of considerable concentrations of radioiodide in the epithelium of the binding and of the propylthiouracil-blocked thyroid gland indicates that an iodide concentrating mechanism is localized at the basal end of the cell. The persistence of the autoradiographic ring for at least 5 minutes after iodide^{125} administration indicates that the apical membrane can limit the transfer of iodide from the cell to the lumen. It is clear that since the epithelial radioiodide concentration is much greater than the concentration in the lumen most of the cellular radioiodide did not arise from diffusion from the lumen.

In propylthiouracil-treated animals variation in the occurrence of rings from follicle to follicle and from animal to animal may be a reflection of variation in metabolic activity of the glands examined. Experiments to be reported elsewhere have demonstrated that in hypophysectomized mice there were autoradiographic rings associated with almost all follicles in all animals studied 10 minutes after radioiodide injection whereas in animals fed a low iodine diet for 2 weeks autoradiographic rings were rarely seen 4 minutes after radioiodide injection.

Summary. At short time intervals after injection of iodide^{125}, the concentration of inorganic iodide^{125} in the thyroid epithelial cells of some follicles was much higher than in the lumen of the follicle or in blood vessels as demonstrated by autoradiographic methods. This finding in both binding and propylthiouracil-blocked thyroid glands suggests that the basal cell membrane is responsible for iodide concentration. The persistence of an autoradiographic image over the follicular cells for at least 5 minutes after iodide^{125} injection suggests that the apical cell membrane exerts some control over the passage of radioiodide from the cell into the follicular lumen.

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Effects of Sulfaguanidine on Rat Submaxillary Gland. (29036)

COSTAN W. BERARD AND STEPHEN C. WOODWARD (Introduced by R. L. Mundy)
Department of Surgical Metabolism and Pathology, Division of Basic Surgical Research, Walter Reed Army Institute of Research, Washington, D. C.

Thyroidectomy or goitrogen administration induces reduction in relative and absolute gland weights and atrophic degranulation of granular tubules in the rat submaxillary gland(1-3). Sulfonamides are unique goitrogens in that their antithyroid action is potentiated by iodides(4). This study reports the effects of sulfaguanidine upon weight and morphology of the rat submaxillary gland.

Methods. Walter Reed strain male albino rats weighing 230-280 g (10-11 weeks old) were used in 28-day experiments. In 2- and 4-month experiments, animals weighed initially 140-160 g (8 weeks old). Basal diet consisted of ground D&G rat biscuits* (iodine content, 800 μg/kg) and tap water *ad lib.* This diet was altered by addition of 2% sulfaguanidine (SG)† or 0.5% NaI, singly or combined, and used for appropriate groups (Tables II and III). Surgical thyroidectomies (Tx) were performed on certain animals under ether anesthesia on the first day of the experiment. Animals were weighed weekly and at sacrifice. In all experiments

* G. L. Baking Co., Frederick, Md.

† Matheson, Coleman, & Bell, E. Rutherford, N. J.

TABLE I. Relative Weight Changes with Age of Submaxillary Glands of Control Rats.

Age (days)	No. of anmials	Duration (mo)	Body wt (g)*	Submaxillary gland wt* Total (mg)	mg/100 g
96	6	1	369 ± 28	637 ± 53	173 ± 12
96	6	1	367 ± 23	663 ± 67	176 ± 16
125	5	2	388 ± 47	588 ± 86	152 ± 15
125	5	2	384 ± 21	583 ± 47	152 ± 11
160	10	4	460 ± 40	616 ± 37	135 ± 10
160	13	4	449 ± 56	561 ± 58	128 ± 15

* Mean ± standard deviation.

TABLE II. Effects of Sulfaguanidine on Rat Submaxillary and Thyroid Gland Weights.

Diet	No. of animals	Duration (mo)	Body wt (g)* Initial	Body wt (g)* Final	Thyroid wt* (mg/100 g)	Submaxillary wt* Total (mg)	Submaxillary wt* (mg/100 g)
Control	6	1	238 ± 20	369 ± 28	5.6 ± 0.6	637 ± 53	173 ± 12
SG	6	1	236 ± 18	316 ± 20[b]†	18.2 ± 4.0[a]	534 ± 24[b]	170 ± 12
Control	5	2	154 ± 3	384 ± 21	6.9 ± 1.2	583 ± 47	152 ± 11
SG	5	2	154 ± 3	345 ± 19[c]	21.5 ± 4.8[a]	535 ± 18	155 ± 5
Control	13	4	166 ± 4	449 ± 56	5.6 ± 0.9	561 ± 58	128 ± 15
SG	12	4	167 ± 5	355 ± 41[a]	20.5 ± 5.3[a]	551 ± 81	155 ± 13[a]

* Mean ± standard deviation.
† P values based on t-test for significance of difference between means of control and SG animals:
[a] represents $P < .001$
[b] " $P < .01$
[c] " $P < .02$

animals were housed in separate cages in a room thermostatically maintained at 76 ± 2°F.

Animals were sacrificed by CO_2 asphyxiation and thyroids and submaxillary glands were immediately removed and weighed on a Mettler balance. Each submaxillary gland was then bisected in its largest plane and fixed in neutral buffered formalin. Seven micron paraffin sections were stained with H&E and PAS-hematoxylin. Multiple levels of tracheas were examined to determine completeness of thyroidectomy. Tubular/acinar area ratios were determined with an ocular grid from 5 contiguous, central, high-power fields in each gland.

Results. Body and gland weights. In normal animals submaxillary gland weight was maximal at about 100 days of age while body weight continued to increase. Control values for relative gland weight thus varied with age (Table I).

Sulfaguanidine alone was markedly goitrogenic and significantly affected body weight, but at no time did it cause relative weight reduction of the submaxillary gland (Table II). Addition of 0.5% NaI to SG increased goiter size and arrested body weight yet caused no decrease in relative gland weight (Table III).

The post-thyroidectomy state, like SG, was attended by reduced body weight and unaltered relative gland weight (Table IV). However, thyroidectomy usually is incomplete(5). As expected, body weight and absolute gland weight were markedly reduced by addition of SG to the diet of thyroidectomized animals. Submaxillary glands, however, were not subnormal on a relative basis (Table IV).

Histopathology. Thyroidectomies were incomplete. Both TX and TX + SG animals demonstrated a total of 2 to 5 high power fields of hyperplastic thyroid remnants attached to the trachea.

The "glandular unit" of the adult rat submaxillary gland, according to Jacoby and Leeson(6) whose terminology is employed here, consists of acini, intercalated ducts, convoluted (*granular*) tubules, and intralobular "striated" ducts (Fig. 1). Control tubular/acinar area ratios increased in our animals

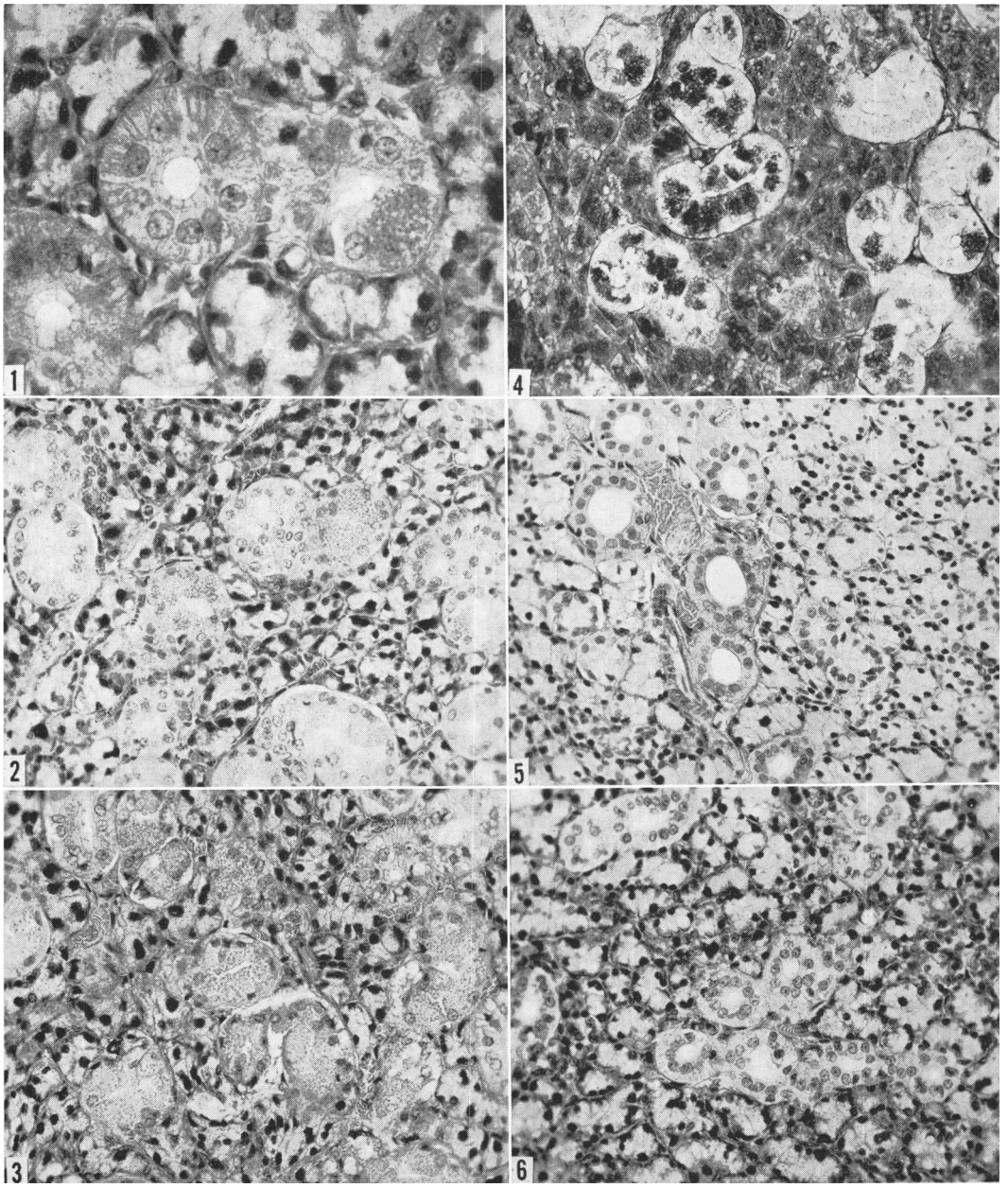

FIG. 1. Striated duct, left center, granular convoluted tubule, right center, surrounded by acini, control animal. (PAS, ×410).

FIG. 2. Tubule granule preservation in 4-month thyroidectomized rat submaxillary gland. (H & E, ×195).

FIG. 3. Intact submaxillary tubular granules in 4-month sulfaguanidine-treated animal. T/A ratio the same as in comparable-aged control. (H & E, ×195).

FIG. 4. PAS-positive granules in 4-month sulfaguanidine-treated animal. Note isolated PAS-positive cells in tubules on right. (PAS, ×195).

FIG. 5. Four-month thyroidectomized, sulfaguanidine-treated rat's submaxillary gland. Obvious tubular degranulation and T/A ratio reversal accompany preserved striated ducts. (H & E, ×195).

FIG. 6. Two-month thyroidectomized, sulfaguanidine-treated rat's submaxillary gland. Appearance similar to Fig. 5. (H & E, ×195).

from 0.6-0.7 at 28 days to 1.2-1.3 at 4 months. At 28 days striated ducts and granular tubules were about equally common but, by 4 months, two-thirds to three-fourths of intralobular tubules contained granules. The remainder were primarily striated ducts.

In structures identified as granular tubules in H&E sections, corresponding PAS sections showed about two-thirds of cells to contain PAS-positive granules (Fig. 4). Other cells contained PAS-negative granules and, occasionally, in the same cell, mixtures of PAS-positive and PAS-negative granules.

The submaxillary glands of all experimental groups except the 2- and 4-month Tx + SG, were histologically indistinguishable from those of appropriate controls. The glands of both 4-month Tx (Fig. 2) and 4-month SG animals (Fig. 3 and 4) contained plentifully granulated tubules while the opposite was found in 2- and 4-month Tx + SG animals (Fig. 5, 6 and 7). Here, tubular granules

TABLE III. Effects of Sulfaguanidine and Sodium Iodide on Rat Submaxillary and Thyroid Gland Weights.

Diet	No. of animals	Duration (mo)	Body wt (g)* Initial	Body wt (g)* Final	Thyroid wt* (mg/100 g)	Submaxillary wt* Total (mg)	Submaxillary wt* (mg/100 g)
Control	18	1	233 ± 25	335 ± 41	6.3 ± .9	627 ± 69	184 ± 16
.5% NaI	6	1	238 ± 24	306 ± 43 } d†	7.9 ± 2.3 } a	576 ± 46 } a	190 ± 18
.5% NaI + SG	6	1	242 ± 18	258 ± 15 } a	25.1 ± 5.1 } d	450 ± 14 } b	175 ± 10
SG	12	1	233 ± 22	310 ± 37	19.3 ± 4.8	519 ± 61	165 ± 13

* Mean ± standard deviation.
† P values based on t-test for significance of difference between means connected by brackets:
[a] represents $P < .001$
[b] " $P < .01$
[d] " $P < .05$

TABLE IV. Effects of Sulfaguanidine and Thyroidectomy on Rat Submaxillary Gland Weight.

Group	No. of animals	Duration (mo)	Body wt (g)* Initial	Body wt (g)* Final	Submaxillary wt Total (mg)	Submaxillary wt mg/100 g
Controls	5	2	159 ± 13	388 ± 47	588 ± 86	152 ± 15
Tx	4	2	158 ± 10	330 ± 83 } c†	492 ± 123 } d	150 ± 21
Tx + SG	4	2	153 ± 2	180 ± 10 } a	325 ± 30 } a	180 ± 16 } c
SG	5	2	154 ± 3	345 ± 19 } c	535 ± 18	155 ± 5
Controls	5	2	154 ± 3	384 ± 21	583 ± 47	152 ± 11
Controls	10	4	158 ± 10	460 ± 40 } a	616 ± 37 } a	135 ± 10
Tx	10	4	158 ± 8	355 ± 70 } a	465 ± 83 } a	133 ± 19 } b
Tx + SG	9	4	163 ± 10	193 ± 17 } a	308 ± 30 } a	160 ± 17
SG	12	4	167 ± 5	355 ± 41 } a	551 ± 81	155 ± 13 } a
Controls	13	4	166 ± 4	449 ± 56	561 ± 58	128 ± 15

* Means ± standard deviation.
† P values based on t-test for significance of difference between means connected by brackets:
[a] represents $P < .001$
[b] " $P < .01$
[c] " $P < .02$
[d] " $P < .05$

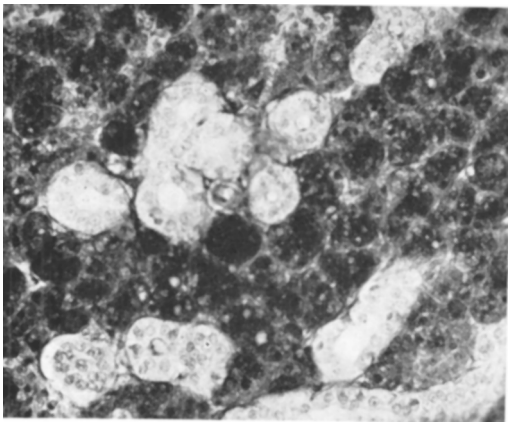

FIG. 7. Absence of PAS-positive cells in tubules of gland shown in Fig. 6. (PAS, ×195).

were absent. The sites presumed to have been occupied by granular tubules contained simple cuboidal ducts. Tubular/acinar ratios were reduced to 0.4-0.6. The morphologic effects of combined thyroidectomy and sulfaguanidine diet were confined to granular tubules. Other glandular structures (acini, ducts, and vasculature) were unaffected; unaltered striated ducts and simple cuboidal ducts were comparably numerous.

Discussion. Several goitrogens have been shown to reduce relative weight of rat submaxillary glands and to cause tubular degranulation. Sulfaguanidine, conversely, even when potentiated by iodide (Table III), did not effect such changes. The only combination resulting in degranulation in this study, surgical thyroidectomy followed by sulfaguanidine diet, probably induced a degree of hypothyroidism attributed to thyroidectomy or other goitrogens alone by others(1-3).

Sulfaguanidine is a relatively weak antithyroid agent(7) strongly potentiated by iodide(4). It appears, however, that thyroid hormonal synthesis adequate for granule preservation must occur even in the profoundly altered thyroid of the rat given sulfaguanidine and iodide. It is possible that different patterns of response would have been elicited in younger rats, since the postnatal period of submaxillary gland development is long(6).

We found poor correlation between submaxillary gland weights and histologic observations. Glands of animals thyroidectomized or given sulfaguanidine (with or without iodide) for 28 days were on an absolute basis significantly lighter than those of controls but showed no tubular degranulation. Conversely, relative gland weight was actually greater than controls in the only groups showing tubular degranulation (thyroidectomy plus sulfaguanidine). Such glands were, however, on an absolute basis the lightest encountered in any group.

Conclusions. 1. Sulfaguanadine, administered in the diet for one to four months, does not result in degranulation of the convoluted tubules of the rat submaxillary gland, even when potentiated by massive doses of sodium iodide. Degranulation results, however, when sulfaguanidine administration follows incomplete surgical thyroidectomy. 2. Alterations in absolute or relative submaxillary gland weight correlate poorly with histologic changes in the convoluted granular tubules.

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