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October, 1949

TO: All members of the faculty.

FROM: Medical Research Committee, Sub-committee for Faculty Research Programs.

The Dean and the Committee on Medical Research feel it necessary to have a complete, current file of all research projects now in progress, or completed within the last four months. This material will be summarized, mimeographed, and distributed among all members of the faculty.

TITLE: (Please use separate sheet for each problem).
The metabolism and destructive action of astatine (element 85) upon the thyroid gland.

NAMES OF ALL INVESTIGATORS CONNECTED WITH STUDY:

Joseph G. Hamilton, M.D., C.W. Asling, and K. G. Scott

BRIEF SUMMARY: (Approximately 50 words). Work is in progress to study the destructive action of astatine upon the thyroid and to investigate in detail its distribution in the other tissues and organs of the body using small laboratory animals. The significant point of interest in this element is that it accumulates in the thyroid to a degree comparable to that observed with iodine. After completion of detailed tracer studies in animals and a careful evaluation of its radio-toxicity, not only from the point of view of thyroid destruction but the possible injury to other tissues and organs; it is planned to initiate first thyroid uptake and excretion studies in man. If the human and animal experiments provide results which indicate the use of quantities of a therapeutic level in hyperthyroidism are safe from the point of view of the patient, it is planned to extend the studies in this direction.

RESULTS:
A preliminary study has been made upon the destructive effect of astatine on the thyroid of the rat and it has been found that a relatively small amount of this alpha active artificial radio-element provokes a profound degree of destruction to the thyroid gland without any apparent involvement of neighboring structures.

We realize that there is a period when one is between problems, and if you are, there will be nothing to report. Please indicate and return this form before November 15th.

J. G. Hamilton

Signature Joseph G. Hamilton, M.D.

Department Radiology, Experimental Medicine, Medical Physics, and Crocker Laboratory

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cinostasis. In our experiments smears and cultures were taken from liver, kidney, and tumor of cortisone-treated mice, particularly in those in which the tumor growth was inhibited. With very few exceptions no bacteria were found on smears or in cultures. Because of this, infection as a contributory factor was ruled out. The fact that the animals appeared well nourished and continued to gain weight spoke against inanition as a factor in producing the retardation of tumor growth.

Summary. 1. Cortisone, when administered during the first few days after transplantation of carcinoma 755 in C57 mice, has a profound inhibitory effect on growth of the tumor but the tumor remains viable. 2. These effects of cortisone appear to be due to the change in the environment and to the delay in new blood vessel formation about the tumor transplant.

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Received May 10, 1954. P.S.E.B.M., 1954, v86.

Accumulation of Astatine[211] by Thyroid Gland in Man.* (21100)

JOSEPH G. HAMILTON, PATRICIA W. DURBIN, AND MARSHALL W. PARROTT.
From the Division of Medical Physics, Experimental Radiology and Medicine, Crocker Laboratory, University of California, Berkeley and San Francisco.

Astatine[211], which is the last member of the halogen group of elements, has been found to be accumulated by the thyroid glands of experimental animals to a degree similar to that of iodine[131](1-4). Since the average energy of the alpha-particles arising from the disintegration of At[211] is 6.8 Mev and the range in tissue is but 70μ, the degree of specific ionization produced as compared to the beta-particles from I[131] is much greater. The maximum energy of I[131] beta-particles is 0.6 Mev and the range is 2,000 μ. The motivation for these extensive studies with At[211] has been the consideration that the short range and high specific ionization of the alpha-particles of At[211] as compared to the much longer range and more weakly ionizing beta-particles from I[131] might have clinical applications in treatment of thyroid disorders, and in particular hyperthyroidism.

For several years this laboratory has been engaged in a study of the rate and degree of accumulation of both I[131] and At[211] in the thyroid gland and other tissues and organs of experimental animals. The acute and chronic effects of relatively large amounts of these two radiohalogens has also been investigated(2-4). (The results of these experiments

* This work was performed under contract of the University of California under the U. S. Atomic Energy Commission.

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TABLE I. Uptake of (

Age	Sex	Thyroid sa
~40	♀	Left L* Right L Cervical ly node
41	♀	Right L
31	♀	Whole G
35	♀	Whole G
52	♂	Right L
43	♀	Left L
56	♂	Left L Right L
68	♂	Whole G

* L = lobe; G = gla

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Garrison, *et al.*(5).
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TABLE I. Uptake of Orally Administered Astatine^{211} (EKA-Iodine) by Human Thyroid Gland in Various Disorders of That Organ; 8 Patients.

Age	Sex	Thyroid sample	Diagnosis	Time, hr	% At^{211} in sample	Conc. At^{211}, %/g wet tissue	mg I_2 in sample	mg I_2/g wet tissue
~40	♀	Left L*	Grossly normal	15	5.95	.54	32	2.94
		Right L	" "	18	11.85	1.19	30.1	3.01
		Cervical lymph node	Papillary adenocarcinoma	18	<.01	<.001	—	—
41	♀	Right L	Non-toxic metaplasia	13¼	2.85	.27	5.19	.49
31	♀	Whole G	Non-toxic nodular goiter with cyst formation	16¼	6.75	.55	6.34	.53
35	♀	Whole G	Toxic goiter (Lugolized)	15	6.66	.21	13.42	.43
52	♂	Right L	Graves' disease (thyroxine, Lugolized)	18	.172	.017	5.8	.58
43	♀	Left L	Non-toxic nodular goiter	14	6.55	.26	—	—
56	♂	Left L	Grossly normal	13½	4.90	.39	3.78	.50
		Right L	Non-toxic nodular goiter	13½	2.56	.024	7.12	.07
68	♂	Whole G	Non-toxic nodular goiter	22	4.61	.021	28.5	.13

* L = lobe; G = gland.

indicated that it would be safe to attempt tracer studies with At^{211} in patients that were to be subjected to surgical thyroidectomy.

Methods. The At^{211} was prepared by a modification of the procedure described by Garrison, *et al.*(5). Each patient received 50 microcuries of At^{211} in a solution of 25 cc of water at intervals which ranged from 13¼ to 22 hours prior to surgery. Food was withheld for at least 2 hours prior to and after the oral administration of the solution of At^{211}. The patients selected in this group were all more than 30 years of age and in the majority of instances, either a complete thyroidectomy was performed or a remaining lobe of the thyroid gland was removed. The series of 8 patients included one with a papillary adenocarcinoma of the thyroid gland with metastases to the cervical lymph nodes. Following removal, the surgical specimen was immediately weighed and a weighed portion was taken for routine hospital pathological studies while the remainder was brought to this laboratory for the assay of its At^{211} content as well as the total iodine content. Before the specimen was to be subjected to physical and chemical processing, a small representative portion was removed by the use of the dissecting microscope. This specimen was then fixed in 10% neutral formalin, subjected to routine paraffin impregnation and clearing technics, and finally stained with hematoxilin and eosin. Since the decay scheme of A^{211} is associated with the emission of 80 Kev x-rays(6) it was possible to make a relatively accurate measurement of the At^{211} content of the wet sample employing a sodium-iodide thallium iodide activated crystal scintillation counter. Two patients had previously received I^{131} which made this type of determination essentially impossible due to the presence of gamma-rays from I^{131}. The stable iodine content in these studies was determined in a carbon tetrachloride solution by means of a spectrophotometer rather than by titration employing dilute solutions of sodium thiosulfate used in earlier experiments (7). The At^{211} was quantitatively isolated from the specimens by a procedure to be reported elsewhere(8).

Results. The results of the experiments are shown in Table I. A number of observations may be made. The accumulation of At^{211} by the thyroid gland appears to be relatively higher than has been observed in some of the

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previously reported experiments which employed laboratory animals(2). Admittedly, the number of patients is too limited to draw conclusions of a statistical nature, but there certainly does appear to be a trend of a relatively higher uptake. It should be noted that in 3 patients only one lobe of the thyroid gland was available for assay. Moreover, histologically, the thyroid tissue obtained from most of these patients was obviously quite abnormal. A very low uptake of At^{211} was noted in a patient that had had a very unusual series of therapeutic attempts to control his disease and at one stage he had received both thyroxin and Lugol's Solution. In the one patient from whom an entire relatively normal thyroid gland was available, the total uptake was approximately 17% of the administered dose. There appears to be a correlation of the amount of At^{211} accumulated per gram of tissue with the stable iodine content per gram of tissue. In general, when there was a relatively high total iodine content, the astatine content was increased. Finally it should be noted that in the patient with a metastatic papillary adenocarcinoma there was no demonstrable accumulation of At^{211} in the cervical lymph nodes which contained essentially nothing but neoplastic tissue showing no tendency towards the formation of either follicles or colloid.

Discussion. With the exception of the one patient who had received thyroxin, there was quite a good correlation between accumulation of At^{211} per gram of thyroid tissue and the amount of stable iodine present. Attempts to correlate the histological findings in thyroid tissue from the 8 patients with the amount of stable iodine present per gram and the uptake of At^{211} is difficult. The interpretation of the apparent relatively greater concentration in At^{211} by human thyroid tissue as contrasted to animal studies is hard to establish. If this apparent effect can still be demonstrated involving a larger number of patients, then consideration must be given to the factors such as total iodine intake and the possible existence of the species difference. The At^{211} uptake studies in the monkey are too limited to be of any value in attempting to make any comparison with humans presented in this paper (2).

The evaluation of the potential use of At^{211} for the therapy of human thyrotoxicosis must of necessity await much more information derived from both further studies with experimental animals and more extensive human uptake studies.

The chemical properties of astatine are considerably different from those of iodine in many respects(9). An indication of the biochemical differences between astatine and iodine have been presented in another paper. The effect of pre-treatment with propyl thiouracil resulted in the enhancement in the accumulation of At^{211} by a factor of nearly 20 in the thyroid gland in the rat while there was at the same time, a decrease of accumulation of I^{131}(10). With these considerations in mind there is a very remote possibility that certain types of neoplasms of the thyroid gland may more effectively accumulate At^{211} than I^{131}. This concept is purely hypothetical and is based upon the probability that At^- may be oxidized to At^0 more readily than I^- might be oxidized to I_2. It should be emphasized that this phase of the discussion is purely speculative in nature and the very questionable validity of this theory can only be tested by doing tracer studies on many patients suffering from various types of neoplasms of the thyroid gland.

Summary. 1. Accumulation of At^{211} by thyroid gland in patients suffering from various disorders of that organ has been demonstrated. 2. Accumulation of At^{211} by thyroid glands of these patients appears to be relatively higher than has been observed in experiments employing rats. 3. There may be a correlation between the uptake of At^{211} and stable iodine in thyroid tissue. 4. One patient with papillary adenocarcinoma showed no discernible accumulation of At^{211} in metastases present in cervical lymph nodes.

Production of At^{211} was the responsibility of Mr. G. Bernard Rossi and the staff of the 60-inch cyclotron at this laboratory. The continued interest and encouragement by Dr. Robert S. Stone, Dr. Earl R. Miller, the Staff of the Division of Radiology; Dr. Theodore L. Althausen, Dr. Morris E. Dailey, Dr. H. Glenn Bell, Dr. Henry H. Searls, and the surgical staff at the Medical School made the experiments with human subjects possible. The cooperation of

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* This work was
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members of the Division of Pathology was most helpful. Dr. William A. Reilly, of the Medical School, and Director of the Isotope Unit at the Veterans Administration Hospital at Fort Miley made available the use of their facilities for one of the human studies.

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Effect of Pretreatment with Propyl Thiouracil on Accumulation of Astatine[211] by Thyroid Gland of the Rat.* (21101)

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From the Division of Medical Physics, Experimental Radiology and Medicine, Crocker Laboratory, University of California, Berkeley and San Francisco.

It has long been known that a variety of chemical agents act as anti-thyroid drugs to reduce or almost completely prevent the introduction of iodine into tyrosine and subsequently the production of thyroid hormone (1,2). Propyl thiouracil and related anti-thyroid drugs have been used extensively in the treatment of human thyrotoxicosis(3,4). Astatine is the heaviest member of the halogen group, and certain of its chemical properties resemble those of iodine. There are, however, some rather significant dissimilarities(5). Although 18 radioactive isotopes of astatine have been identified, no stable isotopes of this element are known to exist(6). The particular radioisotope used in these and other studies is the 7.3 hour At^{211} which decays by the emission of alpha-particles and 80 Kev rays.†

The capacity of the thyroid gland to concentrate and retain At^{211} has been demonstrated in experimental animals and man (7-10). The present studies were undertaken in order to determine the possible effect of propyl thiouracil upon accumulation and retention of At^{211} by the thyroid gland of the rat and to compare this effect with that obtained using carrier-free I^{131}. It was also hoped that these experiments would help to shed some light on the mode of entry of astatine into the thyroid gland and on its chemical state in that organ.

Methods. The animals employed for these studies were 75-day-old female Sprague-Dawley rats weighing about 165 g. all received from the dealer at the same time and maintained for 3 weeks prior to the start of the experiment on tap water and a pelleted stock diet which is in general use throughout the University of California Radiation Laboratory.‡ Both food and water were given

* This work was performed under contract of the University of California under the U. S. Atomic Energy Commission.

† Sixty per cent of the At^{211} nuclei decays by K-capture to form Po^{211} with a 0.5 second half-life, and 40% decays by alpha-particle emission to form Bi^{207}.

‡ This diet is similar in composition to "Diet 14" developed by the University of California Institute of Experimental Biology and contains a fairly large amount of added iodide. To every 270 lb of feed is added 300 ml of an 0.45% solution of KI.

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