BY STATISTICAL DATA AND HISTOLOGICAL STUDIES, A CLOSE RELATIONSHIP HAS BEEN ESTABLISHED BETWEEN ENDEMIC GOITER AND CANCER OF THE THYROID. MALIGNANT GOITER ARISES ALMOST ALWAYS FROM THYROID ADENOMA. MANY CLINICIANS REGARD THE SO-CALLED FETAL ADENOMA AS A PRECANCEROUS LESION, AND THE DIFFERENTIAL DIAGNOSIS BETWEEN ADENOMA AND MALIGNANT GOITER IS OFTEN IMPOSSIBLE FOR THE HISTOPATHOLOGIST (1, 2).

There is, on the other hand, much disagreement about the nature of nodular goiter. It is regarded by some as a localized hyperplasia, by others as a true tumor. Thyroid adenoma presents perplexing problems to the goiter student as well as to the investigator of neoplastic diseases. According to Marine (3), the fact that adenomatous goiter is restricted almost entirely to human beings makes it exceedingly difficult to test experimentally any hypothesis regarding its origin or nature.

In the American literature, no reports on the experimental production of thyroid adenoma could be found. My own observations on this type of goiter may, therefore, be of interest.

Since 1929, I have carried out goiter experiments in a locality (Wichita) which has a very low incidence of endemic goiter (4). In white rats, goiters could be produced within three months by a calcium-rich diet. Until 1934, only diffuse enlargements of the thyroid were obtained. In my last series, however, definite thyroid adenomas developed in animals on the goitrogenic diet.

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Experimental Study

Six male rats, about one year old, served as controls and received our stock diet containing green vegetables, meat, and cereals. The two experimental groups were fed a basal diet consisting of cornmeal and rolled oats, boiled in distilled water. The first group had 2 per cent calcium chloride added to the basal diet, so that the daily intake for each rat was about 0.2 grams. In the second experimental group, each animal received, in addition to the calcium-rich diet, two micrograms of potassium iodide daily. The first experimental group consisted of six white male rats; the second of 10 white rats of the same age, 6 males and 4 females. Males and females were kept in separate Dormer cages. The feeding was continued for a period of 140 days and all animals were killed with chloroform. The thyroid glands were removed immediately after death, weighed, and measured.

![Image](image_url)

**Fig. 2.** Thyroid Adenoma in White Rat on Calcium-Rich and Iodine-Poor Diet. × 6

In the controls, the average weight of the whole fresh gland was 26.3 mg. The animals which had received a calcium-rich and iodine-poor diet presented a marked enlargement of the thyroid. The average weight was 73.8 mg. It was in this group of 6 white rats that two large adenomas were found. Fig. 1 shows the nodules, both of which were located in the right lobe. One measured 4.5 mm. in diameter, the other 3 mm. Both nodules were well circumscribed, and the surrounding thyroid tissue was markedly compressed by their expansive growth. No definite fibrous capsule, however, was present (Figs. 2 and 3). The structure of the adenomas was identical and was tubular and small-follicular (Fig. 4). Larger cysts were found in both nodules, and from their walls branching papillae were protruding into the lumen. The epithelial cells were cuboid or columnar, the nuclei appeared much darker and closer together than in the surrounding thyroid tissue proper. In the larger adenoma, one acinus was lined partly by columnar epithelium, partly by several layers of squamous cells (Fig. 5). Metaplastic squamous epithelium has been described by Wegelin (5) in human fetal adenomas. The marked infiltration with leukocytes
Fig. 3. Thyroid adenoma in white rat after calcium-rich and iodine-poor diet. $\times 30$

Fig. 4. High magnification of thyroid adenoma in white rat: tubular and small-follicular structure. $\times 150$

Fig. 5. Metaplastic squamous epithelium lining acinus in thyroid adenoma of white rat. $\times 150$
which was found in this particular area suggests that an inflammatory process may be responsible for this unusual change in the acinar cell type. Degenerative processes, calcification, fibrosis, and hyalinization, which are so common in human thyroid adenomas, were completely absent in these rat tumors.

The thyroids in the animals of the second experimental group, which had received a calcium-rich and iodine-rich diet, were also definitely enlarged. The average thyroid weight was 40.9 mg. The glands presented the microscopic picture of colloid goiter. One of the 10 animals in this group had a small colloid nodule, 1 mm. in diameter (Fig. 6). It was composed of large acini lined with cuboid epithelium and filled with well stained colloid. The fact that the epithelial cells in the nodule were higher than in the surrounding tissue, and formed even papillae protruding into the lumen of many acini, is not in accord with Rienhoff’s view that colloid nodules are due to involution, but suggests a proliferative process with increased secretory activity.

In normal thyroids of white rats, adenomas have never been observed (Bircher, 6; McCarrison and Madhava, 7; Langhans and Wegelin, 8). This has also been my own experience. American workers who have been able to produce goiters in animals by various methods describe only diffuse hyperplasia of the thyroid, and the three thyroid nodules which I observed in white rats fed on a goitrogenic diet are the first described in this country.

Wegelin (8), in 1919, saw only exceptionally nodose goiters in white rats which were kept in different endemic goiter regions of Switzerland. In his later experiments (1927), however, half of the goiters in white rats showed adenomas. The largest one in his (9) series measured 3 mm. in diameter, and was, therefore, decidedly smaller than the largest one here reported.
Thyroid adenomas in the white rat arise apparently from differentiated thyroid epithelium. Wölfler's (10) assumption that adenomas of the thyroid develop from embryonal cell rests scattered throughout the thyroid tissue is not supported by my findings, since the thyroid of the rat does not contain any fetal rests. The term "fetal adenoma" is, therefore, a misnomer. Aschoff (11) expressed the belief that adenomas originate in the central canaliculi of the thyroid lobule. However, this view must also be rejected, since such centrally situated structures are never found in the thyroid of the rat. The view of Hitzig (12) and Michaud (13) seems to be the most plausible, namely that the nodules are not embryonal rests, but that they develop from differentiated thyroid tissue within a localized area. In their first stage, these proliferative areas represent localized hyperplasias, but after reaching a certain size, they behave like true neoplasms and compress the surrounding thyroid tissue by expansive growth. In this respect there is no distinction between parenchymatous, so-called fetal, adenomas and colloid nodules.

The results of my experimental studies suggest that it is the iodine content of the goitrogenic diet which determines whether a thyroid nodule will be parenchymatous or colloid-rich. The same goitrogenic factor, namely calcium excess, produced, in my experiments, parenchymatous adenomas when the iodine content of the diet was extremely low, and colloid goiter when the iodine intake was relatively high. Epidemiological studies on human goiter (14) point to the same conclusions. In mountainous goiter regions, where there seems to be a definite lack of iodine, parenchymatous adenomas form the most common type of goiter in adults, whereas in level countries, where the iodine content of the food and water is relatively higher, most of the thyroid nodules are colloid-rich.

**Summary**

For the first time in North America, thyroid adenomas were observed in white rats which received a calcium-rich goitrogenic diet. Thyroid nodules originate not from fetal rests, but from differentiated thyroid epithelium. They are due to the same stimulus which causes diffuse hyperplasia.

Thyroid nodules, after reaching a certain size, show all the characteristics of true adenomas. They represent an intermediate stage between hyperplasia and malignant tumor.

**Bibliography**


