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PHYSIOLOGICAL AND BIOCHEMICAL STUDIES OF ASTATINE^{211} (EKA-IODINE)

By

J. G. Hamilton, P. W. Durbin, C. W. Asling, and M. E. Johnston

Crocker Laboratory
University of California
Berkeley, California, U.S.A.

The use of the cyclotron for the production of heretofore unknown elements resulted in 1940 in the positive identification of element 85, among others, the heaviest of the halogens. The instability of its isotopes, all radioactive, with half lives of from a few seconds to 8.3 hours, earned it the name "astatine" (from the Greek astatos, unstable). For the past eight years part of the program of the Crocker Laboratory 60-inch Cyclotron has been the production of At^{211}, the alpha-particle-emitting 7.3-hour isotope,[1] in quantities sufficient to support a sustained inquiry into its chemical and biological properties.[3] Because of the juxtaposition of astatine and iodine in the periodic table, and because of the relationship of iodine to thyroid physiology, the investigations in this laboratory have been focused upon the selective accumulation of astatine by the thyroid gland.

The discovery of At^{211} by Corson, MacKenzie, and Segre[4] was closely followed by studies of its thyroidal accumulation by Hamilton and Soley.[5] The chemistry of astatine has been discussed by Johnson et al.,[6] and by Garrison et al.[7] At^{211} is selectively accumulated by the thyroid glands of rats, guinea pigs, monkeys, and man, but to a lesser degree than I^{131}.[5,8,9,10] The metabolism and acute toxicity of At^{211} were initially reported by Hamilton et al.[8] It was demonstrated that certain of the nuclear characteristics of At^{211} (70-micron tissue range and 7.3-hour half life) in some respects gave it advantages over I^{131} (2000-micron tissue range and 8.1-day half life) in the capacity to deliver an intensive irradiation in a restricted region.[8,11,13,14]

Further comparative studies of At^{211} and I^{131} have shown that the thyroidal accumulation of both may be increased by pituitary throtrophin (TSH)[5] and by a low-iodine diet,[8] or may be decreased by exogenous thyroxine,[15] by high iodine intake,[8] and by thiocyanate.[15] An interesting exception to these similarities is the enhancement of astatine retention (rather than the lowering of the iodine retention) following the administration of goitrogens of thiouracil type.[10,16]

It is the purpose of this paper to indicate some of the potentialities of At^{211} as a tool in biological research by the presentation of two specific experiments: (a) the chemical state of At^{211} in the thyroid gland; and

(b) radiodestruction of the thyroid gland by At^{211} as a function of dose and time.

General Procedures

The At^{211} used in these experiments was separated from the bismuth target by a modification of the method of Garrison et al.[7] It was injected intravenously as At^- in physiologically normal saline. The valence state was stabilized by the addition of sodium sulfite. The rats used were females of the Sprague-Dawley strain, injected when 55 days of age (160 to 180 grams body weight). All animals were maintained for at least two weeks prior to use on tap water and either Purina Lab Chow or "Diet 14" of the University of California Institute of Experimental Biology.[17] All radioassay procedures used were standard and are described by Hamilton et. al.[8] Histological specimens were prepared by Bouin or neutral 10% formalin fixation, dioxane dehydration and clearing, paraffin embedding, and hematoxylin and eosin staining.

I. THE CHEMICAL STATE OF ASTATINE^{211} IN THE THYROID GLAND
A Preliminary Report

Investigation of the possible organic binding of At^{211} by the thyroid gland was stimulated by three observations: (a) the concentration of At^{211} in the thyroid gland of the rat 18 to 24 hours after its intravenous administration is several hundred times that in the plasma;[8,10] (b) the thyroidal accumulation of At^{211} as a function of time closely resembles that of I^{131} under similar conditions;[8] and (c) some preliminary experiments suggested that the At^{211} was closely associated with the thyroid protein.[18] The experiments described are studies of the thyroidal accumulation of At^{211} in the presence of the antithyroid compounds, the propyl thiouracil (PTU) and thiocyanate ion (KSCN), the partition of At^{211} between the protein and nonprotein fractions of thyroid homogenates, and the extent to which At^{211} is leached by various histological fixatives.

Procedures

Groups of 10 to 20 rats were prepared as follows: (A) controls: no pretreatment; (B) KSCN: all animals received a single subcutaneous injection of 0.2 ml of a 10% solution of KSCN 1.5 hours before sacrifice; (C) PTU: tap water was replaced by a 0.1% solution of PTU for 11 days prior to the injection of At^{211} and I^{131}; and (D) PTU and KSCN: animals on the PTU water were given a single subcutaneous injection of KSCN as in Group (B). All the animals received 10 μc of At^{211}, and the control and PTU-treated groups also received 2 μc of I^{131}. After 18 hours, thyroids were removed and homogenized in normal saline; cellular debris was discarded. For At^{211} and (or) I^{131} determinations, an aliquot was taken from each thyroid homogenate. The remainder of each homogenate was treated with an equal volume of either 20% trichloro-acetic acid (TCA) or a saturated solution of ammonium sulfate. Protein precipitates thus obtained were washed once with their precipitating reagent and assayed.[8]

For histological preparations, thyroids were removed from two rats of each group seven hours after At^{211} administration and placed in the fixatives listed in Table I. After eight hours of fixation, the At^{211} activity of the thyroid

glands of their fixing and dehydrating agents was determined by x-ray counting.

Results

Table II again demonstrates that PTU increased the thyroidal accumulation and retention of At^{211}. When KSCN was given 1.5 hours before sacrifice, about 30% of the At^{211} was discharged from the normal thyroid gland and nearly 70% from the PTU-treated gland.

The percent of soluble radiohalogen associated with thyroid protein of both normal and PTU-treated rats is shown in Table III. The results obtained for the I^{131} in both normal and PTU-treated thyroids with the two reagents tested agreed with the findings of Chaikoff and Taurog,[19] so that despite the small number of samples, the data presented appear to be reliable. The amount of I^{131} associated with the protein depended upon the extent of the organic binding of I^{131}, and not on the protein precipitant employed. The behavior of At^{211} was generally similar to that of I^{131} in the normal thyroid gland (controls), although the percent of At^{211} associated with the thyroglobulin (ammonium sulfate precipitable) was lower than the percent of I^{131}. In the PTU-treated glands, however, the behavior of At^{211} from that of I^{131} was quite different. Trichloro-acetic acid precipitated the same proportion of At^{211} from PTU-treated glands as from the controls. The amount of At^{211} precipitated from these glands by ammonium sulfate was about 60% of the control value. In contrast, the I^{131} precipitated by both the TCA and ammonium sulfate was about 25% of the control value.

The leaching of At^{211} from normal and PTU-treated thyroid glands by five histological fixatives is shown in Table I. The astatine was more readily leached from PTU-treated than from normal thyroid glands. This halogen appeared to be more firmly "fixed" by solutions of pH less than 2. Alcohol-based fixatives apparently increased the leaching of At^{211}. It was shown previously that following Bouin fixation, up to 20% of the At^{211} but none of the I^{131} was removed when alcohol was used as a dehydrating agent.[8,20] Leaching of either astatine or iodine was negligible during dioxane dehydration, irrespective of the fixative employed.

Discussion

It has been clearly established that the same factors influence the accumulation of At^{211} and I^{131}, and to a similar degree.[8,10,15] In the case of I^{131}, iodide is presumably oxidized to iodine, which is then organically bound.[19] It is more difficult to understand what happens to astatide after it is collected by the thyroid gland. The large thyroid-to-plasma ratios for At^{211} 8 to 48 hours after administration[8,10] indicate that the At^{211} in the normal thyroid gland is to a great extent combined in some manner with the thyroid protein.

The data presented show that in the normal thyroid gland about two-thirds of the At^{211} is rather firmly bound or "stable," and about one-third is quite labile except in the presence of an organic acid, in which case At^{211} is apparently "fixed" firmly to the denatured protein. The position of astatine in the periodic table, and the present knowledge of its chemistry,[6] make it seem likely that the oxidation potential of the reaction

$$At^- = At^0 + e^- \qquad (1)$$

is less negative than for the reaction

$$2\ I^- = I_2 + 2e^-. \qquad (2)$$

Therefore, it is fairly certain that the normal thyroid gland is capable of oxidizing the At^{211} injected as At^- to At^0. Elemental astatine possesses certain metallic properties[3,4] and, as a metal, could chemically adsorb onto the protoplasm of the thyroidal epithelial cells. If the normal thyroid gland is capable of further oxidizing astatine from the elemental to a positive valence state,

$$At^0 = At^+ + e^-, \qquad (3)$$

then there is the additional possibility of the formation of fairly stable complexes of At^+ with the intra-cellular protein or with the colloid. Autoradiographs presented by Hamilton et al.[8] and the extent of the association of At^{211} with the thyroglobulin fraction suggest that the "stable" At^{211} in the normal thyroid gland is bound in some manner to this protein. The labile fraction may be At^0 chemically adsorbed onto the cellular protein, or may even be astatide ion; iodide ion has been shown to exist in the thyroid gland to some extent.[21]

Hamilton et al.[8] and Shellabarger and Godwin,[10] have shown that the administration of PTU or thiouracil for subacute periods enhances the thyroidal uptake of astatine. Shellabarger[22] has further shown that the thyroid glands of rats given thiouracil for 18 hours accumulated less At^{211} than did control rats. This would rule out direct action of the thiouracils on the accumulation of astatine by the thyroid gland. The goitrogen, PTU, prevents synthesis of thyroid hormone,[23] but does not interfere with the ability of the thyroid gland to collect iodine.[21] The ensuing hypothyroid condition results in hypersecretion of TSH. This, in turn, results in hypertrophy and hyperplasia of the thyroid gland and activation of the thyroid iodide-concentrating mechanism.[21,24] Potentiation by PTU of the effect of TSH on the iodine-trapping mechanism, as postulated by Halmi et al.,[25] could account for the enhanced astatine uptake observed in subacute thiouracil treatment.

The Vanderlaans have shown that the administration of thiocyanate after the organic binding of I^{131} discharges little or no iodine.[21] In this experiment, KSCN discharged approximately 70% of the astatine from the PTU-treated thyroid glands, indicating that most of the astatine initially present was in a labile form. This lability was further emphasized by the increased leaching of astatine from the PTU-treated thyroid glands by certain histological fixatives. The major portion of the astatine in these glands may be in one of the forms previously suggested for the "labile" fraction of astatine in the normal thyroid, as astatide ion by analogy to the above mentioned findings for iodide[21] or as a chemically adsorbed At^0. The prevention of thyroid hormone production by the thiouracils appears to be due to inhibition of oxidative enzymes involved in the iodination of tyrosine.[23] The oxidation of astatide to astatine, however, may still proceed to the point where some of the At^0 is formed, provided that the energy necessary to drive Reaction (1) is sufficiently small. In vitro experiments support the possibility that the administration of KSCN could reverse Reaction (1), releasing At^{211} from the thyroid gland as astatide. The energy necessary for further oxidation of At^0 to At^+ makes it

unlikely that astatine exists in these glands as a true metal-protein complex.

The stability of the At-protein combinations at low pH's is very likely the result of the exposure of new and perhaps more stable astatine-binding sites in the denaturation of the protein.

II. RADIODESTRUCTION OF THE THYROID GLAND BY ASTATINE^{211} AS A FUNCTION OF DOSE AND TIME

The objective of this study was to establish the acute and chronic manifestations of the varying degrees of damage to the thyroid gland that would be produced by increasing dosages of At^{211}. Most experimental groups consisted of five to ten rats. The degree of damage was estimated in each case (a) functionally, by measuring the ability of the remaining thyroid tissue to take up a tracer dose of I^{131}; and (b) structurally, by weight and histological study of the tissue.

Results

Table IV shows the percent of the administered I^{131} found 24 hours after intramuscular injection of 5-to-10 μc tracer dose. It will be seen that the iodine uptake diminished as the dosage of At^{211} increased, reflecting the functional damage to the gland. The maximal effect on iodine uptake of functional damage developed within six days, was reached at the 1.2-μc dose level.[26] This level is close to the MLD_{60}.[14] Over a longer period of time, however, lower doses were effective in bringing about equivalent impairment of function, as shown by the low iodine levels of the 0.8-μc At^{211} groups after 40 days and 1 year. This suggests that the earliest phenomena of damage following At^{211} irradiation of the thyroid are related to impaired cellular physiology, while the subsequent processes reflect cell death and glandular atrophy. To explore this concept, analysis of the degree of structural damage at the different doses and time intervals was necessary.

The weights of the glands removed six days after astatine administration underwent only slight reduction from control values, even at the highest dose level. These weights do not fully represent the gland, however, since edema and extravasation of blood were common and resulted in a misleadingly high weight. The weights a year after astatine administration are more representative of the actual tissue; a marked reduction below control value was achieved even at the lowest dosage group (0.4 μc).

Histologically, the thyroids taken six days after administration of the lower dose levels showed particularly interesting structure (Fig. 2, to be compared with a normal thyroid, Fig. 1). The epithelium of the follicles was unusually high. The abundant vacuolation of the margins of the colloid (especially in the larger peripheral follicles) suggested very active resorption. The abundant capillary vasculature was dilated. Evidences of cell destruction were quite scanty. This structure characterized not only the glands from the 0.8-μc dose level, but also some from an experiment (not tabulated) in which only 0.5 μc of At^{211} per gram of body weight was administered. The impression was that of a very active gland. It is conceivable that functionally these glands were not secreting adequate amounts of normal thyroid hormone, and that the pituitary was, in consequence, putting out excessive TSH, to which the cells could still respond structurally.

At the 1.2-μc dose level (six day interval) the thyroid tissue was divided between follicles like those above, and other follicles in which the cells were arranged as dense sheets or cords. Some proliferation was evident; on the other hand, areas of cell death were also found.

At the 1.5-μc dose level, unqualified evidence of tissue destruction was found (Fig. 3). The greater part of the epithelium was disintegrating, and in patches only amorphous substance appeared at the former site of follicles. There could still be found a variable but small number of structurally normal follicles. Some even showed heightened or proliferating epithelium. The stroma was markedly altered, showing edema, fibrinous exudation, extravasation of blood, and an abundance of macrophages.

At the 1.8-μc dose level, some specimens showed structure like that of the 1.5-μc group. Other specimens, however, showed more extensive epithelial destruction, and the stroma was more profoundly affected.

In the chronic studies (one year after At^{211}) appreciable glandular damage was evident even at the lowest dose level. Substantial areas of fibrosis were seen in which macrophages containing golden-brown pigment were often found. Many well-vascularized follicles could also be found, however, containing intact epithelium (medium to high cuboidal cells) and colloid. These follicles were usually small, whereas in the controls they were mostly medium to large. The impression was that of a gland in which much of the thyroid tissue had disappeared; the residual tissue was possibly under increased stimulation by TSH.

The next two levels (0.6 μc and 0.8 μc) showed greater damage. There was a progressive increase in the proportion of fibrotic tissue, and the epithelial elements tended more to be dense cell clusters than follicles.

Histologic studies were also made from 11 "thyroids" obtained from rats one year after administration of At^{211} at dosages of from 1.1 to 1.6 μc per gram of body weight. (Only one of these levels, 1.2 μc, is represented in Table IV). In only two sections did the sparse epithelial remnants bear any resemblance to thyroid follicles; in the remainder they consisted of dense small clusters or isolated cells in fibrotic tissue (Fig. 4). These cells were sometimes vacuolated; some contained intracellular colloid droplets, suggesting that they were viable and might be under TSH stimulation. Occasionally evidence of epithelial proliferation was found. Vascularity was poor. The remainder of the tissue was fibrous. Often an abundance of pigment-containing macrophages gave evidence of the extravasation of blood that had occurred earlier (see previous descriptions). Developing fat tissue was often seen in these sections. The parathyroids consistently showed structural normality.

Discussion

This experiment indicates that functional tests (I^{131} uptake) and structural tests (weight and histologic change) of thyroid damage after At^{211} administration are complementary. The I^{131} test seems more sensitive; reduction of uptake could be demonstrated after moderate At^{211} dosages in glands that appeared normal or even hyperactive structurally. Furthermore, the finding of even considerable epithelial remnants in the paratracheal region long after a thyroidectomizing dose of At^{211} is not necessarily associated with any substantial evidence of thyroid function. It appears that at the lower levels of At^{211} dosage, cells

retain their capacity to respond to TSH stimulus by hypertrophy and hyperplasia. Obviously, the first consequences of the At^{211} radiation must be sought in impaired biochemical processes within the cells. This reinforces the demonstration for the need of further biochemical studies such as are described in the first section of this report.

SUMMARY

Astatine^{211} is an alpha-particle-emitting halogen which is selectively accumulated by the thyroid gland. It has been possible, by employing standard protein chemistry procedures (trichloro-acetic acid or ammonium sulphate precipitation), to draw some conclusions as to its chemical state in the thyroid. Such biochemical studies have been combined with experimental regimens using antithyroid drugs (propyl thiouracil, potassium thiocyanate), and deductions have been made as to some of the physiological mechanisms which affect the transformations of astatine within the thyroid.

Advantage has been taken of some of the special nuclear properties of At^{211} (short half life, rapid energy release, restricted tissue range) to achieve graded damage to the thyroid gland. Combining functional tests(I^{131} uptake) and structural tests (weight and histology) for thyroid damage has made it possible to assess the effective thyroid-destroying dose over varying time periods. Altered glandular physiology following lower doses has also been demonstrated.

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26) It will be noted that it was possible to check the completeness of thyroid destruction by use of a tracer I^{131} dose six days after At^{211} administration. This indicates a possible advantage of At^{211} over I^{131} as "thyroidectomizing" agent in endocrine experiments. When thyroid destruction is achieved by I^{131}, weeks must pass before such checking, owing to the residual radioactivity in the neck region from the longer-lived I^{131}.

Table I

THE LEACHING OF ASTATINE-211 FROM THE THYROID GLANDS OF NORMAL AND PTU-TREATED RATS IN HISTOLOGICAL FIXATIVES. VALUES ARE EXPRESSED AS PERCENT OF TOTAL THYROID ASTATINE-211.

Fixative	Percent Leached	
	Normal Thyroid	PTU Thyroid
80% Ethanol, pH 6-7	59.2	----
10% Neutral formalin, pH 5	7.9	11.5
10% Formalin in 95% ethanol, pH 6-7	57.5	85.9
Tellyeniczky's fluid (5% formalin and 5% glacial acetic acid in 70% ethanol), pH 5-6	17.1	16.5
Bouin's fluid (25% formalin and 5% glacial acetic acid in saturated picric acid), pH 2	3.3	2.9

Table II

THE EFFECTS OF PRETREATMENT WITH PTU AND KSCN ON THE THYROIDAL ACCUMULATION OF ASTATINE-211 AND IODINE-131 RATS. VALUES ARE EXPRESSED AS PERCENT OF ADMINISTERED DOSE AND ARE PRESENTED WITH THE STANDARD ERROR OF THE MEAN. a)

Group and No. of Rats	At^{211}		I^{131}	
	%/organ	%/gram	%/organ	%/gram
1-Control (20)	0.78 ± 0.03	50.6 ± 2.4	12.6 ± 0.69	811 ± 52
2-KSCN (8)	0.56 ± 0.04	34.8 ± 1.6	-----	----
3-PTU (21)	1.53 ± 0.06	47.0 ± 2.1	0.42 ± 0.03	13.3 ± 1.0
4-PTU + KSCN (10)	0.59 ± 0.04	14.7 ± 0.9	-----	-----

a) Standard error of the mean, S.E. = $\pm \sqrt{\frac{d^2}{n(n-1)}}$

Table III

THE EXTENT OF ASSOCIATION OF ASTATINE-211 WITH THE PROTEIN OF THE THYROID GLAND COMPARED TO IODINE-131.

Group and No. of Rats	Percent Saline Soluble Halide in Thyroid Gland Precipitated By:			
	10% TCA		Half-Saturated $(NH_4)_2SO_4$	
	At^{211}	I^{131}	At^{211}	I^{131}
1-Control (7)	90.0 ± 5.7	93.0 ± 5.1	69.9 ± 4.3	97.5 ± 2.6
3-PTU (7)	90.0 ± 5.7	21.8 ± 1.8	44.3 ± 5.7	24.9 ± 6.7
4-PTU + KSCN (4)	72.4 ± 3.4	----	71.9 ± 1.1	----

Table IV

MEAN WEIGHT AND 24-HOUR IODINE UPTAKE OF RESIDUAL THYROID TISSUE OF RATS FOLLOWING ASTATINE-211 ADMINISTRATION.

Dosage At^{211} μc/gm. Body Wt.	Post-Injection Interval: 6 Days			40 Days [a]		1 Year		
	No. of Rats	Thyroid Weight, mg.	% I^{131} Uptake	No. of Rats	% I^{131} Uptake	No. of Rats	Thyroid Weight, mg.	% I^{131} Uptake
Controls	6	14.3 ± 0.5	9.0 ± 0.7	10	16.7 ± 0.9	9	26.0 ± 1.4	7.4 ± 0.1
0.4	-	----	----	3	4.8 ± 2.1	7	10.6 ± 1.0	2.6 ± 0.2
0.6	-	----	----	-	----	5	11.6 ± 1.7	3.0 ± 0.4
0.8	6	12.7 ± 0.4	4.1 ± 0.7	3	0.8 ± 0.3	6	9.3 ± 0.9	1.6 ± 0.3
1.2	6	11.3 ± 0.3	1.3 ± 0.1	-	----	1	b)	0.2
1.5	5	13.2 ± 0.4	0.3 ± 0.1	-	----	-	----	----
1.8	5	11.3 ± 0.6	1.3 ± 0.2	-	----	-	----	----

a) Data for 40 day group taken from that published by Hamilton, et al (8), thyroid weights unavailable.
b) No thyroid tissue was found at autopsy. The I^{131} uptake was measured on neck tissues en bloc.

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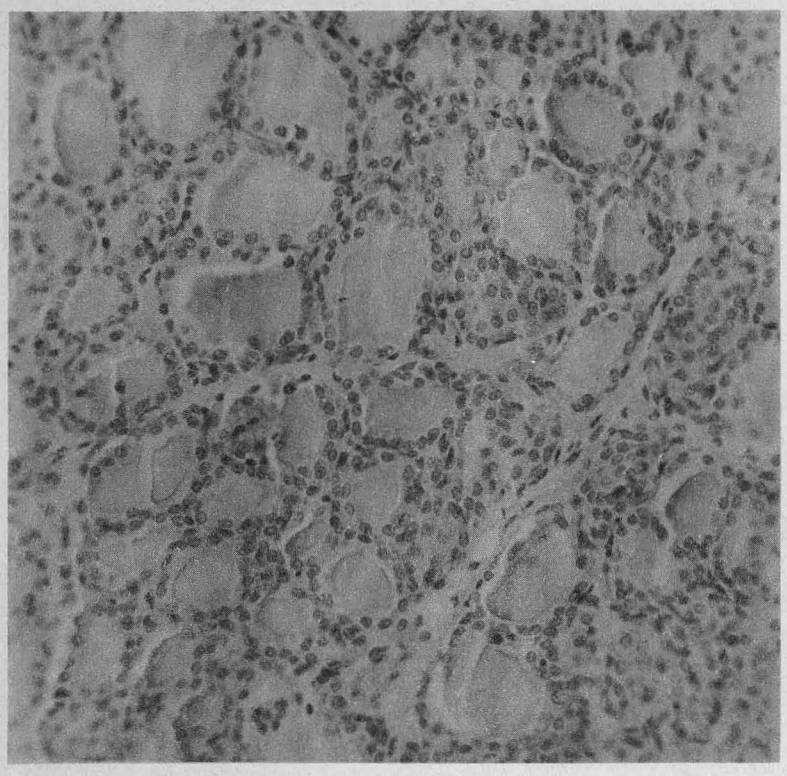

Fig. 1

The thyroid of a normal 55-day old rat illustrates the condition in the controls at the time of At^{211} injection. (All photographs are magnified 267 times).

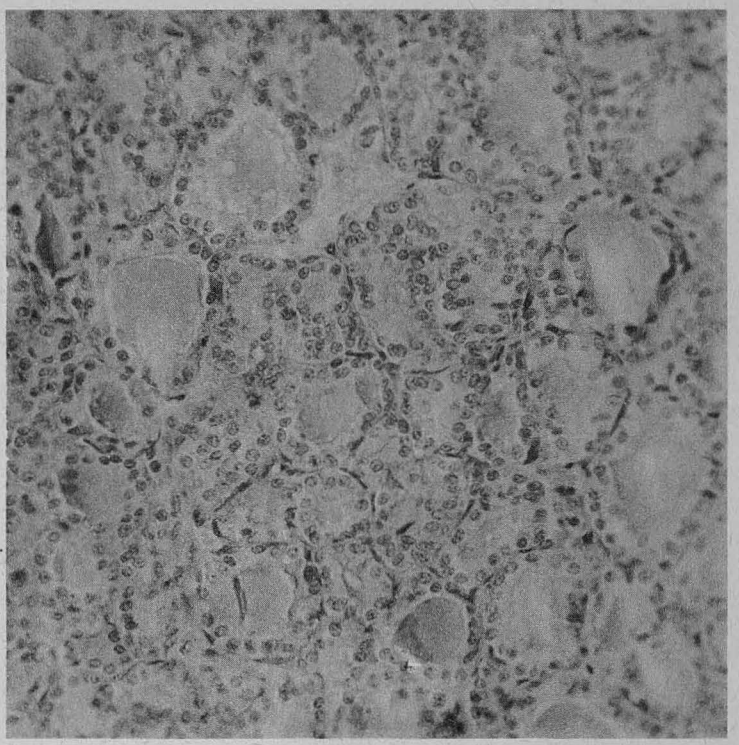

Fig. 2

Six days after administration of 0.8 μc At^{211}/gm body weight, the thyroid shows heightened epithelium, colloid resorption, and an abundant supply of capillaries. (x 267)

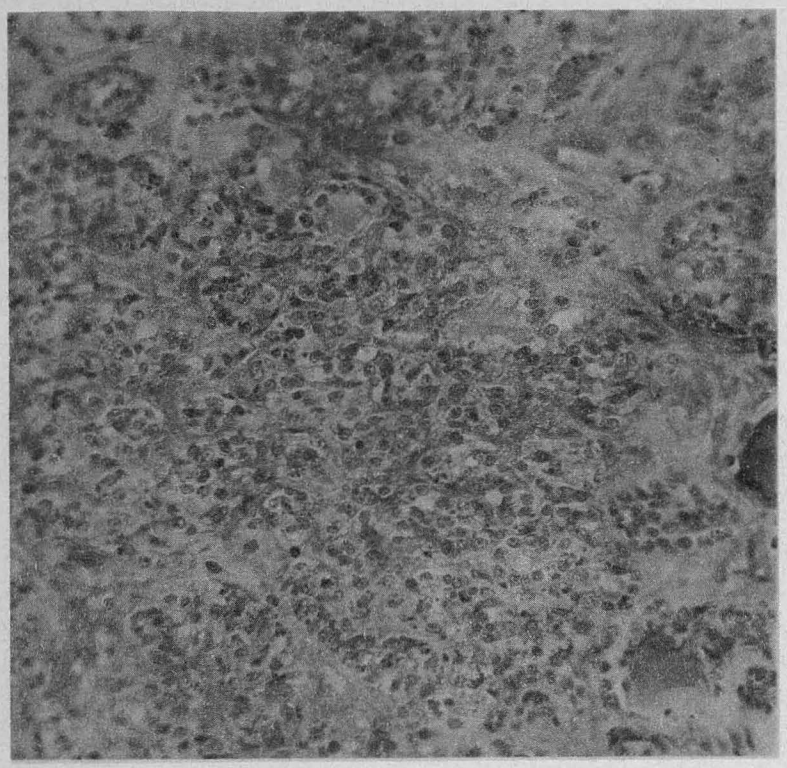

Fig. 3

Six days after administration of 1.5 μc At^{211}/gm body weight, the thyroid shows masses of epithelial cells, many of them degenerating. The stroma between these cell masses is edemetous and hemorrhagic. (x 267)

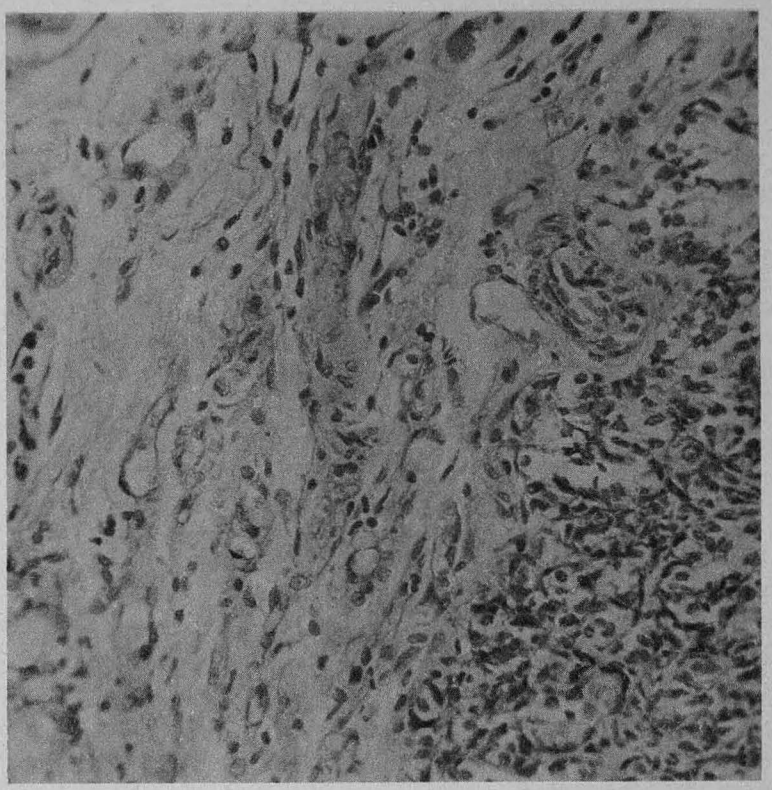

Fig. 4

One year after administration of 1.1 μc At^{211}/gm body weight, no recognizable thyroid tissue is found, although some epithelial remnants are seen. The parathyroid gland (lower right) appears intact. (x 267)

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