ADENOMATOSIS, OR THE DIFFUSE ADENOMATOUS GOITER *

J. EARL ELSE, M.D.
Assistant Professor and Chairman, Executive Committee, Department of Surgery, University of Oregon Medical School
PORTLAND, ORE.

Under the term adenoma, there is described in the literature two definite distinct pathologic entities, adenomatosis, or the diffuse adenomatous goiter, and true adenoma, which is a definite encapsulated growth beginning from a single point and answering all the requirements of the benign tumors.

Adenomatosis of the thyroid is characterized by a diffuse new formation of acini usually involving the entire thyroid gland, beginning with the fetal type without secretion, but later assuming the adult or colloid type, and giving rise to no symptoms at first, but later to those of pure hyperthyroidism.

Wilson, in 1913, briefly described this condition and applied the term adenomatosis. Goetsch, in 1920 and 1921, described the early stage under the term diffuse adenomatosis, but he referred to the new formation of acini as "an abortive attempt at the formation of young small alveoli." Plummer, in his writings, has grouped adenomatosis with the adenomas, treating them as a single entity. In addition to these references, I have referred to this condition in several communications, but up to the present there has been no description of the disease tracing it through its entire course.

PATHOLOGY

The pathlogic picture varies with the stage of the disease.

Early Adenomatosis.—The thyroid gland is moderately enlarged, the surface is smooth, and the consistency is somewhat increased over the normal. On

* From the goiter clinic of the University of Oregon Medical School and the pathologic laboratory of Good Samaritan Hospital.

* Read before the Section on Surgery, General and Abdominal, at the Seventy-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., May, 1925.

section, the cut surface presents a more dense appearance than in the normal gland; and, while some colloid is present, there is not the same semitranslucent appearance characteristic of the normal thyroid. In the early stage the gland is homogeneous, and nowhere is there to be seen any tendency toward nodular formation. On microscopic examination (Fig. 1), it is found to contain both fetal acini and apparently normal or colloid acini. Between these two types of acini are found all possible variations, the appearance being indistinguishable from that of the mixed adenoma. In other fields there may be an apparent increase in the interstitial cells. In some areas these cells are arranged in masses, many of them showing the definite beginning of acinus formation. It was these areas that Goetsch referred to as being abortive attempts at the formation of young small alveoli. A study of a series of cases, however, demonstrates that this is not an abortive attempt, but is instead the real beginning of the new acini.

Late Adenomatosis.—The gland shows a marked enlargement. The surface is more or less lobulated, often with very definite nodules projecting. On cut section (Fig. 2), the nodular arrangement is still more manifest. On close observation, these nodular masses are seen to be made up of groups of acini distended with colloid. Many of these masses have a thin, membranous capsule and can be enucleated, presenting an appearance not unlike that of an adenoma, but differing from an adenoma in that the capsule is only a thin membrane instead of the well developed capsule of the adenoma (Fig. 3). Between these nodules is found compressed thyroid tissue. In some places degeneration has taken place, while in other areas there may be marked connective tissue proliferation, marking the site of a former degenerative process or a hemorrhage. Sometimes cystic formation is present, while hemorrhagic areas, either into some of the nodules giving a sharply circumscribed hemorrhagic mass, or infiltrating between the nodules, may be found. On microscopic examination of the colloid nodules, the picture is very similar to that seen in a colloid adenoma. Sections made from the tissue between the nodules often show the same type of structure, differing only in the amount of colloid present in the acini. Solitary lymph follicles may be found.

The blood supply in adenomatosis is increased, and in many cases there is a very definite increase in the collateral circulation.

PATHOGENESIS

It is impossible to trace any one given thyroid gland through its course from the beginning new formation of acini to the development of colloid adenomatosis, but by studying a series of cases, the method of development can be fairly well ascertained. The very first evidence of the beginning of an adenomatosis is the

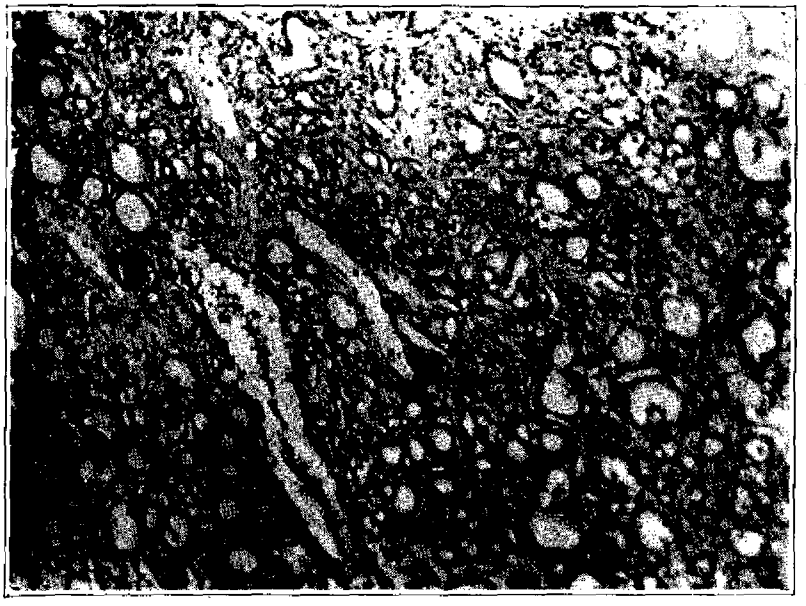

Fig. 1.—Early adenomatosis: thyroid only slightly enlarged, with no nodules; diffuse new formation of acini; fetal and adult acini present throughout thyroid.

formation of undifferentiated cells in masses (Fig. 4). These cells are probably identical with those described by Wölfler as interstitial cells. They do not differ from the appearance of the cells seen in the beginning of the development of new acini within old acini, as seen in compensatory hyperplasia (Fig. 5). Just as in well developed compensatory hyperplasia one sees in the center the undifferentiated cells, external to this the fetal acini, and next to the wall of the parent acini the colloid acini, so in adenomatosis (Fig. 6) one finds first a group of the undifferentiated cells, then the newly formed acini of the fetal type, and then the acini that are taking on the power of secreting colloid. From

this stage the process goes on to the stage at which the acini are overdistended with colloid. In some areas the development becomes more rapid, pushing the neighboring acini to one side, thus giving an appearance similar to that seen in adenomas, but differing in that there is either no capsule at all or usually only a thin membranous capsule. Sometimes there is a fairly definite capsule about some of the nodules, but rarely does it attain a thickness or appearance resembling that seen in the adenomas.

Taking the picture as a whole, it gives one the impression of a diffuse new acinous formation in which

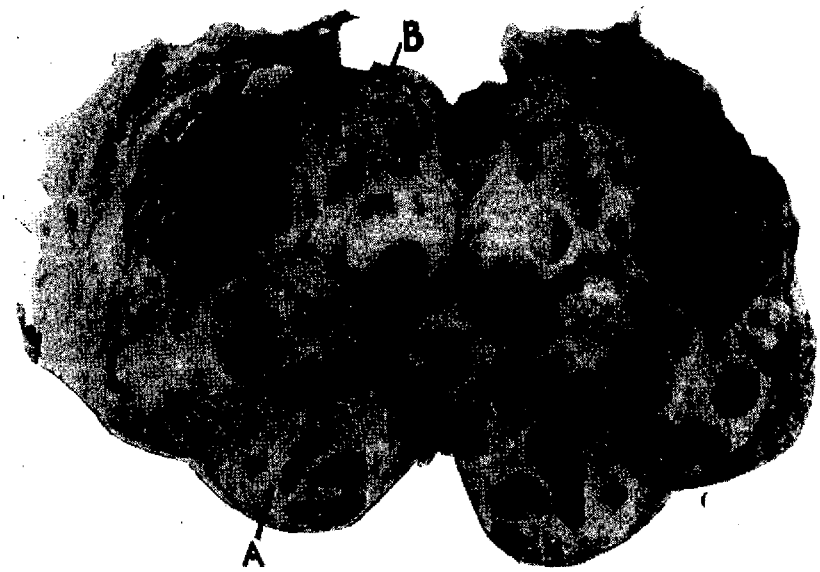

Fig. 2.—Adenomatosis: cut surface showing adenomatous nodules: *A*, unencapsulated nodules; *B*, nodule with thin capsule; to be contrasted with Figure 3.

certain areas have developed more rapidly than others, thus producing the nodular effect.

The origin of the cells from which the new acini spring is not known. A study of a series of cases of adenomatosis suggests three different theories: (1) congenital; (2) origin from the Wölfler or interstitial cells; (3) a hyperplasia of the cells lining the normal acini.

According to the first theory, either the acini are present at the time of birth, being an abnormal fetal development, or else there are present certain undifferentiated cells at birth not normally found in the thyroid gland from which the acini develop. According to

the second theory, the new acini form from the interstitial cells of Wölfler, which are normally found in the thyroid gland. The function of these cells is not definitely known, but it may be that they are for the purpose of regeneration in thyroids that have been partially destroyed or removed, or in thyroids secreting an insufficient amount of thyroxin. In other organs, the regenerative ability is usually present. In the liver, for example, where there has been a slow destruction of the liver lobules, as in cirrhosis, there is often a new development of liver substance in adenomatous-like masses sufficient to carry on the liver function so long

Fig. 3.—Multiple adenomas: three adenomas in one lobe; definitely encapsulated. Difference from Figure 2 may be noted.

as the blood supply is not interfered with. This new formation in the liver probably develops from the bile radicles. The thyroid gland, not having ducts through which the secretion may be discharged and from which regeneration may take place, may have instead the so-called interstitial cells for this purpose, and from these, according to this theory, may come a diffuse atypical acinous formation.

The third theory is that a new formation of acini similar to that seen in compensatory hyperplasia may develop from the cells lining the old acini, but outside the walls of these acini instead of inside, as in compensatory hyperplasia.

It would appear from the glands studied that the theory that these new acini develop from the inter-

stitial cells was more tenable than any other theory however, without the opportunity of studying a large number of thyroid glands of children or of the age of adolescence, one cannot be certain that there may not be some which show the characteristic findings of adenomatosis from birth. Accepting the theory of the development from the interstitial cells as being correct, the source of the interstitial cells is the next problem

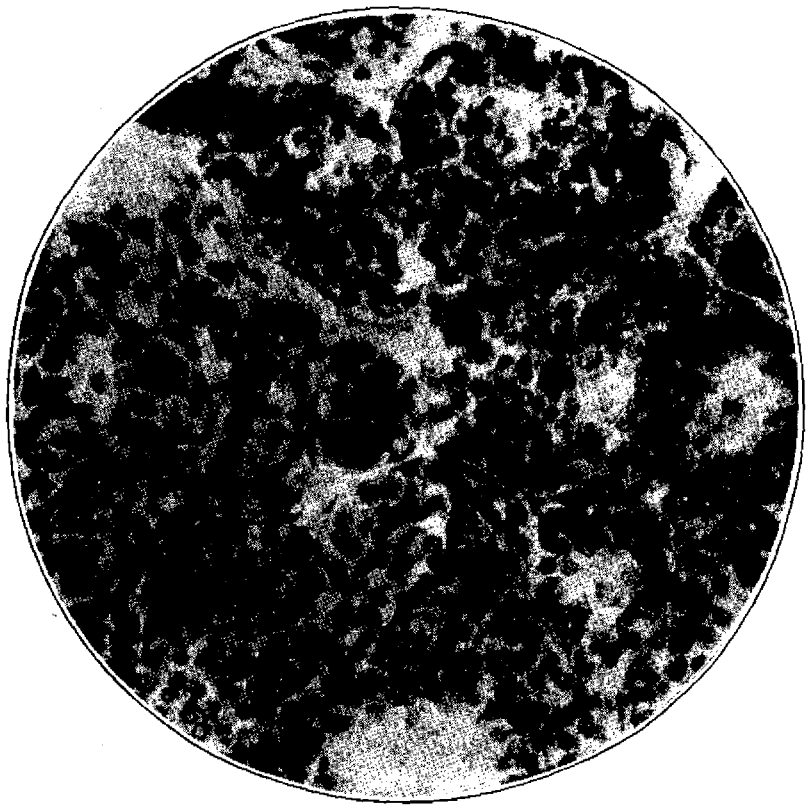

Fig. 4.—Adenomatosis, showing transition from undifferentiated cells to fetal acini.

in pathogenesis. These may be congenital, put there for the purpose of regeneration, as stated, or it may be that they spring from the epithelial cells of the acini.

ETIOLOGY

Three theories of causation are apparent: (1) that it is congenital; (2) that it develops from uncured adolescent goiter; (3) that it is developed as the result of a stimulus from the mild hypothyroidism due to iodin deficiency in the food and drink intake.

1. The congenital theory has already been discussed under pathogenesis.

2. The patients having adenomatosis that I have seen may be divided into three groups so far as a history of adolescent goiter is concerned. The first group, by far the largest, gives a history of having had an adolescent goiter. The second group is uncertain whether a goiter was present or not during the adolescent period, and the third group, which is the smallest, is certain

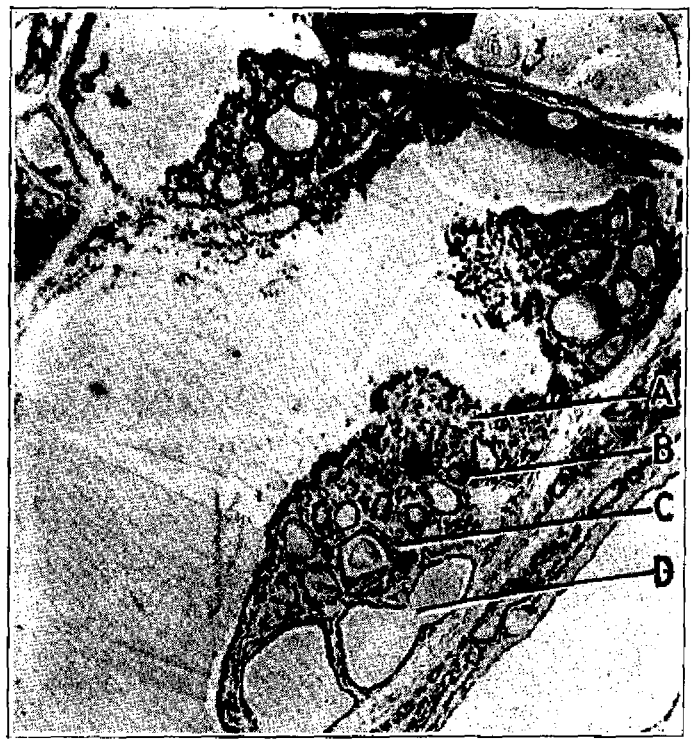

Fig. 5.—Compensatory hyperplasia, showing manner of the development of new acini within old acini: *A*, undifferentiated cells; *B*, fetal acini; *C*, intermediate cells; *D*, adult acini.

that there was not a goiter; but many if not all of these patients may be mistaken. The adolescent goiter probably leaves the thyroid in a somewhat atypical state with a reduced reserve, so that when increased demand is thrown on the thyroid gland in later life the changes characteristic of adenomatosis take place. Patients with other forms of goiter in adult life gave the same history regarding adolescent goiter; hence, it appears probable that an uncured adolescent goiter may predispose to the development of all types of adult goiter.

3. It is known that mild hypothyroidism due to a deficient iodin intake may result in: (1) an oversecretion of colloid, for the thyroid in its attempt to secrete more thyroxin may secrete too much colloid; (2) a hyperplasia of the cells within the acini, as seen in hyperplastic adolescent goiters, in which the hyperplasia may be either diffuse or localized and in the latter case often mistaken for adenomas, and (3) the new formation of acini, as seen in compensatory hyperplasia. To summarize our knowledge of the etiology,

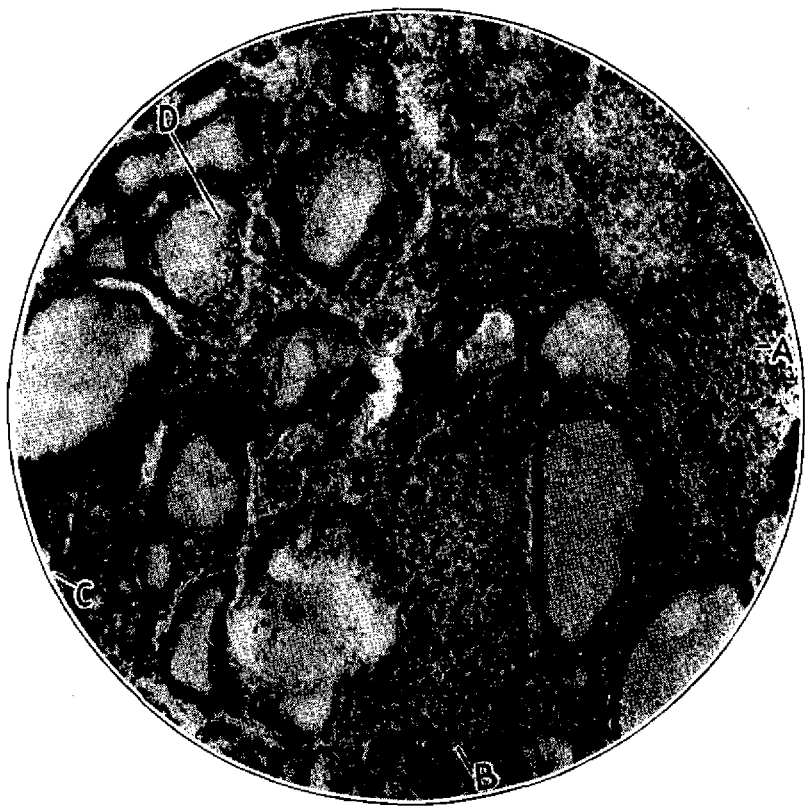

Fig. 6.—Adenomatosis: *A*, undifferentiated cells; *B*, beginning fetal acinus formation; *C*, intermediate acini; *D*, adult acini.

it would seem that a simple nontoxic goiter, as the goiter of childhood, the adolescent goiter, or the colloid goiter of adult life, but more especially the adolescent goiter, predispose to the development of adenomatosis, and that an iodin deficiency in the food intake is an important factor.

SYMPTOMATOLOGY

Early in the development of this disease, the only evidence of the presence of an adenomatosis is a slight

enlargement of the thyroid gland. It is probable that considerable time elapses between the beginning of the adenomatosis and the beginning of the symptoms in those that become toxic, the same as occurs in true adenomas. The onset of the symptoms is insidious, so that the patient does not come seeking treatment until the symptomatology has become fairly definite. At this time the most frequent complaints are tiring easily, nervousness, shortness of breath, tachycardia and palpitation. The appetite is usually very good, while the weight is variable, some patients losing and others having no change. There is never a history of acute symptoms as seen in exophthalmic goiter. The most common clinical findings are tachycardia, tremor, moderate rise in the basal metabolic rate, moist skin and palms. The size, shape and consistency of the thyroid vary with the stage of the disease.

Early the gland is only moderately enlarged and smooth; later it may be markedly enlarged and nodular. The largest goiters that we have seen belonged to this type. Increase in the systolic pressure occurs, followed gradually by an increase in the diastolic. The blood pressure of adenomatosis, like that in toxic adenomas and compensatory hyperplasia, differs from that in exophthalmic goiter in that the diastolic pressure is usually not lowered or, if lowered, is lowered but slightly, while the systolic pressure rises, thus giving an increase in the pulse pressure characteristic of toxic goiter. With the development of tachycardia and hypertension, cardiac hypertrophy takes place.

DIAGNOSIS

The diagnosis of hyperthyroidism is made on the history of tachycardia and palpitation, increased nervousness, tiring easily, increased sweating, increased pulse pressure accompanying a tachycardia, and an increase of the basal metabolic rate. The differential diagnosis between adenomatosis and toxic hyperplastic (exophthalmic) goiter is made, first, on the history and, secondly on the clinical symptoms. In adenomatosis there is usually a history of a goiter having existed for a considerable time. The onset of the symptoms is insidious. The most common complaints are tachycardia, palpitation, tiring easily and getting out of breath easily. There is a good appetite and usually little disturbance with the weight, unless the patient is

seen late in the disease. On physical examination, the goiter is found to be small and smooth and fairly firm early in the disease, and large, soft and lobulated late in the disease. There is an increase in pulse pressure resulting from a rise in the systolic pressure as a late sign. The diastolic pressure rises late in the disease but does not keep pace with the rise of the systolic pressure. Tremor is present. There is no exophthalmos, lagging of the upper lids, or hyperthyroid crisis. The basal metabolic rate is moderately increased, being found usually between a plus 30 and a plus 50.

In the toxic hyperplastic goiter (exophthalmic) as seen in the first attack, there is a definite tachycardia with fibrillation in the extreme cases, well marked tremor, evidence of a loss of weight, and lagging of the upper lids, with exophthalmos in the majority of patients. The skin is always moist, and the palms are sweaty. The patients give a history of being warm without a rise in temperature. Many of them want the living room cooler than other members of the family, and fewer covers at night. In a well marked attack, the basal metabolic rate is fairly high, usually 50 or more. The patients are usually nervous, and many of them talk rapidly. In secondary attacks, the findings are not so definite. There is an increase in the pulse pressure, resulting from a lowering of the diastolic, rather than to a raising of the systolic pressure. The systolic pressure may be normal, below normal or occasionally above normal. The diastolic pressure is rarely above normal.

A differential diagnosis between adenomatosis and toxic adenoma must be made by palpitation of the thyroid, as the clinical manifestations are the same. In the adenomas, there is one or at most two or three definitely isolated nodules. In adenomatosis, at first the gland shows only a diffuse enlargement without any nodular formations. Later the gland presents a lobulated sensation to the examining fingers instead of the definite isolated nodules of adenomas. In some instances in which there has been a rapid development in some areas there may be fairly definite nodules, but these are always accompanied by a more or less lobulated gland.

PROGNOSIS

The prognosis varies with the intensity of the disease and the length of time elapsing after the toxic symp-

toms develop. The prognosis of cure with proper treatment so far as the hyperthyroidism is concerned is usually good. Early in the disease a good prognosis for the relief of symptoms may be given, but after definite cardiac hypertrophy has developed, after definite hypertension has been established, and after the patient has become distinctly nervous, the prognosis, so far as relief from symptoms is concerned, becomes less favorable.

In the cases showing a marked hypertension, there is practically always a reduction in the blood pressure following operation, but it usually does not go entirely back to normal. A damaged heart muscle remains a damaged heart muscle. A badly disordered nervous system resulting from a prolonged or a pronounced hyperthyroidism may not become entirely normal again. To give a good prognosis, the proper treatment must be instituted early.

TREATMENT

A cure can be obtained in only one way; that is, early adequate removal of thyroid substance. Like all patients with hyperthyroidism, each patient must be carefully studied in order to determine the treatment for that individual. Patients seen fairly early will stand the radical operation well. It has been our experience that because of the increased collateral circulation, ligation of the superior thyroid poles is of little value. Patients in whom the condition is moderately severe are put in bed for a few days previous to operation with an ice collar about the neck, sufficient sedatives, barbital or morphin, to keep them quiet, and digalen, 10 minims (0.6 c.c.) intravenously or intramuscularly every four hours if the pulse is over 120. In the severe cases we use the roentgen ray rather than superior pole ligation to decrease the activity of the thyroid in order to make the patient a safe risk. On the night before the operation, the patients are always given barbital or morphin. There is no preoperative preparation. The patient's rest is not disturbed, even by giving an enema on the morning of operation. If the patient is found excessively apprehensive or nervous, the operation is postponed.

The operation must be a subtotal double lobectomy. We leave only the posterior capsule and a thin layer of thyroid gland adherent to it. If more is left there

is danger of recurrence. It is possible with this type of operation that there may be an occasional patient who will show the evidence of hypothyroidism for a short time, but we have never seen such a case. With a careful study of each individual case and with the proper preliminary preparation of the patient, there should be only a very slight mortality.

CONCLUSIONS

1. Adenomatosis is a definite pathologic entity differing from adenoma in that the process is diffuse and does not have a true capsule.

2. Adenomatosis produces a hyperthyroidism of the cardiovascular type.

3. It is important to differentiate between adenoma and adenomatosis because the former requires simple enucleation of the tumor growth, while the latter requires subtotal double lobectomy.

709 Stevens Building.

Reprinted from The Journal of the American Medical Association
December 12, 1925, Vol. 85, pp. 1878-1882