutic purposes.

The rates of absorption will be measured with the aid of a Geiger Counter which permits accurate determination of exceedingly minute quantities of radioactive material and the detection of such substances in the blood stream within a few seconds after they have been administered. The activity of body fluids such as: blood, urine, spinal fluid, sweat, saliva, gastric juice, and feces, may be measured with an electroscope.

By this method it is possible to follow more closely the metabolism of many of the described substances than has been previously feasible. The total sodium content of a living human subject has been calculated by giving the patient radio-sodium and then taking samples of urine, spinal fluid, and blood and determining the radioactivity and the total sodium content of the latter. At the time the samples were taken the radioactivity of the patient was measured and from those values the total body sodium was estimated in the following manner:

$$\frac{\text{activity of subject at T1}}{\text{activity of sample at T1/per cc}} \times \text{X sodium per cc in sample} = \text{total body sodium}$$

The average of eight determinations was 36.0 Gm Na for a 55 kg. man. Similar studies are to be done using other elements which are present in the body in ionic form, such as K and the halogen group. It is planned to observe the rate and degree of concentration of Br<sup>-</sup> and I<sup>-</sup> in the spinal fluid in normal humans and individuals suffering from C.S. luos.

3. Investigation of the degrees of toxicity of the above described radioactive elements in animals with particular attention to the effect upon the haemopoietic system. In addition animals in whom various malignant states have been induced will be treated with these substances. The concentration of the artificial radio-elements will be measured in the organs such as: the Ca, P, Pb, and Mg in the bones, Fe, N, and Pa in the erythrocytes, etc.

4. The use of the radio-elements other than radio-sodium in the treatment of the lymphoma, and other malignant states which tend to become widely disseminated through the body. For example, the use of radio-phosphorus in myelogenous leukemia and multiple myeloma has been planned. At present it is difficult to predict what substances listed above will be used since the data

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2 - Hamilton

concerning half-life periods, character and energy of radiations, and the ease of preparation is not complete for all the elements mentioned.

The funds are to be expended in the following manner:

- a) \$125.00 for chemical analysis of the body fluids following the administration of the radio-elements, in order to study the metabolism of the substances to be investigated.
- b) \$110.00 for the procurement and maintenance of animals. (It is felt that most of the work will be done with the small laboratory animals.)
- c) \$15.00 for the construction of a suitable container for the handling and transportation of the radioactive material to and from the hospital and in the wards.

All of the problems described are to be done under the direction and advice of Dr. Robert S. Stone, Dr. Wm. J. Kerr and Professor Ernest O. Lawrence.

Submitted by  
Joseph G. Hamilton, M.D.

Jch/h

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April 15, 1937

Report on research work for the year 1936-37 -- Dr. Joseph G. Hamilton.

Amount granted: \$100.00.

Problem: Studies on the use of Radio-Sodium.

Work done on problem previous to request for support from Breon Fund:

Radio-sodium became available for clinical study at the University of California Hospital in the Spring of 1936. It was felt that many of the disadvantages of internal radium therapy could be avoided by the use of radio-sodium, since this latter substance does not tend to become fixed in the body tissues and the duration of its effect is limited by its short half-life of only 14.8 hours.

Initial investigations were made of the clinical effect and the rate of excretion of the radio-sodium following its intravenous administration to 2 human leukemic subjects. An approximately isotonic solution of sodium chloride was used in each experiment. Each sample was measured with an electroscope just prior to administration and periodic determinations of the degree of activity of the patient's body was carried out. At the same time all the stool and urine samples were collected and their activities measured. The activity of 100 cc. of blood from the second patient was determined. The first patient received 15 m.e. (milli-Curie equivalents) of radio-sodium and the measured and theoretical decay curves were shown on a chart. The theoretical values were computed from the first measurement of the patient's activity. To the second patient were administered 15 m.e. of radio-sodium.

The difference between the activity of the sample of radio-sodium just before administration and the initial activity measurement of the patient is felt to be due to the absorption of the gamma rays by the patient's body. A relatively large proportion of the radio-sodium was eliminated in the sweat, while in the second case the activity of the sweat was too small to be determined. The interval between the actual and theoretical decay curves in each experiment is felt to represent the quantity of radio-sodium lost through the various channels of elimination. This view is borne out by the fact that the quantities excreted by each subject correspond approximately to the difference between the two curves shown in Figs. 1 and 2 of the attached reprint.

Work done with funds made available in the Spring of 1937.

One patient was given 126 m.e. of radio-sodium by mouth and the same routine studies carried out as before. In addition 3 samples each of blood and urine, and 2 of spinal fluid were taken during the experiment, their radio-activities measured and then they were sent to Dr. David Greenberg, Department of Biochemistry, for sodium analysis.

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Hamilton (report)

The sodium values were used as described in the following report to determine the total body sodium.

The cost for these determinations was \$15.00. Two more experiments are planned for the next three months and the results are to be written and submitted for publication.

Joseph C. Hamilton, M.D.

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April 19, 1938.  
April 19, 1938.

Research request for the year 1938-39 -- Jos. G. Hamilton

Amount requested: \$250.00.

Problems to be studied:

1. Measurement of circulation time in normal human subjects and patients with circulatory disturbances. This will be done by administering a small quantity of Radio-Sodium as isotonic NaCl in sterile solution intravenously, while in the opposite hand is held, within a large lead case, the counter tube of a Geiger Counter. The interval of time from the injection of the Radio-Sodium to the time when the hand within the lead case becomes radioactive will represent the interval required for the blood to travel back to the heart and out to the opposite extremity.
2. The rates of absorption of Calcium, Magnesium, Phosphorus, and carbon, (as NaHCO<sub>3</sub>) following oral administration; and Nitrogen and Carbon (as CO<sub>2</sub>) following inhalation.
3. A study of the deposition of Iodine in the thyroid gland which will soon be possible since a new Radio-iodine has been discovered which has a long "Half-life". This new Radio-Isotope can be measured for a period of several weeks and therefore could be given to patients a week or more prior to a thyroidectomy and the proportion deposited measured after the gland has been removed.
4. Rates of diffusion of various of the Radio-Elements following parenteral administration.
5. Continuation of the present work with particular reference to the application of the rates of absorption and excretion as a diagnostic tool.

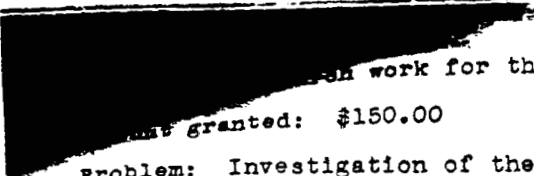
The funds are to be expended in the following manner:

1. Chemicals and Materials for preparation of the Radio Elements used \$150.00.
2. Procurement and Maintenance of Laboratory Animals \$75.00.
3. Expenses incident to publication; such as, photographs, slides, graph paper, etc. \$25.00.

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1938

work for the year 1937-38 -- Jos. G. Hamilton

granted: \$150.00

**Problem:** Investigation of the rates of absorption and excretion of certain of the artificially prepared Radio-Elements in health and disease. A study of the immediate physiological effect of these substances when introduced directly into the blood stream.

1. The rates of absorption of Sodium, Potassium, Chlorine, Bromine, and Iodine have been studied. Radio-Sodium was first used and in the enclosed reprint a description of the technique employed and the results observed may be found. The same methods were applied to observe the rates of absorption of the other four Radio-Elements. In this second group of experiments 8 normal human subjects were used for each Radio-Element and the equivalent quantities of each substance administered to the subjects in the fasting state. At the present time composite curves are being prepared for the purpose of comparison. In addition the rates of absorption of Sodium and Potassium were studied in five cases of Cushing's Disease and one case of Addison's Disease, similar curves are now also being made for this group.
2. The rates of excretion of the Sodium and Potassium given to the patients were measured. This was also done for the normal subjects in the case of Sodium, Potassium, and Bromine. This could not be done in the case of Chlorine and Iodine due to their short "Half-life" periods.
3. With the assistance of Drs. Chauncey Leake and Gordon Alles of the Dept. of Pharmacology the immediate physiological effect of several of the Radio-Elements was studied. The method employed was the observation of the change of blood pressure in dogs following the intra-arterial injection of isotonic solutions of these substances as compared with their non-radioactive isotopes. A definite effect was noted with Radio-Potassium and to a less definite degree with Radio-Rubidium. No effect was noted with Radio-Sodium and Radio-Emanation, although these substances were far more strongly radioactive than the Potassium and Rubidium. It has been planned to repeat these experiments within the next two weeks with more intense samples of Radio-Rubidium and Radio-Potassium before making a report.
4. Chemical determinations of the Sodium and Potassium in the urine collected from the normal subjects and patients is being done for the purpose of calculating the total body Sodium and Potassium in these individuals. Expense is being defrayed by the Federal Government as a WPA project.

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Requests for research funds for the year 1938-39 -- Roberto Escanilla, M.D.

Amount requested: \$75.00.

Report on work during 1937-38:

With the help of the money granted last year (\$25.00), several patients with Simmonds' Disease have been followed carefully. At present one paper is in press in California and Western Medicine on this subject, reporting several cases of Simmonds' Disease with early impressions on the effects of treatment. At least three others are contemplated.

Problem to be investigated:

1. My work on the clinical investigation of pituitary disease, particularly Simmonds' Disease, is to be continued. Further studies on myxedema will also be included as the opportunity arises, particularly with regard to internal manifestations.
2. Amount requested: \$75.00.
3. This money would be used when necessary to pay for the expensive endocrine preparations which are needed for treatment in continuing these studies.

Submitted by Dr. Roberto Escanilla.

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Annual Report for 1938-1939; M. H. Soley.

The final group of reports are in preparation. Some of the manuscripts are already finished;

1. Reliability of measurement of basal respiratory functions in adolescent children compared with adults. M. H. Soley and M. H. Soley.
2. Absorption of radio-active iodine by the thyroid gland after oral and intravenous administration. M. H. Soley and J. G. Hamilton.
3. Decrement of respiratory volume with varying periods of rest and position. M. H. Soley and M. W. Shock.
4. A new method of enhancing aortic and mitral diastolic murmurs, confirmed by phonocardiography. M. H. Soley, C. A. Noble and M. Goldman.

Most of the work outlined above already published, in press, or in preparation is self-explanatory. It should be mentioned, however, that the study of thyroid physiology and iodine metabolism by the use of radio-active iodine is as yet in its infancy. Also, while we have completed some of the studies on carbon dioxide response in normal individuals we still have further work to do on this subject. Finally, the work on the physiological manifestations of anxiety is still in progress, although it has been temporarily suspended until the Tissot metabolism machine which has just been delivered is set up and in use.

I would like to express Dr. Shock's and my appreciation for the additional funds of \$200.00 granted this year from the Breon Fund, since these funds have enabled us to carry on the work that would have otherwise been incomplete.

Respectfully submitted,

Mayo H. Soley, M.D.

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Report on research work for the year 1938-39 -- Jos. G. Hamilton.

Amount granted; \$250.00

Problem:

- 1 a. The metabolism of iodine following oral administration in a group of normal human subjects and patients suffering from various types of thyroid disease has been investigated by the use of a newly discovered radioactive isotope of iodine. This work has been conducted with the collaboration of Dr. Mayo H. Soley of the Department of Medicine.

The rates of excretion of iodine in the urine and feces have been quantitatively measured in both the normal subjects and the thyroid patients. These excretion studies were conducted over a period of five days with each individual. The thyroid glands were obtained from the patients who came to surgery and both the total iodine content and the amount of radio-iodine present were quantitatively determined. In all of these cases the glands were removed from 48 to 53 hours after administration of the radio-iodine.

It has been found that the rates of excretion in normal subjects and patients with toxic and non-toxic goiters were without significant variations. The rates of excretion in two patients with spontaneous myxedema were much slower than in any of the other group of patients, and normal subjects. The uptake of the radio-iodine in the thyroid gland at the end of the two day period following its administration varied from one to nine per cent in a group of ten patients with toxic goiters. No definite correlation to the gross pathology was observed and in two cases which received no Lugol's Solution the radio-iodine uptake fell within the above range. Two cases of non-toxic nodular goiters who had received no Lugol's Solution were studied by this method and the gland of the first patient took up 17.5 per cent of the radio-iodine at the end of the two day period, while in the second case the uptake was 12.5 per cent under the same experimental conditions. One case of a patient with a small non-toxic diffuse hyperplasia and who had received Lugol's Solution prior to the administration of the radio-iodine was investigated by this method and the gland only took up .07 per cent of the radio-iodine. The radio-iodine content was determined in one case of thyroid carcinoma and the uptake in the two day period was found to be .39 per cent.

This material is now being written up for publication and will be read at the meeting of the Federated Societies at Toronto, Canada, April 26-29, 1939.

- 1 b. The rate of uptake of radio-iodine in the thyroid gland is now being investigated by the use of a Geiger counter. In these experiments the radio-iodine is given to the patient or subject by mouth and then the radioactivity of the gland is determined at frequent intervals thereafter. By this method it is possible to measure directly the rapidity

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with which radio-iodine is taken up by the gland and then the rate that the radio-iodine is released from the gland. This procedure permits us to follow the metabolic activity of the gland without surgical extirpation. Furthermore, the "half-life" period of the radio-iodine used for these experiments is eight days which makes it possible to carry out these experiments for a period of time up to a month. Since this project has just been started it can only be said at this time that the method is practical and that after the second day following the administration of the radio-iodine it is discharged quite slowly from the thyroid.

- 1 c. The comparison of uptake of radio-iodine into the thyroid gland of rats following intragastric and intravenous administration has been made. In two groups of five animals it was found that at the end of two hours the glands of the animals receiving the radio-iodine by vein took up twice as much of the radio-iodine as the animals which had received it by way of the digestive tract. These studies will be repeated upon a larger group of animals, some of which will have artificially induced thyroid hyperplasia.
2. Measurement of the circulation time in normal human subjects and patients with cardio-vascular disturbances has been measured in a group of over 60 individuals by the use of radio-sodium. This is done by administering a small quantity of radio-sodium as isotonic NaCl in sterile solution intravenously, while in the opposite hand is held, within a large lead case, the counter tube of a Geiger Counter. The interval of time from the injection of the radio-sodium to the time when the hand within the lead case becomes radioactive will represent the interval required for the blood to travel back to the heart and out to the opposite extremity. In each individual the radio-sodium circulation time was compared with the arm to tongue time by the use of desoholin. This work has been conducted with the collaboration of Dr. Espey Cannon of the Department of Medicine.

It has been found, as is to be expected, that the circulation time is prolonged in the majority of the pathological group and that the deviation from the normal group is greatest in those patients having the most extensive myocardial damage. These observed effects were noted with both the radio-sodium and desoholin; but it is felt that the radio-sodium method gave more accurate information due to the fact that the procedure is completely objective.

During these experiments it was observed that in the patients with severe myocardial damage the rate of increase of radioactivity in the hand holding the counter tube was much slower than in the normal group or the patient with less severe heart lesions. By the use of suitable electrical and photographic equipment it has been possible to obtain a continuous and permanent record of this phenomena in a group of cardiac patients and normals comprising 20 individuals. All of this data is now being analyzed and will be soon submitted for publication.

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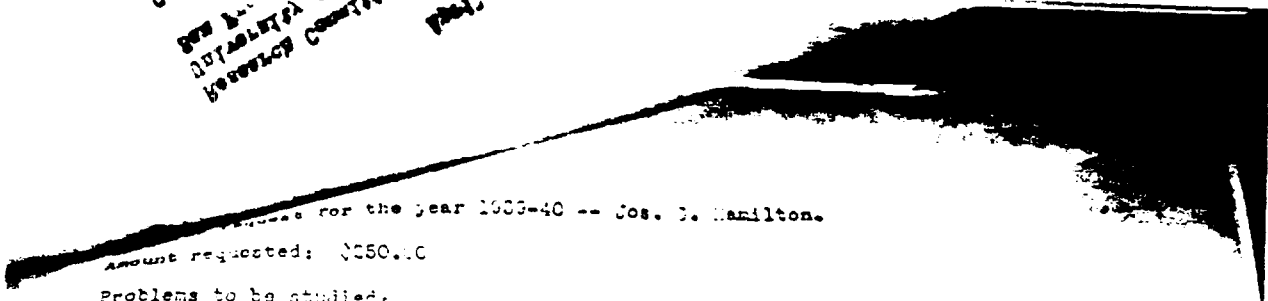
3. Information concerning the rates of absorption of sodium, potassium, chlorine, bromine and iodine in normal human subjects is included in the enclosed reprint.
4. The results of studies upon the immediate physiological effects of several of the artificially prepared radioactive elements and radium emanation is given in the enclosed reprint.

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Amount requested: \$350.00

Problems to be studied:

1. Continuation of present studies of iodine metabolism with particular reference to the correlation of the experimental findings to the clinical, pathological, and biochemical changes observed in diseases of the thyroid.
2. The determination of the rates of absorption, excretion and deposition in the thyroid gland of di-iodotyrosine and thyroxine in normal human beings and patients with various types of thyroid disturbances. This will be accomplished by the synthesis of di-iodotyrosine and thyroxine from radio-iodine.
3. Separation of the inorganic and organic fractions of iodine from the thyroid gland in patients who have previously been given radio-iodine. The organic fraction will be separated into the acid soluble and acid insoluble components which enables one to directly measure the amount of di-iodotyrosine and thyroxine synthesized by the gland as well as the inorganic fraction.
4. Investigation of the possibility of synthesis of bromine organic compounds in the thyroid in different types of goiter, by the use of radio-bromine.
5. The use of radio-carbon as carbon dioxide for the study of the metabolism of that substance.

The funds are to be expended in the following manner.

1. Chemicals and materials for the preparation of the radio-elements and compounds to be synthesized from them for the above studies. \$150.00
2. Special equipment such as lead shields, etc. \$75.00
3. Expense incident to publication; such as, photographs, slides, graph paper, etc. \$25.00

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