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DIVISION OF PEDIATRICS

REQUESTS FOR RESEARCH FUNDS, 1941 - 1942

1. $500.00 for the continuation of studies on experimental diabetes in the dog by Dr. Francis Scott Smyth and Dr. Mary B. Olney.

2. $477.00 for continuation of study of bone growth and factors influencing mineralization by Dr. Amos Christie. (See letter.)

3. $350.00 for Geiger-Müller Counter for use of Dr. William A. Reilly in his studies of iodine metabolism in the thyroid gland. Doctor Reilly is also seeking a fund of from three to five hundred dollars for the quantitative study of estrogen excretion in normal children and in girls with abnormalities of the menses or with endocrinopathies. He hopes to receive a grant from the Council of Pediatric Research for this latter study.

4. Dr. William C. Deamer and Dr. George Bates have received a grant from the Committee of the Fleischner Memorial Endowment Fund of $1,200.00 for the continuation of their study of tetanus antitoxin level in infants following prophylaxis with combined tetanus-diphtheria alum toxoid. In the past Doctor Bates has received a part time salary from the Com Fund but beginning July 1st he will have a salary of $600.00 a year for part time work from the Fleischner Fund and the balance will be used to cover the cost of guinea-pigs used in their research work at the Cutter Laboratory, the Laboratory supplying a place to work and equipment. (See letter.)

This coming year Doctor Olney and I plan to attack the problem of the dog made diabetic by partial pancreatectomy for the assay of the diabetogenic factor of the hypophysis. Hypophyses in conditions of health and disease will be selected.

We have selected this particular problem to obtain information on the interrelationship of the hypophysis and pancreas.

The work will be done in the surgery of the Animal House and in the Pediatric Chemistry Laboratory. (See slip attached for amount of money requested and details as to proposed use.)

In the past year diabetes has been induced in dogs by total pancreatectomy. These dogs were subject to careful study with regard to the use of insulin, combining protamine with standard insulin. This study was undertaken because of skepticism from some of our Eastern colleagues on our clinical use of this combination. The Lilly Laboratories also implied that such a combination should not be attended by the results we were obtaining and it was with the effort to prove our point that the work was carried on. Our results have attracted considerable attention though it is safe to say that following our initial reports, Wilder and others are using this method of insulin therapy. A report of these studies is to be made to the American Academy of Pediatrics this week.

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April 28, 1941.

Dr. Francis Scott Smyth,

Dear Doctor Smyth:

I would like to request $350.00 from the Research Funds for the purpose of buying a Geiger-Müller Counter to facilitate the study of iodine metabolism in the thyroid gland in children, normal, hypothyroid and hyperthyroid and before and after therapy. These children would be studied by the use of radio-activated iodine detected by a Geiger-Müller Counter.

This problem can be studied with the help of the house staff, the members of which will be instructed in the use of the Geiger-Müller Counter. The radio-iodine will be supplied gratis by the Radiation Laboratory through the cooperation of Dr. E. O. Lawrence and Dr. J. G. Hamilton.

It has been shown by Hamilton and Soley (Am. J. Physiol. November 1940) and by Reilly, Hamilton and Soley (Am. J. Dis. Children read at meeting of Society for Pediatric Research June 1940) that hypothyroid gland takes up only traces of iodine. This was suspected by Marine years ago. Iodine metabolism of the gland was studied in life for the first time in the University of California Hospital. The method radio-iodine plus the Counter will open up a field of fundamental thyroid r research and possibly solve some of the hitherto unknown iodine and the thyroid hormone.

The work will be done preferably in the Out-Patient Department by the house officer. The only available equipment is present Geiger-Müller Counter in Endocrinology Clinic. Dr. Hamilton wishes to keep this for his own use. It belongs to the Crocker Radiation Laboratory. A new Counter can be bought for $350.00 with the guarantee of the Crocker Radiation Laboratory and could be used in the Pediatric Department for other problems of radio-activity.

I have been hoping to obtain from some source, possibly the Council of Pediatric Research, a fund of from three to five hundred dollars for the study of estrogen in the blood and urine of normal and endocrinopathic children, especially girls with particular attention paid to problems of the age of menarche, normal puberty and precocious puberty. There is great need for normal excretion studies as well as those of early puberty.

I have long wanted to study the hormone excretion of children, particularly the adrenal cortical hormone, because so little is known and so much should be investigated in order to answer certain questions of precocious puberty and disturbances of the adrenal cortex. Since we have a personnel interested in endocrine problems and there is urgent need for the solution of these problems the time seems to be ripe for such a study. Doctors Evans and Anderson feel that the problem is too comprehensive and would entail too great expense for them to assume it but consider it worth while if limited to estrogen studies with Dr. Allan Palmer.

The work would be done in the laboratory in the old Medical School building but there is no available equipment. We would need a small colony of mice, quarters and technical assistance. It was suggested that Doctor Palmer's laboratory and staff could take on this work for the Pediatric Department and Doctors Palmer and Lynch as well as yourself are favorably inclined if financing can be arranged. The Council of Pediatric Research was favorably inclined last year to consider distributing $300.00 to such a project. However, the undertaking would require more funds on.

[illegible] miracle a[illegible] though it is safe to say [illegible] Very truly yours, [illegible] are using this method [illegible] of these studies is to be made to the American [illegible]

William AL Reilly, M.D.

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April 28, 1941.

Dr. Francis Scott Smyth,

Dear Doctor Smyth:

Dr. George Bates and I would like to continue our joint study of immunization in infants and children for which we have been granted $1,200.00 by the Committee of the Fleischner Memorial Endowment Fund, half of this to be used for part time salary of Doctor Bates and half for the cost of guinea-pigs, the Cutter Laboratory supplying space and equipment for the research on the guinea-pigs.

This study was undertaken to afford data on the question of the advisability of its routine use in infancy. Over 500 infants have received three injections of combined diphtheria and tetanus alum toxoid in amounts of one cc. The interval between the first and last injections was usually 8 to 10 weeks, sometimes longer. A blood sample is taken two months or more after immunization for the determination of its tetanus antitoxin content and a Schick test done. Standard tetanus toxin was used in antitoxin determinations which were done in guinea-pigs.

Analysis of the data on 134 infants in whom immunization was completed in a period of 8 to 9 weeks shows great variation in tetanus antitoxin response. The poorest response was between 1/100 and 3/100 of a unit of antitoxin per cc. of serum. The best response was between 3 and 10 units. Only four infants showed less than a tenth of a unit of antitoxin. In these four, blood was taken at 10, 13, 25 and 41 weeks respectively after the last dose of toxoid. Two of these four cases were studied again after several months and both were found to have developed more antitoxin. Evidently they formed antitoxin slowly. The usual peak response appeared to occur 8 to 10 weeks after the last injection of toxoid. An analysis of 107 cases studied at this time showed less than a tenth of a unit in only one instance. It was also apparent that an interval of over ten weeks between the first and the last injection led to better response than did shorter intervals.

In interpreting this data it should be remembered that these are the initial responses. The program of tetanus prevention includes a "recall" injection of toxoid at the time of injury or possibly at regular intervals of several years. Reports indicate that such recall injections lead to marked and prompt antitoxin formation within the incubation period of tetanus. Data from the present war suggests that even without the recall injections, immunized soldiers were not likely to get tetanus.

In our cases local reactions were not troublesome although induration, tenderness and redness at the site of injection were frequently encountered. No abscess formation occurred in nearly 1500 injections in infants. Sterile abscesses did form in two girls of 7 years of age who were identical twins.

We obtained 96 per cent negative Schick tests. There was no correlation of positive Schick tests and low tetanus antitoxin titres.

A report on the progress of this work is being made at the meetings of the American Academy of Pediatrics and to the American Pediatric Society at Hot Springs, Virginia, on May 23rd.

Very truly yours,

William C. Deamer, M.D.

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Research request for the year 1941-42 -- Dr. J. G. Hamilton. April 29, 1941

Amount requested: $325.00.

Progress Report -- Dr. J. G. Hamilton

1. Continuation of present work dealing with the study of the iodine metabolism of the thyroid gland in normal subjects and in patients suffering from various types of thyroid disease. [illegible] done, but the results have been published [illegible] in the literature.

2. The possible therapeutic use of radio-iodine in the treatment of thyrotoxicosis. Preliminary work with animals relevant to this problem already has been started and will be described in the following sentences with various types of animal. [illegible] Journal, pp. 135-143, Nov. 1940, Hamilton, J.G.

3. The study of the metabolism of di-iodotyrosine and thyroxine with the aid of radio-hydrogen and radio-iodine. This technique makes it possible to tag both the iodine and the benzene ring of these compounds and thus follow by directly follow the breakdown of di-iodotyrosine and thyroxine in the body as well as to study their synthesis in the thyroid. [illegible] Dr. Hamilton, who developed a new method of quantitative fractionation of the iodine, thyroxine and di-iodotyrosine in the thyroid and other tissues will be available since he is to be a member of the Radiation Laboratory Staff during the next fiscal year. His assistance will considerably expedite this work since many technical difficulties have been overcome. Before these methods of fractionation, [illegible] and quantitative procedure.

A comparison of the above problem represents the application of iodine as a tracer for [illegible] apply radio-iodine as a tracer for [illegible] agent. It is the hope that applicant and his associates have [illegible] the absorption and excretion of iodine in normal subjects and [illegible] with various types of thyroid disease and at [illegible] of iodine in the thyroid gland of these individuals has been observed. Moreover, they have developed a new method which makes it possible to compare the deposition of radioactive iodine in thyroid tissue, to its histological structure with a study of the metabolism of iodine and with that of the recently discovered new element, Element 85, has been made. It might be added at this point that the results of this last procedure were employed by [illegible] the identification of this new element. The iodine in thyroid tissue and its histological structure has been described in this report. The results of these experiments have indicated that the [illegible] fiscal year is to be [illegible] dependent at the Radiation Laboratory and the University Hospital. An [illegible] of radio-iodine and radio-hydrogen will be made available through the cooperation of Prof. E. O. Lawrence and his associates. The necessary equipment for most of the work to be done next year is on hand and in operation. [illegible] some additional equipment with [illegible] together with chemical, photographic supplies, glassware, etc. the iodine seemed to be evenly distributed between the cells and the colloid. Two patients with thyroid carcinoma were included in these series, and in [illegible] was apparently incapable of accumulating [illegible] administered iodine.

Glassware.....	25.00
Photographic supplies.....	25.00
Lantern slides.....	25.00
Miscellaneous.....	25.00
Total...	$325.00

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April 29, 1941

Fraction Report [illegible] Dr. J. G. Hamilton [illegible] year b t as yet has not been reported.

[illegible] of iodine 131 in human thyroid tissue [illegible] been demonstrated.

A. The following items have not only been done, but the results have been published in the current scientific literature [illegible] also noted.

1. Studies in iodine metabolism of the thyroid gland in situ by the use of radio-iodine in normal human subjects and in patients with various types of goiter. Amer. Jour. Physiol. 131:155-163, Nov. 1940. Hamilton, J.G. and Soley, M.H. [illegible] iodine. The uptake of the administered [illegible] increased by this technique, and it

This report not only describes a method for following the iodine metabolism of the thyroid gland in situ, but the results of the experiments described in this report indicate that the iodine metabolism of the thyroids in normal subjects, patients with thyrotoxicosis, endemic goiter, and hypothyroidism without goiter have a definite and consistent pattern which is characteristic of each of the four groups of individuals. It is possible to produce marked pathological changes in the thyroid tissue of these animals without [illegible]

2. A comparison of the metabolism of iodine and bromine 82, (Br-iodine). Proc. Soc. Exp. Biol. and Med. 45:87-89, January 1940. Hamilton, J.G. and Soley, M.H. [illegible] normal thyroid are exceedingly large and many times [illegible] amount of radiation needed to adequately treat [illegible]

A comparison of the elimination of iodine and of bromine 82 [illegible] these two halogens were excreted by guinea pigs [illegible] and in both the kidneys served as the chief channel of elimination. The uptake by the thyroid glands of normal and thyrotoxic guinea pigs of these two halogens was very similar, although the [illegible] by the thyroids of both groups of animals was [illegible]. A method for the measurement [illegible] of tissues has been developed, and the rather [illegible]

3. [illegible] University Calif. Pubs. in Pathol. 2: No. 28 339, 1940. Hamilton, J.G. and Soley, M.H. and Michern, K.

A method for the study of the correlation between the deposition of recently accumulated iodine in thyroid tissue and its histological structure has been described in this report. The results of these experiments have indicated that the pattern of distribution of the recently accumulated iodine is dependent upon the degree of physiological activity of the thyroid tissue. When the tissue has undergone hyperinvolution, the uptake of iodine is limited and appears limited to the cells surrounding the large lakes of colloid. In hyperplastic thyroid tissue the bulk of the accumulated iodine appears to be stored in the colloid. Normal human thyroid tissue seemed to lie between these two extremes, and the iodine seemed to be evenly distributed between the cells and the colloid. Two patients with thyroid carcinoma were included in these series, and in both instances the malignant tissue was apparently incapable of accumulating an appreciable fraction of the administered iodine.

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[illegible] 4. [illegible]

B. Work accomplished during the past year but as yet has not been reported.

1. The uptake of Element 85 in human thyroid tissue has been demonstrated, and its metabolic characteristics were found to resemble closely those of iodine. The excretion of this recently discovered halogen was also noted to be very similar to that of iodine.

2. The uptake of iodine by the thyroid gland in situ has been studied by administering the radio-iodine as a solution of sodium iodide containing less than a total of one microgram of iodine. The uptake of the administered iodine has been found to be greatly increased by this technique, and it offers a better approach for the study of the metabolism of iodine by the thyroid in patients suffering from hyperthyroidism than the procedure employed in previous studies.

3. Large quantities of radio-iodine have been administered to rabbits and to two dogs. It has been observed that it is possible to produce marked pathological changes in the thyroid tissue of these animals without causing appreciable damage to other tissues. This observation is of considerable significance, since the amounts of radiation required to produce marked changes in normal thyroid are exceedingly large and between the times greater than the amount of radiation needed to adequately treat a case of human hyperthyroidism. This work is to be continued before [illegible] are made to employ radio-iodine as a therapeutic agent in the treatment of human hyperthyroidism.

4. A technique has been developed to [illegible] there is no one available radio-hydrogen and radio-iodine. Moreover, a method for the measurement of the radio-hydrogen content of tissues has been developed, and the rather elaborate and expensive equipment needed for this purpose is available and in proper working order.

III. Detail

[illegible] are now engaged in chemotherapeutic [illegible] made possible by a research grant from the Eli Lilly Company. [illegible] very important that the University should back research [illegible] to an extent [illegible] interest and support, if we are to be [illegible] to ask for any further aid of outside individuals or firms.

Respectfully submitted,

[illegible] C. Reed, M.D.

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Request for research funds for the year 1941-42 — Drs. Maye E. Soley and Nathan W. Shock.

Report on research work for the year 1940-41 on Thyroid Physiology in conjunction with Dr. Joseph G. Hamilton — Maye E. Soley.

Amount granted: $200.00.

[illegible] — $150.00) —

[illegible] for work continued with hyper-[illegible] The appended reports indicate [illegible]

For the year 1940-41, $200.00 was requested and granted for further studies in thyroid physiology (in conjunction with Dr. Joseph G. Hamilton). Reprints of the work completed and published this year are appended. The work is being continued.

The amount of $[illegible].00 is requested for continuation of the work on respiratory physiology and effect of [illegible] which still is being carried [illegible] Nathan W. Shock of the Department of Physiology. We have already studied (1) the effect of breathing pure oxygen on the respiratory [illegible] the metabolism of iodine and of [illegible] carbon dioxide. Hamilton and M.E. Soley, [illegible] August, 1940. [illegible] respiratory volume of normal human subjects. (3) The rate of adjustment of respiratory volume to postural changes. [illegible] iodine concentrated in the thyroid after various modes of [illegible]. We are now [illegible] Soley and J.G. Hamilton, [illegible] Pharmacological [illegible] response of [illegible] August, 1940, [illegible] per cent carbon dioxide. This added request above is for necessary technical assistance. In addition to these [illegible] of radioactive iodine in human thyroid glands [illegible] Hamilton, spontaneous [illegible] Maye E. Soley and Karl E. Mishora, [illegible] technical [illegible] available and which is being continuously employed.

Studies in iodine metabolism of the thyroid gland in situ by the use of radioiodine in normal subjects and in patients with various types of goiter. J.G. Hamilton and M.E. Soley, Amer. J. Physiology, 131: 135-145, November, 1940.

The rate of respiratory adjustment to postural changes. Maye E. Soley and Nathan W. Shock, Amer. J. Physiology, [illegible], Oct. 1940.

Other publications and work by Dr. M.E. Soley — [illegible] respiratory response of normal subjects to carbon dioxide. [illegible] Shock and Maye E. "New" drugs: Recent advances in pharmacology and therapeutics. (with Alice E. Lignire, Amer. J. Nursing, 40:755-758, July, 1940.

Carbon dioxid therapy. Maye E. Soley, Karolina [illegible] and Nathan W. [illegible]

A study of [illegible] to be presented at the Association for the Study of Internal Secretions, May 1, 1941. The manuscript will be ready for departmental judgment within one or two months.

In conjunction with Dr. Karl E. Mishora, some 500 patients with various types of thyroid disease are being reviewed from both the clinical and pathological standpoints. This work will require another six months or longer for completion.

A review of seventy or more cases of Graves' Disease treated with x-ray should be completed within the next few months.

Maye E. Soley, M.D.

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