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THE EFFECT OF PROPYL THIOURACIL ON THE RECOVERY OF RAT THYROID GLAND FROM IRRADIATION WITH ASTATINE-211

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BERKELEY, CALIFORNIA

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February 7, 1957

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and the Departments of Medicine, Anatomy, and Radiology of the
University of California, Berkeley and San Francisco

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ABSTRACT

The thyroid glands of female rats have been studied structurally and functionally at intervals up to 1 year after (a) hyperplasia induced by propyl thiouracil (PTU) (1% in the drinking water for 11 days), (b) radiation damage by At^{211} alpha particles (75 μC of At^{211} per rat), and (c) the combination of these two agents.

During 1 year, normal control thyroid glands nearly doubled in size and showed a substantial increase in their colloid content. Uptake of I^{131} did not increase proportionately to increased gland weight.

One month after withdrawal of PTU both structural and functional recovery of the thyroid glands were essentially complete. Irradiation with At^{211} permanently reduced gland size. The glands showed a series of early degenerative changes followed by reparative changes, but were not structurally normal at 1 year, although I^{131} uptake was within normal limits within 8 days postirradiation. When At^{211} was given to rats with thyroid glands made hyperplastic by PTU, gland weight declined rapidly, and at the end of a month was the same as in those glands influenced by At^{211} alone. The irradiated hyperplastic glands suffered structural damage similar to the irradiated normal glands, but the absolute amount of tissue lost was greater and the recovery period was prolonged. The possible role of stimulation of damage thyroid tissue by pituitary thyrotropin (TSH) in retarding recovery is discussed.

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INTRODUCTION

Destruction of the thyroid gland by the alpha particles of At^{211} , an isotope of the heaviest halogen, was first described by Hamilton et al. (1950). Such destruction has been found to depend directly on the amount of At^{211} administered (Hamilton et al., '53, '56), and presumably on the thyroid uptake of the isotope. The accumulation of At^{211} by the thyroid gland of the rat can be diminished by increasing the iodide intake or by the parenteral administration of potassium thiocyanate or thyroxine, and can be augmented by thyrotropic hormone (TSH), by maintenance on a low-iodine diet, or by feeding propylthiouracil (PTU) until thyroid hyperplasia has been induced (Hamilton et al., '53; Shellabarger et al., '54; Hamilton and Soley, '40; Shellabarger and Godwin, '54; and Durbin et al., '54).

Hamilton and his co-workers have described the extent of thyroid destruction in rats following various doses of At^{211} at intervals of 6 and 40 days and 1 year postinjection (Hamilton et al., '50, '53, '54, '56). The amounts of At^{211} administered in these experiments ranged from 0.8 $\mu\text{C/g}$ body weight, a permanently thyroidectomizing dose, to 1.8 $\mu\text{C/g}$, a 100% lethal dose (Hamilton et al., '54, '56; and Watts, '55). Unfortunately, earlier experiments carried out with lower dose levels cannot be compared, because they were performed on several strains of rats of different ages maintained on at least three different diets of widely varying iodine content.

Autoradiographs have shown that At^{211} accumulated by the normal thyroid gland is mainly associated with the colloid 18 to 24 hours after administration (Hamilton et al., '53). The nonuniformity of thyroid damage in the rat described by Hamilton et al. ('54) was ascribed, in part, to the dissipation of much of the alpha-particle energy in the nonliving colloid, because the mean range of the At^{211} alpha particles in tissue (70 microns, calculated from range-energy data) is often much less than the follicular diameter in the normal gland. It was further postulated that injury induced by At^{211} was more severe in the smaller centrally located follicles; not only because their size was more nearly equal to the alpha-particle range, but also because these follicles were more active metabolically, thus enhancing their accumulation of the isotope. Such concentration differences between small and large follicles have been demonstrated for I^{131} (Nadler and Bogorach, '54).

The microscopic appearance of the PTU-poisoned thyroid glands, with their greater uptake of At^{211} , suggested that a high degree of uniform damage could be effected in the thyroid glands of PTU-treated rats.

This report concerns a systematic investigation of the capacity of the thyroid gland to recover both functionally and structurally from a moderately injurious dose of At^{211} , and of the effect of PTU pretreatment on that recovery.

METHODS

Starting at 35 days of age, female rats of the Sprague-Dawley strain were conditioned for 9 days on Purina Laboratory Chow¹ and tap water ad lib. At age 44 days half the animals were placed on distilled water containing 0.1% PTU. After 11 days, at which time the PTU-induced thyroid hyperplasia was maximal (Freisleben et al., '45), At^{211} prepared by the method of Garrison et al. ('51) was administered intravenously to half the PTU-treated animals and to half the control animals. The At^{211} dosage was adjusted to 0.5 $\mu\text{C/g}$ body weight by varying the volume administered to each rat. All PTU treatment was discontinued 24 hours after the At^{211} injection. In all, there were four experimental groups, designated as follows: control, At^{211} , PTU, and PTU plus At^{211} . Five to 8 rats from each experimental group were sacrificed at intervals of 3, 8, 12, 31, and 300 days after the At^{211} injection. (No animals treated with PTU only were available at 300 days). A tracer dose of 5 μC of I^{131} was given 24 hours before sacrifice. The animals were sacrificed with chloroform, and the thyroids dissected and weighted to the nearest 0.2 mg on a torsion balance. The thyroids were fixed in individual vials containing 5 ml of Bouin's fluid. After 24-hour fixation the glands and fixative were assayed separately for I^{131} with a scintillation counter. The thyroids were embedded in paraffin, sectioned at 6 μ , and stained with hematoxylin and eosin.

The localization of At^{211} in the normal and PTU-poisoned thyroid gland was studied in a subsidiary experiment. Four rats each from the At^{211} and the PTU-plus- At^{211} groups were sacrificed 7 hours after the At^{211} administration. The thyroids were dissected and fixed in Bouin's fluid for 8 hours, dehydrated and cleared with dioxane, and embedded in paraffin. The foregoing combination has been found to provide the best conditions for preparation of autoradiographs from sections containing At^{211} , i. e., leaching of the isotope is minimal (Johnston et al., '55). Autoradiographs of the At^{211} in these sections, and of the I^{131} in sections from at least one thyroid in each of the four experimental groups at the three earlier times, were prepared on 10- μ Eastman Kodak NTA stripping film.

¹ The iodine content of this diet was determined by two independent laboratories as 1.1 ppm.

RESULTS

Figure 17 shows that in the normal thyroid gland the At^{211} alpha tracks appear to originate chiefly from the colloid. In the PTU_2 poisoned gland with virtually no colloid present, as shown in Fig. 18, the At^{211} is almost uniformly distributed throughout the gland.

Controls

From Table I and Fig. 19 it can be seen that the mean weight of the thyroid glands of the 11-month old rats was twice that of the 2-month-old animals ($P < 0.01$). The amount of thyroid per 100 g body weight was also increased significantly. No parallel increase in I^{131} uptake occurred, and consequently the thyroidal I^{131} concentration in percent dose per gram of tissue was significantly less for the older glands. This measure of glandular activity, combined with the histological findings, suggests that in the older glands there is more hormone storage and probably less secretory activity than in the glands of younger animals.

Figure 13 illustrates the normal structure of the thyroid as seen in young controls. The more centrally located follicles were smaller in size, with a cuboidal epithelium; the peripheral follicles were generally larger, and had a more flattened epithelium. The connective tissue of the stroma was scanty, and contained an abundant capillary network.

No substantial change took place in the normal thyroid glands during the first month of the experiment (3-, 8-, 16-, and 31-day controls were classed as young controls; their chronologic age was 58 to 86 days). The thyroids of the controls at the 1-year interval (14 months of age), as seen in Fig. 14, were distinctly different from those of the younger animals. Small follicles were rare; the follicular dimensions ranged from medium to very large, and the majority were as large as the largest found in the younger glands. The epithelium was lower--usually squamous to low cuboidal. Resorptive activity was less apparent than in the young glands. There was a tendency towards increased quantities of connective tissue.

Astatine-211

After experiencing an initial weight loss of from 3 to 10 g, the At^{211} -treated animals resumed growth, but at a slower rate than the controls. The At^{211} animals gained an average of 34 g over their starting weights by the 31st day, as compared with 53 g for the controls.

Three days after At^{211} administration, I^{131} uptake was reduced to one-fourth of normal. At 8, 16, and 31 days both I^{131} uptake and concentration had returned to the lower limit of normal. There was a general trend, after the initial period of edema had passed, toward reduced thyroid size as measured by gland weight. By the 16th day postinjection the reduction in gland weight, combined with the growth of the animals, resulted in a significantly diminished amount of thyroid tissue per 100 g body weight.

At 1 year the thyroid weight (both absolute and in terms of percent of body weight) and the I^{131} uptake were about one-half the corresponding control

TABLE I

Effect of 0.5 $\mu\text{C/g}$ of At^{211} and (or) days' maintenance on 0.1% PTU in drinking water on 24-hour I^{131} uptake and thyroid weight of female Sprague-Dawley rats. At^{211} was injected intravenously at age 55 days. PTU was withdrawn 24 hours after At^{211} administration.

	No.	Thyroid weight		I^{131} uptake		% I^{131} thyroid leached by Bouin's
		mg	mg/100g	% dose	%/g	
Young controls	28	13.3 \pm .40	7.5 \pm .19	8.66 \pm .58	677 \pm 53	1.5
Old controls	31	24.4 \pm .72	8.7 \pm .29	9.94 \pm .70	412 \pm 28	-
<u>At^{211}</u>						
3d	8	15.1 \pm .8	8.4 \pm .4	<u>2.12</u> ^a \pm .48	151 \pm 44	3.0
8d	7	13.0 \pm .7	7.2 \pm .5	<u>7.37</u> \pm 1.24	586 \pm 94	7.5
16d	5	12.2 \pm .8	<u>6.2</u> \pm .3	5.78 \pm 1.01	478 \pm 54	1.9
31d	5	11.3 \pm .9	<u>5.4</u> \pm .1	6.50 \pm 1.14	560 \pm 69	1.9
300d	9	<u>10.4</u> \pm .7	<u>3.7</u> \pm .2	<u>4.66</u> \pm .37	452 \pm 31	-
<u>PTU</u>						
3d	7	<u>50.9</u> \pm 3.4	<u>29.9</u> \pm 2.1	<u>1.01</u> \pm .20	<u>19</u> \pm 3	51.6
8d	7	<u>34.8</u> \pm 2.0	<u>20.1</u> \pm 1.1	<u>4.93</u> \pm 1.59	<u>141</u> \pm 41	7.9
16d	7	<u>28.6</u> \pm 1.5	<u>14.4</u> \pm .7	<u>7.85</u> \pm 1.29	<u>282</u> \pm 52	3.9
31d	5	<u>29.4</u> \pm 2.4	<u>13.9</u> \pm 1.3	10.6 \pm 1.00	373 \pm 43	1.0
<u>PTU + At^{211}</u>						
3d	7	<u>30.1</u> \pm 4.7	<u>18.8</u> \pm 2.4	<u>1.00</u> \pm .16	<u>40</u> \pm 10	34.1
8d	7	<u>22.3</u> \pm 2.8	<u>12.9</u> \pm 1.4	<u>1.79</u> \pm .27	<u>80</u> \pm 5	11.4
16d	7	<u>19.1</u> \pm 2.2	<u>10.8</u> \pm 1.2	<u>1.66</u> \pm .32	<u>80</u> \pm 12	6.8
31d	3 ^b	11.7 \pm 1.5	<u>6.1</u> \pm .6	<u>3.98</u> \pm 1.81	340 \pm 116	3.2
300d	8	<u>9.2</u> \pm .7	<u>3.5</u> \pm .2	<u>4.69</u> \pm .56	503 \pm 52	-

^a Underlined mean value indicates that it was tested against the appropriate control mean by the t-test, and the P value was at or beyond the 1% level of confidence (t-test: Fisher, 1950).

^b Two rats died before autopsy.

values. The concentration of I^{131} per g of thyroid, although low, was within the normal range for animals of that age. If a correction were made for the nonglandular tissue present at that time, the I^{131} concentration would be the same as for the controls. Only small amounts of radioiodine were leached by the fixative (1.5% to 7.5% of the I^{131} present in the glands), suggesting that the I^{131} accumulated by these glands was firmly bound at all the times tested.

Histologically, 3 days after the At^{211} injection all specimens continued to show a general organization characteristic of thyroid tissue as illustrated in Fig. 3. Some follicles, however, were breaking down, and cells were being shed into the follicular space. In others the cell height was increased slightly, and the periphery of the colloid was vacuolated and foamy, suggesting increased resorption. The stroma was edematous in many cases, although insufficient to produce a statistically significant increase in gland weight. There were fewer capillaries than normal. Occasionally, small areas of extravasation of erythrocytes were seen. Autoradiographically, iodine was associated as much with cell cluster as with colloid.

Figure 4 shows that at 8 days there was extensive destruction, the damaged area varying in individual sections from 10% to 70%. The follicles in these areas were broken down; their epithelium was fragmented and was desquamating into the lumen. In such regions there were small foci of extravasation of erythrocytes. In the less damaged areas, the follicles were usually quite small, and had a high cuboidal epithelium. Resorption of colloid was very active. The edema of the stroma noted at 3 days persisted. Autoradiographically, iodine could be demonstrated only where colloid was found.

At 16 days, as shown in Fig. 9, two of the seven specimens possessed virtually no recognizable thyroid tissue; the section consisted chiefly of loose fibrous tissue containing a number of lymphocytes. (These specimens were not included in the mean I^{131} uptakes shown in Table I). In the remaining specimens almost all showed follicular degeneration to some extent, with disintegrating and desquamating epithelium. Small follicles could still be found that looked quite active. These had high cuboidal epithelium and active colloid resorption. In such areas the vasculature was abundant; in the degenerating areas it was reduced. Radioiodine was demonstrated only in those follicles containing colloid, and in those cell clusters without lumen but with apparently intact epithelium.

Thirty-one days after the At^{211} injection, as shown in Fig. 10, the majority of specimens consisted of tiny follicles with medium cuboidal epithelium. Such follicles had small lumens, often containing only a drop of colloid. The stroma was nearly normal in appearance. There were specimens that were within normal structural range, as well as glands that were densely cellular, with only suggestions of a follicular arrangement. In these latter the cell clusters appeared to contain viable epithelium.

One year after the administration of the At^{211} the over-all dimensions of the glands were reduced; substantial amounts of glandular tissue were replaced by adipose or connective tissue. In Fig. 15 it can be seen that in

the glands proper the majority of follicles were small or medium-sized, none large. They had high cuboidal epithelium and contained a colloid that was often inhomogeneous -- that is, small deeply staining cores of colloid surrounded by lighter-staining colloid, with a sharp demarcation between the two. There was little evidence of colloid resorption. Occasionally, rounded clusters of cells were found that were not arranged in follicles. The stroma of the glandular portion was within normal limits.

Propyl Thiouracil

All animals in this treatment group continued to gain weight at the same rate as the controls throughout the experimental period. At 3 days the I^{131} uptake was only one-eighth normal, and 50% of this was soluble in the fixative, indicating little if any organic binding of iodine. By the 8th day, although the I^{131} was still well below normal, the small amount of the I^{131} removed by the Bouin's fluid, and the autoradiographic demonstration of I^{131} in association with colloidlike material, suggested that hormone synthesis had been resumed. Throughout the remainder of the experiment I^{131} uptakes were within normal limits. The failure of these glands to return to normal weight within a month after cessation of PTU treatment may be the result of a tendency to store excessive amounts of colloid.

Figure 1 shows the hyperplastic appearance of the glands on the third day after cessation of the PTU treatment. The epithelial cells were very tall columnar, and the follicles were empty of colloid. There were occasional mitoses in the epithelium. Vascularity was markedly increased. Even after long exposures, autoradiographic demonstration of I^{131} was difficult; however, an occasional grain could be found associated with the epithelium.

On the eight day after PTU withdrawal, the epithelial height was generally reduced to high cuboidal, and small follicular spaces were often apparent (see Fig. 2). Although colloid was rarely found, the follicular spaces contained a scanty amount of granular material. Mitotic activity was reduced, and the vasculature, although still abundant, was not as extreme as at 3 days. Iodine was demonstrated autoradiographically over the granular material in the follicles. When such material was associated with a minute amount of colloid, the autoradiograph was stronger over the colloid.

Figure 7 shows that the glands were still moderately hyperplastic at 16 days. Cell height was generally still high cuboidal. Most follicles possessed a substantial follicular space containing abundant colloid. Mitoses were rare. The vasculature continued to be somewhat rich, but was within the upper limits or normal. Strong I^{131} autoradiographs were found over the colloid, none over the cells.

One month after cessation of PTU, all glands, although still twice normal weight, had a virtually normal histological appearance, as shown in Fig. 8. The amount of colloid present was excessive for the age of the animals.

At²¹¹ plus PTU

The body weights of the animals in this group were similar in all respects to those of the group that received only At²¹¹. It is noteworthy

that the only deaths in the experiment occurred in this group, in which two of the animals succumbed between the 16th and the 31st day after the At^{211} injection. (Unfortunately, the degree of autolysis was such that autopsy revealed little more than the absence of the lung lesions usually seen in animals that die of respiratory infection).

The I^{131} uptakes and thyroid weights of this group at the three earlier times were significantly different ($P < 0.01$) from the corresponding control values. (The lack of statistical differences in the measurements at 31 days is probably the result of wide individual variations within a small group). Furthermore, with few exceptions, the uptakes and weights were also different from the comparable measurements for the other two experimental groups. Uptake of I^{131} was depressed to about one-ninth of normal on the third day, and rose much more slowly than the uptakes of animals that had been given only At^{211} or PTU. Throughout the experiment the thyroid glands were smaller than those of the PTU group, although presumably both had been the same on the day that the At^{211} was injected. The rate of decline of thyroid weight for this group was greater than for the glands influenced by PTU alone. By the end of 1 year the functional measurements, although different from the controls, were indistinguishable from those made on animals that had received At^{211} alone.

Microscopically, 3 days after the At^{211} administration the majority of the follicles in these glands possessed a high cuboidal epithelium, as shown in Fig. 5, but somewhat lower than with the PTU alone. In contrast to the group that received only PTU, the nuclei were smaller and more deeply stained; there were few mitoses, and the vasculature was much less rich. The edema in the stroma was like that found in the thyroid glands of rats receiving only At^{211} . In all specimens there were areas of disrupted follicular organization; these areas were usually restricted to islands of a few follicles. The cells in such regions had degenerating, pyknotic nuclei. Autoradiographically, there were very rare grains over some of the cells, and in the rare follicles with colloid, there were some grains associated with the colloid.

Figure 6 shows that there was substantial epithelial disintegration in most specimens 8 days after the At^{211} irradiation. There were cell clusters that showed their former follicular organization only by the persistence of the partitions in the stroma. Nuclear stainability was variable. When destruction was advanced, only clusters of irregularly shaped cells were found. Breakdown of capillary endothelium with extravasation of erythrocytes was often seen. Some specimens showed a few islands of degenerating tissue surrounded by very small follicles having a high cuboidal epithelium. Colloid was rare in such follicles. Autoradiographs showed that I^{131} was localized only in those rare peripheral follicles which retained some colloid.

Sixteen days after administration of At^{211} , the glands consisted of closely packed cells having, for the most part, only vestiges of their former follicular organization, as shown in Fig. 11. Some of these cells showed degeneration, but others were apparently viable. Follicles with a hyperplastic epithelium, usually high cuboidal in form, could still be found. Such follicles rarely contained colloid. Small collections of extravasated erythrocytes were occasionally seen. The vascularity was adequate but not abundant. Iodine

was demonstrated autoradiographically in some follicles that still retained traces of colloid; however, the grains were almost equally distributed between cells and follicular space.

The glands continued to be densely cellular, with little organization, 31 days after At^{211} irradiation, as illustrated in Fig. 12. Some clusters of cells were organized into tiny follicles with cuboidal epithelium; at best, these had only droplets of colloid. The stroma was slightly increased; its vasculature was nearly normal or slightly diminished.

Figure 16 shows that 1 year later the thyroid glands of the animals in this treatment group could not be distinguished microscopically from those taken from animals receiving At^{211} alone.

DISCUSSION

In the assessment of the functional capacity of these glands during and after the recovery period, it was necessary to distinguish between the uptake of the tracer dose of I^{131} (expressed as percent of the administered dose found in the entire gland) and the ability of the gland to concentrate I^{131} (expressed as percent of dose per gram of "thyroid" tissue). A third, but less quantitative, judgment of function was derived from estimates of the amount of I^{131} that could be leached from the tissue by the fixative, and presumably was not organically bound.

In this experiment structural changes, in the main, coincided with estimates of functional capacity. The chief exception appeared in one group (3 days after At^{211} irradiation of the normal thyroid gland) in which evidences of structural impairment appeared to lag behind functional impairment.

In the glands recovering from PTU-induced hyperplasia, it was demonstrated that total uptake of I^{131} rose to normal levels after 2 weeks, and that during this 2-week period the ability of the glands to bind I^{131} improved, also returning to normal levels. The concentrating power of these glands, however, remained low for the 31-day experimental period, reflecting the failure of the glands to return to pretreatment weights.

With At^{211} alone (the dose employed here was about 60% of a permanently thyroid-destructive dose, Hamilton et al., '56), the ability of the glands to accumulate and concentrate I^{131} was only transiently reduced. Uptake and concentration were both within the normal range after the third day of the recovery period. Throughout the experimental period little I^{131} was detected in the fixing solutions, indicating that the At^{211} -damaged glands retained their ability to bind such I^{131} as they accumulated. These glands did not, however, follow the normal pattern of age change in their I^{131} uptake. Whereas in normal glands the ability to concentrate I^{131} diminishes with advancing age (reflecting an increase in weight), these smaller glands, although taking up less I^{131} , sustained their concentrating power.

When At^{211} was given to animals with hyperplastic thyroid glands (induced by PTU), the thyroid glands showed reduced functional capacity which remained low throughout the 31-day recovery period. Thus, judged

functionally, the damage induced by At^{211} was augmented by the prior administration of PTU. Additional support for this view comes from the observation that two animals in this group died, presumably as a result of the combination of these two agents, neither of which was given in sufficient quantity to be lethal by itself.

Both the functional capacity and the structural changes in the thyroid glands of the various groups must be judged in the light of the probable level of stimulation of the glands by the anterior pituitary thyrotropic hormone (TSH). No estimates of the level of TSH were made.² It is well recognized that this hormone is produced in excess during PTU administration (Riggs, '52; and Greer, '52), and in the group that received only the latter agent it would be expected that the glands were under the influence of a declining TSH level during the experimental (recovery) period. The At^{211} -treated animals were very likely under the influence of normal levels of TSH at the time of injection. It is questionable whether the TSH level had opportunity to rise very much, since these glands appeared functionally adequate within 8 days after the At^{211} administration and were probably furnishing some thyroid hormone.

In the group that received At^{211} while under the influence of PTU, high levels of TSH were present, and the glands were presumable under strong stimulation when irradiated. Even after the withdrawal of the PTU, it is likely that owing to the radiation damage thyroid hormone synthesis remained depressed and the TSH level consequently remained high. The inhibition of recovery of these thyroid glands was very likely the result of a combination of two factors, (a) irradiation of stimulated tissue, and - perhaps even more important - (b) continued stimulation of tissue damaged by the radiation. There is some evidence for potentiation of damage in mammalian tissues when they are irradiated under conditions that enhance their activity, such as increased oxygen tension or augmented blood supply (Patt, '53). Lethality of whole-body irradiation is significantly enhanced when it is followed by a forced increase in metabolic activity. This has been well established for such conditions as the feeding of thyroid substance or dinitrophenol (Blount and Smith, '49; Smith and Smith, '51), environmental stress (Smith et al., '49; Hempelmann et al., '49), or exhaustive exercise (Kimeldorf et al., '50).

Maloof ('52) and Montag ('50) have made an additional observation concerning the ability of irradiated thyroid tissue to respond to TSH stimulation. Both reported finding unusual and bizarre cell types as a result of feeding goitrogens to rats whose thyroid glands had been irradiated with either x-ray or I^{131} beta particles. Maloof further claims that those glands were able to respond to TSH stimulation by hypertrophy but not by proliferation.

² Histological examination of the pituitaries of the animals sacrificed 1 year after receiving At^{211} with or without pretreatment with PTU showed no changes suggestive of thyroid deficiency; the morphology and number of acidophils and basophils were within normal limits.

SUMMARY

1. The thyroid glands of young female rats have been studied structurally (weight and histology) and functionally (I^{131} uptake) for 1 month following (a) PTU-induced hyperplasia, (b) radiation damage by At^{211} , and (c) the combination of these two agents. Observations were extended to 1 year in the latter two groups and in the untreated controls.

2. The thyroid glands of the untreated controls nearly doubled in weight during the course of a year; histologically, they showed a substantial increase in the amount of colloid. Radioiodine uptake did not increase significantly during this period of gradually increasing gland size, and therefore the ability of the gland to concentrate a tracer dose of I^{131} seemed diminished.

3. Substantial structural and functional recovery occurred in the month following cessation of PTU administration. Gland weight gradually declined, but was still nearly twice that of the controls after 1 month.

4. When At^{211} was given alone ($0.5 \mu\text{C/g}$), the thyroid glands were permanently reduced in size. These glands showed a series of early degenerative changes and subsequent reparative changes, but normality of structure was not attained even at 1 year postinjection. Uptake of a tracer dose of I^{131} , however, returned nearly to control levels as early as 8 days postirradiation.

5. When At^{211} was given to rats whose thyroid glands had been made hyperplastic by pretreatment with PTU, the gland weight declined rapidly, and at the end of a month was the same as that for the glands influenced by At^{211} alone. The glands of both At^{211} -irradiated groups failed to increase in weight as normal glands do.

6. Histologically, the glands of the group influenced by both agents (At^{211} and PTU) suffered damage similar to that seen in the thyroid glands of rats that received At^{211} alone, although the recovery period seemed somewhat more prolonged. One year postinjection the glands from the top At^{211} -treated groups were indistinguishable. Functionally, the I^{131} concentrations for these glands were within normal limits after a year, although the I^{131} uptakes remained depressed.

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Plate I. Photomicrographs of thyroid tissue of female rats, H and E, X 140.

- Fig. 1. Third day after cessation of PTU treatment.
 - Fig. 2. Eighth day after cessation of PTU treatment.
 - Fig. 3. Third day after At²¹¹ administration.
 - Fig. 4. Eighth day after At²¹¹ administration.
 - Fig. 5. Third day after cessation of PTU treatment and administration of At²¹¹.
 - Fig. 6. Eighth day after cessation of PTU treatment and administration of At²¹¹.
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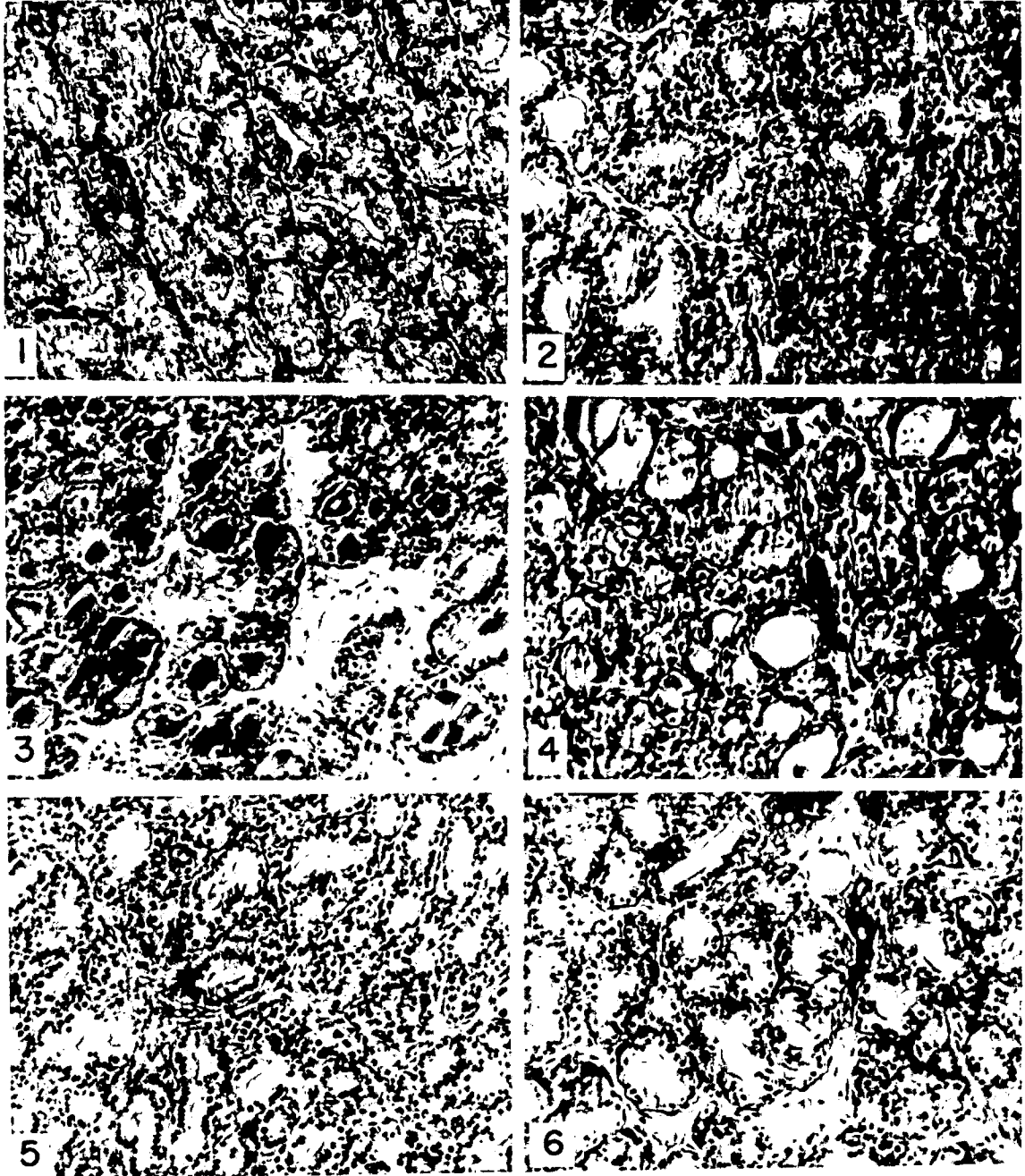


Plate II. Photomicrographs of thyroid tissue of female rats, H and E, X 140.

Fig. 7. Sixteenth day after cessation of PTU treatment.

Fig. 8. One month after cessation of PTU treatment.

Fig. 9. Sixteenth day after At²¹¹ administration.

Fig. 10. One month after At²¹¹ administration.

Fig. 11. Sixteenth day after cessation of PTU treatment and administration of At²¹¹.

Fig. 12. One month after cessation of PTU treatment and administration of At²¹¹.

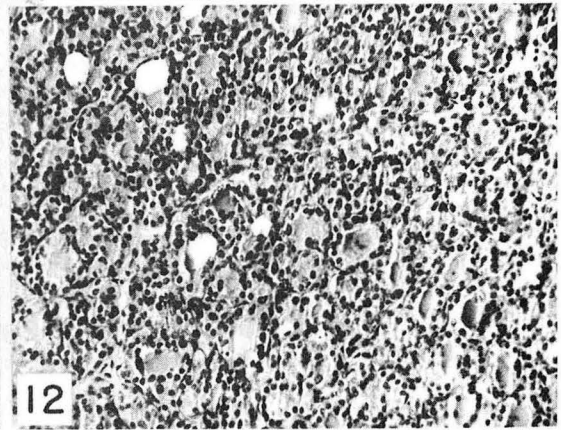
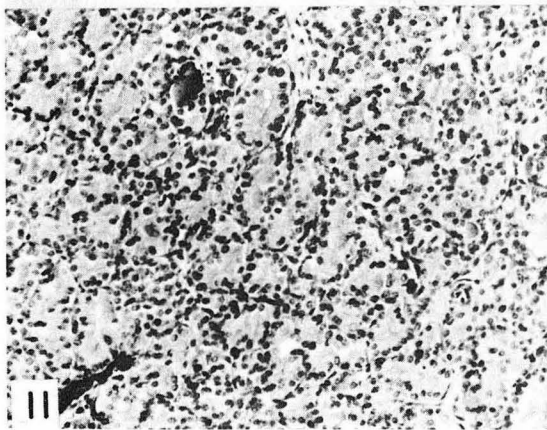
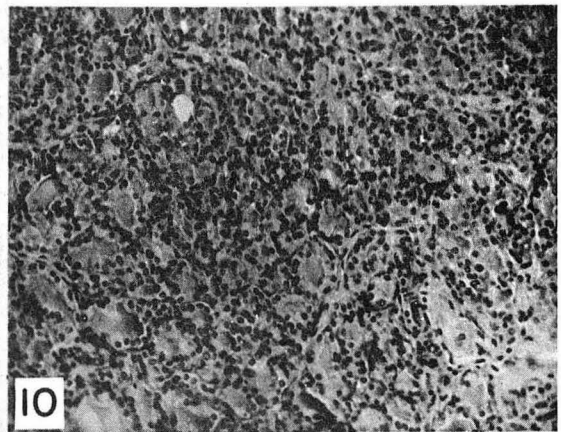
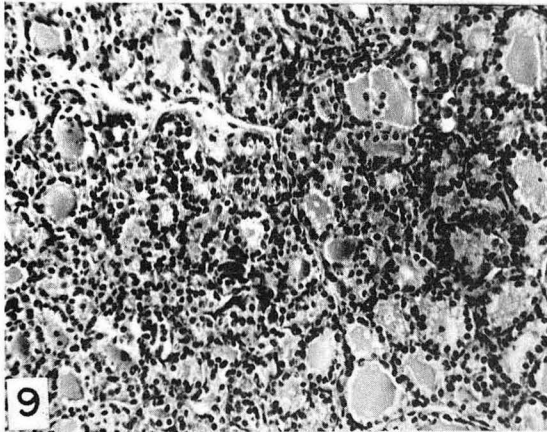
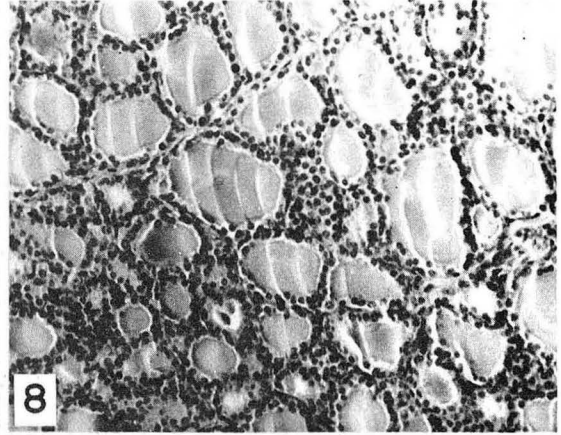
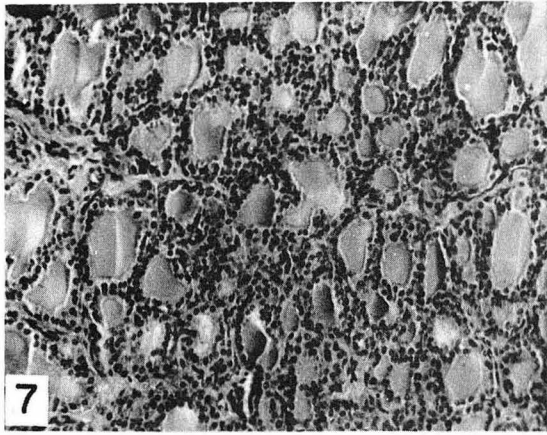
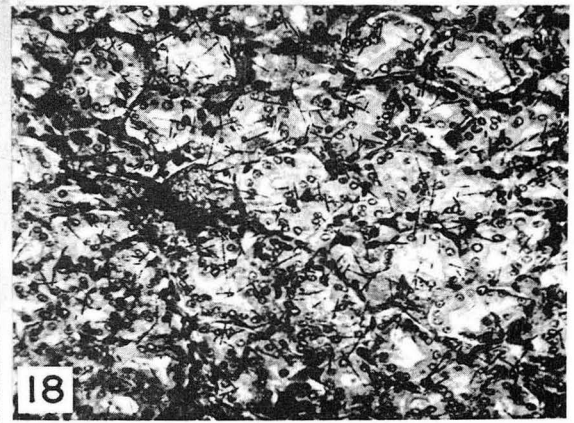
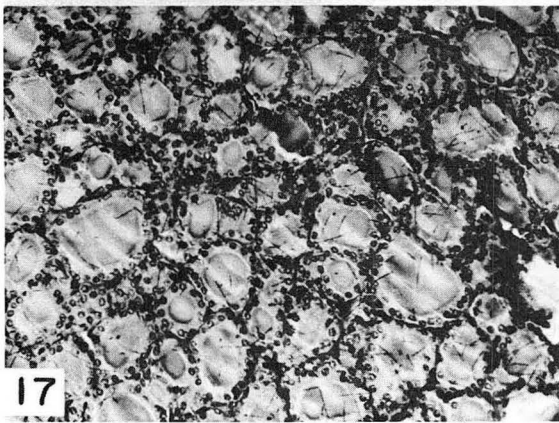
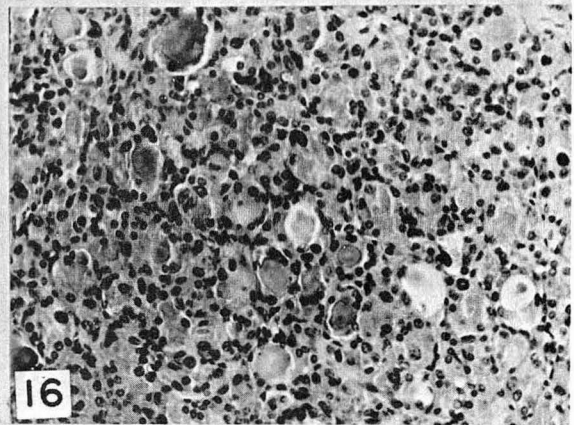
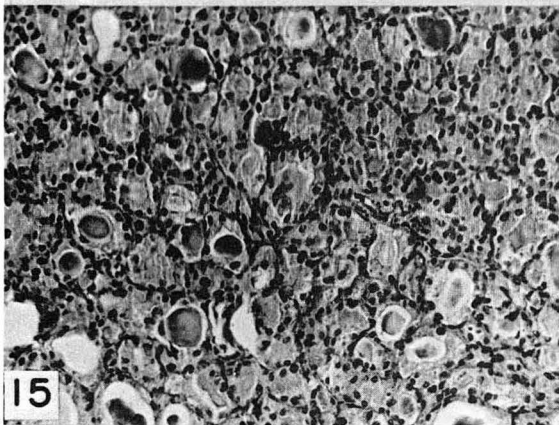
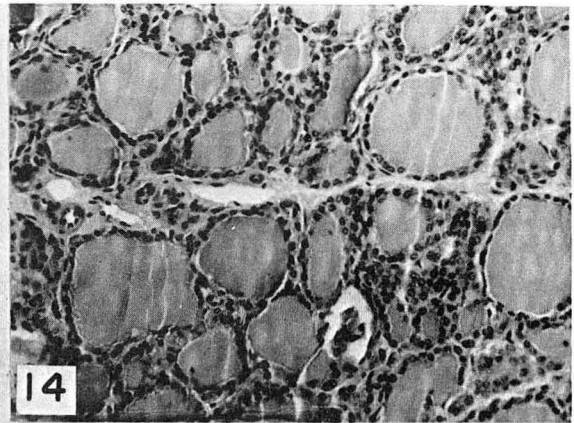
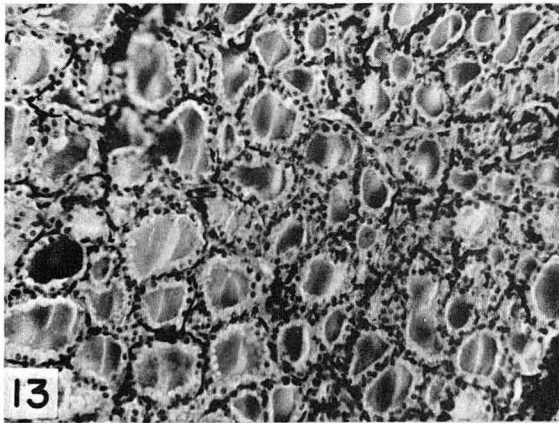


Plate III. Photomicrographs of thyroid tissue of female rats, H and E, X 140.

- Fig. 13. Normal control, 60 days of age. Periphery of gland toward left.
- Fig. 14. Normal control, 14 months of age. Field comparable to that shown in Fig. 13.
- Fig. 15. One year after administration of At^{211} .
- Fig. 16. One year after cessation of PTU and administration of At^{211} .
- Fig. 17. Autoradiograph showing distribution of At^{211} (alpha-particle tracks on NTA stripping film) in thyroid gland of normal 60-day-old rat.
- Fig. 18. Autoradiograph showing At^{211} distribution in thyroid gland following 11 days of treatment with propyl thiouracil.
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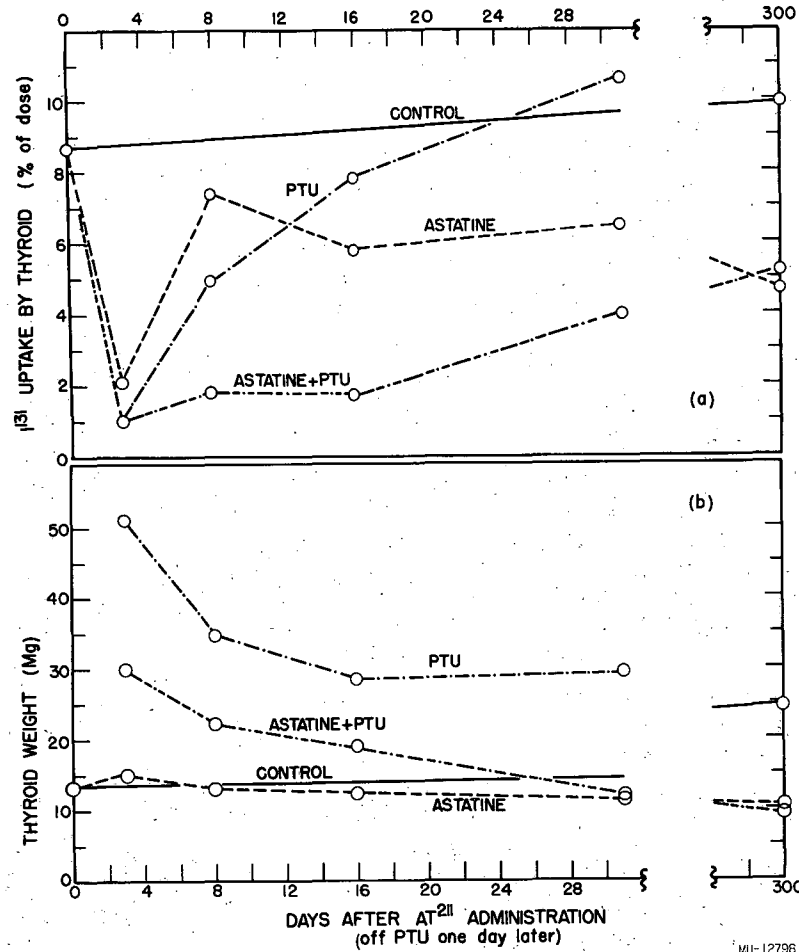


Fig. 19 Time sequence of changes in (a) thyroidal I¹³¹ uptake and (b) weight of rat thyroid glands after At²¹¹ irradiation. Glands of the At²¹¹ group were normal and of the PTU and PTU-plus-At²¹¹ groups were hyperplastic when radiation was administered. Standard errors and the number of animals represented at each point on the curves are shown in Table I.

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