MALIGNANT DISEASE OF THE THYROID GLAND

A CLINICO-PATHOLOGICAL ANALYSIS OF 54 CASES OF THYROID MALIGNANCY

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The material presented in this paper represents a careful clinico-pathological study of the 54 cases of thyroid malignancy which have been reported by the pathological laboratory of the New York Hospital during the past thirteen years, supplementing a previous report (9). During this period a total of approximately 100,000 admissions to the hospital have been made. Of this number, slightly over 28,000 have had surgical specimens diagnosed pathologically. Among these 28,000 surgical specimens, some 1,600 have been thyroid glands; 855 of which have represented thyroid tumors, an incidence of a little more than 50 per cent. In this group of tumors 42 have been histologically and clinically malignant and are included in this report. The other 12 cases have come from outside sources, chiefly through the kindness of Dr. John Rogers, to whom we are indebted both for the material and for the clinical histories. One case, of particular interest as representing an intermediate phase between adenoma and subsequent pseudo-sarcomatous malignant degeneration, was sent us through Dr. John Scott of Louisville, Kentucky.

Analyzing these figures, we see that the incidence of thyroid malignancy in the New York Hospital series represents almost exactly 2.5 per cent of all thyroid specimens, and about 4.7 per cent of all thyroid tumors. These percentages are quite comparable to those of other observers. In 1929, one of us (LWS) reported another series of 67 cases of thyroid malignancy from the Lahey Clinic, in which the incidence was 1.68 per cent. In the Mayo Clinic, the figure runs about the same: 1.6 per cent of all thyroid specimens from 1910 to 1916. Graham in Cleveland reports a simi-
lar figure, as do Craver (4) and Haagensen (7) from the Memorial Hospital in New York.

Sex: In this series, as in most others reported, there is a much higher incidence of the disease in females than in males: 41 females as against 13 males, roughly a 4:1 ratio. This is somewhat lower than the ratio 6.4:1 observed in the original Lahey Clinic report, but is quite comparable.

Age: The age incidence as observed in the various types of malignancy is noted in the subsequent classification (pp. 4–5). The youngest patient in this series was twenty-two years, the oldest sixty-nine years of age at the time of hospitalization. The average age of the 54 patients was 48.8 years. There were 3 cases in the third decade, 10 in the fourth, 16 in the fifth, and 12 each in the sixth and seventh decades. The disease obviously, then, is a disease of late life, with the peak at about fifty years of age (Chart I).

Pre-existing Adenoma: The preoperative duration of an existent thyroid enlargement is of considerable interest and significance. Twenty patients, or 37 per cent of the total series, acknowledged a duration of over eight years; an additional 8 patients, making a total of over 51 per cent, recognized an appreciable enlargement of the neck for a period of at least four years. In 10 more of the cases the increase in size had been present for more than a year. Thus in over 70 per cent of the cases the patient himself had recognized the existence of a definite pathological process for over a year. In the light of our knowledge of the development of thyroid malignancy from pre-existing adenomata with just such histories, the question arises whether or not we are
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doing all our duty, both to the individual and to the public, in failing to emphasize the possible dangers of such enlargements of the thyroid. While it is true that roughly only 5 per cent of clinically recognized adenomata actually do become malignant, yet we cannot overlook the importance of the possibility of saving life by early prophylactic removal of such nodules.

Even in the remaining 16 cases a nodular enlargement of the gland had been noticed as the expression of neoplastic growth, of varying duration, from a few weeks up to ten or eleven months. In five instances no note was made of the preoperative duration of the tumor. Microscopically, we believe, an adenomatous origin could definitely be traced in all but four of the cases: one the epidermoid carcinoma, the other three in the small round-cell group of cases, of diffuse type. In these it was difficult to follow the sequence of events histologically, as they were so far advanced that the initial phase of the process could not be made out.

Thus in 92.6 per cent of the cases the previous existence of an adenoma was recognized as being the essential factor in the development of the subsequent malignancy. This again is entirely in keeping with our previous group of cases, in which 94.4 per cent were considered similarly as having an antecedent history of adenoma, and again conforms with the Mayo Clinic figure of 87 per cent, and Graham's statement of 90 per cent, as well as with the percentages cited by many pathologists in European literature.

While we must accept the evidence that cancers of the thyroid are preceded by and develop in adenomata in the vast majority of cases, there are no available figures as to the actual proportion of adenomata which become malignant, because unquestionably only a small percentage of patients with adenomata present themselves to the physician for advice and treatment. It may be, therefore, that undue weight is being attached to the probability of cancer developing in an adenoma. As one reviews the statistics of three or four decades ago, when goitre operations were unusual and patients harboring adenomata did not in general accept surgical intervention, one is impressed by the fact that few cancers of the thyroid were noted, indeed, far fewer than should be expected if adenomata present the marked tendency towards malignancy which is generally assumed to-day.

Pathology

The classification of thyroid malignancy has always presented many almost insurmountable difficulties, because of the very marked variation in the histological picture, and especially the fact that innocent tumors show many of the criteria which are usually accepted as evidence of malignancy: viz. anaplasia, heterotopia,
mitoses, etc. In reviewing the literature the confusion is seen to be heightened by the lack of uniformity of terminology. For that reason we attempted, several years ago, to formulate a simplified working classification of the various types of thyroid malignancy encountered, especially with a view towards possible gradation, or, in other words, estimation of the prognosis. Now, after five years of further experience with this classification, in our own hands and those of others, we are still of the opinion that with minor modifications it presents the most useful method of histological classification available. It departs somewhat from the time-honored system of dividing cancers into medullary, alveolar, and scirrhous forms, but so does the pathology of the thyroid depart from the regular features of other glandular neoplasms. The classification is based on the assumption that cancer of the thyroid is derived from pre-existing adenomata, and that, while diffuse alveolar or scirrhous carcinomata and sarcomata of the gland may theoretically exist, they are so rare that for practical purposes they may be disregarded.

Classification of Thyroid Malignancy

I. Papillary Type of Adenocarcinoma: Presumably of lateral anlage origin; usually seen in young individuals; often histologically essentially benign, but tending to undergo unmistakable malignant degeneration with capsule invasion and lymphatic metastases. Apt to recur unless completely removed surgically. Only slightly radiosensitive. Makes up about 30 per cent of all cases (27.7 per cent in this series).
   A. Papillary Adenocystoma: Low-grade malignancy.
   B. Papillary Adenocarcinoma: Moderate malignancy.

II. Fetal Type of Adenocarcinoma: The most common of all thyroid cancers; of mesial anlage origin; seen at all ages, but most frequently from thirty-five to fifty years. Presents extreme variability in its histology, from embryonal solid tumors to tumors showing extensive cystic degeneration. Only regular criterion of malignancy is evidence of blood vessel invasion; may show capsule invasion. Extremely resistant to radium therapy. Makes up nearly 45 per cent of all cases (42.4 per cent in this series).
   A. Malignant Adenoma: Low-grade malignancy.
   B. Alveolar Type of Adenocarcinoma: Moderate malignancy.

III. Epidermoid Type of Carcinoma: Of thyroglossal duct origin; an extremely rare form of thyroid tumor; usually seen after sixty years of age; uniformly fatal. Runs course of other epidermoid carcinomata, and its radiosensitivity corresponds to the degree of cell differentiation. Makes up 1 to 2 per cent of all cases.

IV. Giant-cell Type of Carcinoma: Origin can usually be traced to pre-existing adenoma. Characterized clinically by sudden, rapid increase in size, in individuals fifty to sixty-five years of age. Almost certainly fatal within six to eighteen months. Radiosensitive. Makes up about 10 per cent of all cases (9.2 per cent in this series).
   A. Polyhedral-cell Type: Enormous “tumor giant cells” with multiple mitoses, scant stroma, marked vascularity; often “perithelial” arrangement; much necrosis; extreme anaplasia; invasion of entire gland,
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regional vessels, and lymphatics. Resembles extremely malignant forms of mammary cancer at times.

B. **Spindle-cell Type**: Cases range from quite orderly pressure “spindling” of epithelial cells, as seen in a rapidly growing fetal adenoma, to rapidly growing tumor resembling fibrosarcoma with many “tumor giant cells.”

V. **SMALL ROUND-CELL TYPE OF CARCINOMA**: Origin open to dispute in many instances. Occurs in two forms:

A. **Compact Type**: Origin can usually be definitely traced to pre-existing fetal type of adenoma. Made up of small round cells resembling fetal type of epithelium; shows some tendency to form acini; invades entire gland and blood vessels, metastasizing by them.

B. **Diffuse Type**: Similar histologically in appearance, but difficult to trace any adenomatous origin. Small round cells, often impossible to differentiate from lymphocytes; no apparent tendency to form acini; invades blood vessels and apparently metastasizes by them.

Clinically both “compact” and “diffuse” types behave similarly. They occur usually in individuals over fifty years, and run a rapid, uniformly fatal course within a year after onset, often within three to four months. They are apparently uniformly extremely radioresistant.

Histologically the picture is a replacement of the gland by small round cells. Often it is seen in association with marked areas of lymphocytic hyperplasia; frequently there is associated acinar hypertrophy which confuses the picture with that of struma lymphomatosa or Hashimoto’s disease.

VI. **SARCOMA**: The existence of true sarcomata is still open to conclusive proof, although certain cases of “spindle” type adenocarcinoma as described above have been reported as fibrosarcomata and may exist as such. Likewise, certain of the small round-cell carcinomata of the “diffuse” form have been held to be lymphosarcomata arising from struma lymphomatosa, and similarly may actually occur as such.

I. **Papillary Type**: **Papillary Adenomata and Adenocarcinomata**: Reviewing our cases in respect to classification, it may be of some interest to note the more salient statistical features. In the first group, adenomata of the papillary type in which evidence of malignant degeneration was noted microscopically, there were 15 cases, or 27.7 per cent of the entire series. Eleven of these were in females, 4 in males. The age incidence varied from twenty years (Case 14) to sixty-one years (Cases 5 and 10), with 45.9 years as the average. Six of the patients had noticed enlargement of the thyroid for over eight years, while in only 3 instances had the growth existed for less than a year. In 2 cases the preoperative duration was not known, one case being discovered incidentally at autopsy as the cause of death.

At least 6 of the patients were alive and well without evidence of recurrence at the end of a year. It has been noted that in cases of recurrent malignancy the recurrence almost invariably takes place in from six months to a year, so that we can almost assuredly assume the permanent recovery of these 6 patients. One
of them had been alive five and another over eight years postoperatively. In addition, 4 patients were alive and well for the first three months postoperatively, but were lost sight of after their first follow-up. Two patients died in the hospital and may be considered essentially as operative deaths. One patient, as noted elsewhere, came to the hospital moribund and diagnosis was made only at autopsy. A fourth patient died of recurrence approximately three months later, and a fifth died six years postoperatively of an entirely dissociated malignant tumor of the mediastinum—a liposarcoma—with no evidence of local or metastatic recurrence of the original thyroid tumor.

Thus, of the 15 cases, we have fairly accurate follow-up data on 11. At least 7 of these (63.5 per cent) may be considered as operatively cured, and it is quite possible that this percentage might be increased 10 points if it were possible to secure follow-up data on the other four cases. This is in accord with other published figures. In other words, this group represents one in which the prognosis is relatively good, as evidenced by the clinical side of the picture. The microscopic pathology is distinctly of value in identifying this group of cases, thereby offering a prognosis of some comfort to both the patient and the surgeon.

The essential features of the pathology have been briefly outlined in the preceding classification, but bear amplifying at this point. As has been noted in a previous paper (8), we are inclined to feel that adenomas of the papilliform type, seen both in the thyroid gland proper and as lateral aberrant tumors, arise from the lateral anlage of the thyroid. This accounts for the characteristic microscopic picture of tumors of this group, and distinguishes them from the mesial anlage tumors or pseudo-tumors which give rise to the several varieties of “fetal” adenomata. They are of relatively low-grade malignancy and may exist for as long as thirty to forty years as benign cystic tumors, not infrequently undergoing extensive calcification. Their microscopic appearance is quite comparable to the cystadenomata of the ovary, and even to the polypoid tumors of the gastro-intestinal tract. They are usually well encapsulated. They are made up of delicate connective-tissue stalks with a rather inadequate capillary blood supply. A single layer of cuboidal to columnar epithelium covers these stalks. In places the epithelium becomes heaped up in several layers. Mucinous degeneration of the stroma takes place and calcium becomes deposited.

With the development of malignancy, these cells show first a greater tendency towards heaping up, with a definite hyperplasia, producing irregularly nodular papillae. Gradually the cells revert towards the more primitive, less differentiated form. Their nuclei
FIG. 1. Papillary Adenoma Malignum in Female of Thirty-eight; Nodule Present for Five Years; No Symptoms; Histologically Marked Papillary Proliferation with Cystic Degeneration, Calcification, and Beginning Invasion of Capsule

FIG. 2. Case II: Papillary Adenocarcinoma in Male of Forty-five; Weakness for Ten Weeks; Death from Metastases in Lungs, Liver, and Kidneys; Microscopically Infiltrating Tumor Tissue in Thyroid Substance
become larger and clearer, with the chromatin less regularly arranged. The cytoplasm in many instances may appear almost syncytial. Mitoses become more and more noticeable, and gradually invasion of the capsule occurs. At times invasion of the blood vessels may be observed.

In general these tumors behave much as do the ordinary adenocarcinomata, such as those found in the intestine, the ovary, the lymph nodes, remaining relatively localized for a long period of time. Occasionally, as in the case of the other thyroid cancers, blood vessel invasion is the means of distant extension of the tumor. Locally, the growths may attain considerable size, tumors of 15 cm. to 20 cm. in diameter being not uncommon, with marked involvement of the regional structures, including the muscle and fascia, which may enclose nerve trunks and produce secondary pressure symptoms.

II. **Fetal Type: Malignant Adenoma and Adenocarcinoma:** In the second group of the suggested classification, the fetal adenoma which include all transitions from malignant adenoma to frank adenocarcinoma, we find the majority of the carcinomata of the thyroid. Indeed, in the subsequent subclasses of the total 54 cases, 38, or 70.3 per cent, presumably have their origin from such variants of the so-called fetal adenoma. On the basis of the suggested subdivisions of the classification, of the simpler forms of the malignant adenocarcinomatous group we have 23 cases, or 42.4 per cent. Eighteen of these were in females, 5 in males. The age incidence varied from thirty-six years (Case 18) to seventy years (Case 37), with fifty years as the average age at the time of operation.

Nine of the patients had noticed enlargement of the neck for over eight years; 4 of the others had symptoms for over four years, and an additional 5 had been aware of their condition for over a year, making a total of 18 cases or nearly 80 per cent with definitely recognized thyroid pathology for more than a year. Of the remaining 5 patients, 3 had symptoms for between three months and a year, one had noticed enlargement of the neck for less than three months, and the other patient was moribund when first seen, unaware of any thyroid pathology.

In this group the follow-up data is unsatisfactorily meagre. In 10 of the cases no information beyond the initial hospital period is available. One patient is known to be alive six years and 4 others over a year after operation. Two had recurrence at the end of fifteen and forty-two months respectively, but knowledge of their actual death is lacking; two patients died postoperatively, one as previously noted entered in a moribund state, and the other two patients died within a year of operation, of recurrence or ex-
Fig. 3. Embryonal Adenoma: High-Power Photomicrograph Showing Cell Detail

Fig. 4. Fetal Adenoma in Patient of Twenty Years; Small Nodular Mass in Neck for One Month, with Toxic Symptoms; Histologically Typical, Small, Poorly Differentiated Acini with Little or No Colloid; Loose Hyaline Stroma; Vascular Invasion
tension of the tumor. In two cases autopsies were obtained (Cases 22 and 35) which confirmed the original diagnosis. It is unfortunate the data are so incomplete, because, according to Clute and Warren’s (3) report, the expectancy of cure in this group should be at least 40 per cent. We have definite information of only five cures. By correcting our figures and basing the percentage solely on the 10 cases of which we do have the complete data, this expectancy is equalled, being an even 50 per cent.

Here again the pathological diagnosis is of considerable although of less value than in the preceding group of cases. As has been noted by Graham (6) and other observers, the chief microscopic criterion of malignancy in this group of cases in their early phase is evidence of blood vessel invasion. This was present in the entire 23 cases in this group. On the other hand, as Warren (3) has pointed out, only approximately a third of these cases showing vascular invasion go on to recurrence or metastasis as one might expect them all to do. We are inclined to interpret this as meaning that the majority of these invasive growths of the blood vessels become localized through thrombosis and re-endothelialization of the vessels. The possibility, too, that isolated cells or groups of cells, distributed by the blood stream to distant parts of the body, may not find suitable soil to grow in, is somewhat more than a purely speculative hypothesis. From observation over the past ten years, it has become increasingly apparent that most recurrences in this group of cases take place within a year, so that, while a prognosis in any given case must of necessity be guarded, yet one may fairly assure the patient or the family that if nothing happens within the year all should be well.

The pathological anatomy of this group of cases is most complex. The adenomata range from the most primitive embryonal form to well differentiated thyroid tissue. The most frequently encountered form is the so-called “fetal” adenoma, in which we find the tumor made up of masses of small, highly chromatic, low cuboidal epithelium arranged in beginning acinar form, but with rarely any demonstrable colloid in the lumina. Often these lumina are difficult to identify. The tumors grow from the center out, so that the zone of greatest activity is always the periphery. Centrally they may frequently undergo cystic degeneration, often accompanied by hemorrhage. The stroma is a delicate capillary network with a few supporting fibrous strands which increase in numbers centrally, giving the impression of a central core of connective tissue. The difficulty which the pathologist encounters in establishing a diagnosis of malignancy in these cases, unless actual invasion of the capsule is present, is due to the fact that they are usually histologically entirely benign except for the evidence of
capillary infiltration, and this requires multiple sections and diligent search as a rule. Mitoses are rare, and anaplasia is ordinarily entirely absent. As malignancy develops, one finds loss of structural detail, a tendency for the cells to occur in clumps or cords without lumen formation, but even then mitotic figures are the exception rather than the rule. The most characteristic changes are those of actual local invasion of the capsule and surrounding structures, even to infiltration of the walls of the carotid arteries and jugular veins. Rarely can one demonstrate, even in

FIG. 5. CASE 30: FETAL TYPE OF ADENOCARCINOMA IN FEMALE OF THIRTY-NINE YEARS; MASS IN NECK FOR TWO YEARS; AN EXAMPLE OF "SPINDLING" OF THE CELLS

the more obviously malignant cases, evidence of lymphatic extension, although occasionally this may occur.

This problem of the origin of malignant tumors from these pre-existing adenomata requires careful scrutiny. As our knowledge of the structural detail of the thyroid gland has developed, so have our ideas regarding the nature of these isolated nodular tumor growths within the substance of the gland. Originally pathologists rather blindly accepted Cohnheim's statement and theory that these focal areas of cell overgrowth represented originally abnormally placed embryonal cell rests which in course of time developed the faculty of growth as tumors, and many pathologists hailed this particular tumor as perhaps the most striking example
of this theoretical origin of tumors in general. Then, in accord with this idea, came Wolff with his theory of interacinar thyroid cells which might be the source of such adenomata. More recently, with the work of Williamson (15), Rienhoff (11), Wilson (16), and others, the origin of these apparently interacinar cells from outpocketings and overgrowth of the normal thyroid acini has been so well established as to be beyond dispute. To-day, as Boyd (1) and others have emphasized, the probability is that these focal neoplastic appearing groups of cells are not truly tumors at all, but represent mislaid cells in the course of abnormal or even normal functional hyperplasia and involution of the gland. In this respect they may be closely related to the ordinary nodular goitre, with which, incidentally, they are often seen in association. In other words, the origin of these adenomatoid structures is probably the result of irregular functional activity of the gland, rather than a true neoplastic process. It is, of course, impossible to make this as an established and sweeping statement, but the evidence points in this direction.

At all events, we have to deal with a group of cells which become semi-isolated and shut off from the rest of the gland by irregular involutinal fibrosis of the stroma. These cells, as a rule, appear to lose their functional capacity, but retain their growth capacity and undergo hyperplasia as relatively undifferentiated thyroid epithelium. In turn they press upon the surrounding thyroid tissue and develop a fibrous capsule, this process becoming more or less of a vicious circle. Whether or not these adenomatous structures represent true tumors or functional irregularities is of no especial significance in their natural history in respect to malignant degeneration. Their recognition is important, and their removal surgically is indicated as a prophylactic measure.

In the "embryonal" form of these tumors it seems more definite that we are dealing with a true neoplastic process. The cells are much more primitive, tending to be almost columnar in form and to be arranged in closely packed cords and trabeculae without lumen formation. The arrangement is, however, more or less orderly, and the cells are uniform in appearance. Mitoses are rare, but can usually be found, and the general low-power picture is strongly suggestive of malignancy, so that one has to be very guarded in making a histologic diagnosis. The tumors grossly are solid, rarely showing cystic change; they are apt to be quite yellow in appearance, and for these various reasons have at times been thought to represent adrenal carcinomatous metastases. They are often of considerable size, not infrequently reaching 20 to 30 cm. In general the same features of vascular and capsular in-
FIG. 6. CASE 30: INTERMEDIATE FORM OF THYROID TUMOR IN FEMALE OF THIRTY-NINE, SHOWING TRANSITION FROM SOLID ADENOMA TO SPINDLE-CELL TYPE OF TUMOR.

FIG. 7. CASE 43: GIANT-CELL CARCINOMA, SPINDLE-CELL TYPE, ILLUSTRATING EXTREME MALIGNANCY HISTOLOGICALLY AND THE POSSIBILITY OF CONFUSION OF DIAGNOSIS WITH FIBROSARCOMA, WITHOUT ADEQUATE NUMBER OF SECTIONS.
Invasion are the chief microscopic criteria for establishing malignancy.

The group of possible adenomata which show good acinar differentiation and colloid deposition are more difficult to identify as neoplastic. They usually represent local areas of irregular involution which become walled off and develop a false capsule by pressure. The same evidence of malignancy may be noted in this smaller group of cases, but much less frequently.

III. Epidermoid Carcinomata: The epidermoid group of cases, as has already been noted, is essentially negligible. We have but one example (Case 39), occurring in a fifty-year-old male, who had

![Image](image_url)

**Fig. 8. Case 39: Epidermoid Carcinoma in Male of Fifty; Mass in Neck for Sixteen Years; Rapid Growth; Death Five Months Postoperatively with Clinical Evidence of Metastasis; No Autopsy**

a history of enlargement of the thyroid for sixteen years. It increased in size and density four months before admission. At operation a typical epidermoid carcinoma involving the left lobe and regional lymph nodes was found. In spite of intensive postoperative irradiation, the patient died five months later.

In general it may be said these tumors arise from thyroglossal duct inclusions and behave much as epidermoid carcinoma elsewhere. The difficulty, both clinically and pathologically, is to exclude some other source, such as branchiogenic cysts, the larynx, or the esophagus, as the initial site of the tumor. In this case, as in the one reported by one of us from the Lahey Clinic (2), we believed that we could definitely exclude these other possibilities. As far as the literature discloses, tumors of this group rarely oc-
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IV. "Giant-cell" Carcinomata: In the fourth group in this suggested classification we have only 5 cases, or 9.2 per cent of the entire series. Four of these were in females, and one in a male. The age of two of the patients was not stated, two were sixty-five years of age, and the fifth was just under fifty, making the average age in the three cases in which the age was cited sixty years.

Postoperatively all five patients were dead within three months. Two deaths occurred before discharge from the hospital and may be considered as operative deaths. The other three patients died of recurrence or extension of the original tumor two to three months later. In no instance was an autopsy obtained.

Pathologically, these cases are most interesting. Even to the initiated pathologist their origin from thyroid tissue is not readily apparent at times, and multiple sections are often necessary to clarify the picture. They constitute a group of cases in which the diagnosis of fibrosarcoma has sometimes been applied. In reporting (12) previously on a series of 18 of these cases collected from various sources, we were able to show conclusively an adenomatous origin for 16 of them, and a presumptive similar origin in the other 2 instances. In examining any considerable number of sections from any such case, it is almost regularly possible microscopically to demonstrate transitions from essentially low cuboidal epithelium arranged in more or less definite acinar form (fetal adenoma) to solid masses of spindle cells arranged with no regard to function, and showing evidence of malignant degeneration, with irregular multilobulated "giant" nuclei and atypical mitoses. The stroma is composed of capillaries and a few strands of connective tissue which merge with the "spindled" epithelium so closely that without the use of special fibrillar stains it is impossible to tell which is of epithelial and which is of mesothelial origin. Indeed, it is not unlikely that we may have a sympathetic malignant change in the stroma just as we occasionally do in the incorrectly termed carcinosarcomata of other organs, as the breast or uterus.

At times the microscopic picture is that of a perithelial tumor, with the cells concentrically arranged about blood vessels, and large areas of necrosis lying between islands of tumor tissue. In this form of the process the tumor is frankly epithelial and shows little of the more or less orderly degeneration of the epithelium commented upon in the preceding paragraph, characterized by spindling as a result of pressure. Instead we have a wild overgrowth of anaplastic cells, with a tendency toward the formation of large polyhedral cells, again with multilobulated "giant" nuclei and atypical mitoses.
There is little or no tendency to form well defined acini and as a rule no colloid can be found. The stroma, however, sometimes has occasional masses of the hyalin or colloid-like substance between the cells which we associate with the simpler adenomata. Definite vascular invasion may usually be observed, especially in the peripheral portions of the tumor. Centrifugal growth with capsule invasion and local extension of the tumor into the surrounding structures of the neck is further microscopic evidence of the extreme malignancy of the cases. They may be classed histologically among the most malignant tumors one encounters, from any part of the body, and the microscopic picture in this instance in no way belies the clinical behavior.

The gross appearance is fairly characteristic. The tumors are apt to be relatively large, on section grayish-yellow in color, and firm in consistence, except for the areas of softening noted previously. The tumors are usually unilateral and arise clinically from an adenomatous nodule, often of many years’ duration. They suddenly take on the mantle of malignancy, grow extremely rapidly after years of quiescence, and invade the tissues locally, even to involve the skin, although rarely if ever do they ulcerate through to the surface. They tend to retain an ovoid or spherical outline, often conforming to the general outline of the involved lobe, but having an irregularly nodular surface. Their course is uniformly fatally progressive, regardless of operative intervention or physical therapy, as, in spite of their marked microscopic anaplasia, they are extremely radioresistant.

As one sees these cases pathologically, they are apt to be so far advanced that it is difficult to demonstrate the adenomatous origin microscopically. In some instances they have extended through the isthmus to involve the opposite lobe, and a diffuse parenchymatous origin is hard to eliminate. The gross picture, however, and the clinical history usually successfully establish the hypothesis of their adenomatous ancestry.

As we have already said, basically these cases belong, as the most malignant form, in the group of fetal adenomatous tumors, and certain of them offer difficulty of arbitrary classification, as they show transitional changes from the ordinary adenocarcinoma towards this extremely malignant form. Only those cases which are made up chiefly of these anaplastic cells are included as the “giant”-cell tumors. Clinically they make up a fairly definite group, occurring usually in individuals past fifty-five years of age, with a history of long continued symptomless goitre, showing sudden increase in size, and responding to no form of treatment.

V. “Small-cell” Carcinomata: In the fifth division of our classification, the small-cell neoplasms of the thyroid, we have 10 cases,
FIG. 9. GIANT-CELL TYPE OF TUMOR, SHOWING CHARACTERISTIC ANAPLASIA OF CELLS WITH TUMOR GIANT-CELL MULTIPLE MITOSES, PERIVASCULAR ARRANGEMENT, NECROSIS, HEMORRHAGE AND CELLULAR INFILTRATION

FIG. 10. CASE 40: GIANT-CELL TYPE OF TUMOR IN FEMALE OF FORTY-NINE; MASS IN NECK FOR MANY YEARS; RAPID GROWTH FOR ONE MONTH; DEATH TWO DAYS POST-OPERATIVELY; NO AUTOPSY; CHARACTERISTIC ANAPLASIA
or 18.5 per cent of the total series. Of these, 8 occurred in females and 2 in males. The age varied from twenty-eight to sixty-six years, with 48.5 years as the average for the nine cases in which the age was given. As we have already noted, however, in the classification, these small round-cell tumors occur in two forms: the compact and the diffuse. Separating the two groups, we find that the average age for the compact group is fifty-six years, while for the diffuse group (4 cases) it is thirty-nine years.

The compact group (Cases 47, 48, 49, 51, 52, and 54) presents definite clinical evidence of an origin from a pre-existing adenoma, which, as in the case of the giant-cell carcinomata, had existed quiescently in several instances for many years—although this feature is not as regularly noted as in the previous group—and then suddenly had begun to increase in size. In one instance the tumor had existed for over twenty-five years before showing this malignant degeneration.

The cases are of interest clinically because they tend to occur, as do the giant-cell tumors, in the older age group and to run a uniformly fatal course. Unfortunately in this series our follow-up data is incomplete in 2 of the 6 cases. The other 4 patients were dead within a year, 2 of them within three months after operation, of recurrence or extension of the original tumor.

In the “diffuse” type we have a somewhat different problem, both clinically and histologically. The original series of 11 such cases which one of us (L.W.S) reported from the Lahey Clinic all happened to fall in the older age group, the youngest patient being forty-eight years of age. Of this present group of 4 cases, 2 occurred in relatively youthful individuals, twenty-eight and twenty-nine years of age, the third one in an individual of forty-eight, and the fourth one in an “elderly” woman whose age could not be ascertained.

The duration in these “diffuse” cases is apt to be relatively shorter. In Case 45 it was only two weeks, in two of the others not over six months, and in only one instance had there been any previous history of thyroid enlargement existing for several years, with the recent increase in size which we usually associate with the “compact” type.

Postoperatively one patient died while still in the hospital, of cardiac failure, one was living four and a half years later, and the other two cases were unfortunately lost sight of. Thus, of the entire series, half were dead within a year, one patient only was known to be living, and the other four were lost. From previous experience, and from a survey of similar cases in the literature, we might almost assume that these four patients were dead within the year.
Fig. 11. Case 50: Small-Cell Carcinoma: Field showing the invasion and replacement of the hypertrophied thyroid acini by small round cells; often difficult to differentiate from Hashimoto's or Riedel's Struma, or even from lymphosarcoma.

Fig. 12. Hashimoto Phase of Riedel's Struma in Male of Sixty-nine, illustrating the characteristic lymph follicle formation seen in this type of chronic thyroid disease; difficult at times to differentiate from small-cell carcinoma; may possibly give rise to lymphosarcoma.
Pathologically, perhaps more from an academic than a practical standpoint, these cases are the most interesting of the entire group of thyroid malignancies, as their diagnosis is most difficult, and their classification under dispute. From the prognostic side, it is of very great importance that we recognize these cases differentially from the benign so-called "struma lymphomatosa." In this particular series we have one example (Case 53) in which some difference of opinion existed as to the diagnosis. The case was reviewed and the slides examined by a number of the leading pathologists of the country, as it was submitted to the Lymphatic Tumor Registry of the American College of Surgeons for that purpose. The diagnoses ranged widely: struma lymphomatosa, Hashimoto's disease, early Riedel's struma, lymphoblastoma, lymphosarcoma, and small round-cell carcinoma (diffuse type). The opinions as to malignancy were about equally divided. From bitter experience we have come to believe that with the small round-cell type of carcinoma the patient should not be expected to be alive at the end of a year after diagnosis has been established. This patient was alive and well nearly five years after operation. In the Lahey series, also, we had one exception to the remainder of the cases, and, while the ultimate classification of these doubtful instances may never be universally agreed upon, yet in both we were able to find all the microscopic as well as gross pathologic features of malignancy, and, in spite of their favorable outcome, we still cannot exclude the cases from the malignant small round-cell group of thyroid tumors.

The list of diagnoses which were submitted in this case represent the problem with which we are faced each time such a tumor is submitted for examination. The most important question from the pathologist's standpoint is whether the picture is malignant. Every bit of evidence from the clinical side is necessary, as well as the microscopic criteria, to establish this point.

Once malignancy is determined upon, the prognosis may almost confidently be expressed as absolutely bad, although the rare instances cited above cast a reasonable doubt upon the accuracy of any such statement. Whether we believe that these tumors are of lymphoblastic or of epithelial origin is of little moment. Their recognition as highly malignant, unusually rapidly fatal cases is important. That the majority of these cases are carcinomata arising from pre-existing adenomata seems well established both clinically and pathologically. The fact that ordinarily they metastasize distantly by the blood stream, as well as locally by direct extension, is entirely in keeping with their epithelial and adenomatous origin. That they are extremely radioresistant both before and after operation is almost prima facie evidence of their
thyroid epithelial nature. In all the published cases there is only one example (7) wherein radiation has seemed to show the effects which one might expect to see regularly were these tumors lympho-
blastic in nature, as certain investigators are inclined to believe (Graham; Mallory). Certainly the evidence to date points defi-
nitely to the fact that the “compact” type is epithelial in origin.

Microscopically, these tumors are seen to be composed of ir-
regular clumps and cords of small round cells embedded in a loose areolar vascular stroma. Here and there definite attempts to form acini by these small cells may be noted. In addition—and this is a point which we feel has led to considerable confusion—there is marked invasion of the parenchyma proper with the per-
sisting functional acini tending to undergo hypertrophy of the individual cells, a picture not unlike that of so-called “struma lymphomatosa.” The cells, however, when stained variously—by phloxin-methylene blue, by phosphotungstic acid, by hematoxylin-
eosin, by Wright’s stain, by Masson’s trichrome method—do not show the characteristic clock-face arrangement of the nuclear chromatin, and their cytoplasm when demonstrable does not react specifically to the usual blood stains for lymphocytes. Thus, by exclusion, one may rule out lymphocytes or lymphoblasts as being the chief cell in these tumors. It is equally true that there are apt to be lymphocytic infiltration and other evidence of chronicity, but the general architecture, the tendency toward acinar formation, the nature of the metastases, all point towards the carcinomatous nature of this “compact” group of cases.

When we turn to the “diffuse” parenchymatous small round-
cell group of cases, there is more room for doubt. This opens up an entirely different field and problem. We have seen at least three and possibly four cases in which the establishment of the epithelial nature of the tumor is much more difficult. The clinical side does not help us. These tumors are apt to occur in younger people, they have no antecedent history of adenoma or goitre, they run a relatively rapid course, and typically and fatally without benefit by any form of therapy.

Microscopically, one can find field after field which is an exact duplicate architecturally of the “compact” type, but, on the other hand, there is an absence of demonstrable acinar arrangement, and lymphocytes certainly predominate in the picture. Often the cells are somewhat larger, approaching the large lymphocyte in size. It is perhaps a waste of time to argue over these minutiae in differ-
tential diagnosis, but certain facts of interest and perhaps of clinical importance may well result from such a pedagogic discus-
sion. In the first place, it may well be that radiation therapy in some form will be curative if these tumors are true lymphosar-
comata and accordingly radiosensitive, as has been suggested by the one published case above mentioned. In the second place, the origin of these tumors is of importance from the pathologist's point of view.

The first point can be established only by the recognition of the second, and the accumulating of experimental data in this direction. The second problem, that of origin, raises many nice histological points. At the very outset, it delves into the entire controversy of struma lymphomatosa, Hashimoto's disease, and Riedel's struma. It skirts perilously close, on that basis, to the problem of hyperthyroidism and the lymphatic constitutional factors associated with that condition.

This whole group of allied conditions offers a tempting wealth of speculative hypotheses. From the very considerable material which we have had the opportunity to study, we are inclined to feel that there is a very close relationship among them, if not an actual potential developmental cycle. There seems to be a good deal of evidence to accord with Warthin's (14) theory that hyperthyroidism is likely to be associated with the general lymphatic constitution, often with an enlarged or persistent thymus. It is certainly true that a very considerable proportion of Graves' disease cases show this lymphatic hyperplasia, manifested not only as general lymph node enlargement, but also by a more or less diffuse lymphoid infiltration of the thyroid gland itself. We have come to believe that this picture is not evidence of old inflammatory changes in the gland, but a definite constitutional, anatomical peculiarity of these individuals. We are not convinced, as Warthin and his group are, that this is a necessary precursor in the development of hyperthyroidism, as in the examination of over 2000 such glands we have not noted its presence in more than 60 or 70 per cent of the cases. However, it does seem probable that hyperthyroidism is more likely to be found in individuals in whom this condition exists.

It is only a step from this common finding of diffuse lymphoid infiltration of the thyroid to an exaggerated picture where lymph follicle formation becomes prominent, crowding the acinar structures. In association with this condition the acinar epithelium undergoes a defensive hypertrophy, with the cells becoming large and tending to stain intensely with eosin. Gradually the lymphoid hyperplasia and infiltration gain ground, and slowly choke the thyroid epithelium to death.

This phase of the process has been designated by some as "struma lymphomatosa," by which is meant the essential replacement of the thyroid parenchyma by lymphocytes, and especially the development of actual lymphoid architecture with follicle for-
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mation. It is apt to occur in rather chronic cases of hyperthyroidism in which the toxic symptoms have been minimal, but prolonged—an exhaustion of the thyroid function through long-continued efforts at compensation hypertrophy and hyperplasia. Hashimoto (7a) considered this a primary disease of the thyroid and described a number of cases in which this picture was presented.

At about the same time that Hashimoto recorded this lymphoid condition of the thyroid, which to-day more or less universally bears his name, Riedel (10) came forward with a report describing several cases in which the thyroid gland had been replaced by dense connective tissue in which remnants of acinar structures persisted. This he felt was probably a chronic inflammatory process and he was inclined to link it with syphilis as the etiologic agent. Subsequent investigators pretty well established the fact that none of the ordinary infectious agents, including syphilis, was responsible for the development of the condition, and had to admit defeat in determining any specific etiology. Riedel's struma is usually seen at a later age than Hashimoto's disease and for that reason has frequently offered much difficulty in differentiation from malignancy, as both conditions are apt to be unilateral and to display an extremely firm, almost cartilaginous consistency with involvement of the capsule and regional structures. Even the skin may become adherent in both instances, although this is less likely in Riedel's struma.

Because of the unusual hardness of the tissue involved, this condition has become known by several names—"cast-iron struma," chronic ligneous thyroiditis, etc., as well as the more usual term, Riedel's struma. Most pathologists have gradually come to accept Ewing's interpretation, that Riedel's struma represents the end stage, or fibrous tissue replacement, of Hashimoto's struma lymphomatosa. This is in keeping with one of the almost inevitable histological sequences; fibrosis following chronic inflammatory lymphoid infiltration of tissues. Ewing (5) has designated the condition as a "benign granuloma" and has traced the entire cycle in a series of cases from the typical struma lymphomatosa to the hypoplastic fibrotic gland of Riedel's disease. Graham (6), on the other hand, considers the two processes as distinct pathological conditions, the one perhaps purely anatomical and physiological, the other an inflammatory reaction to some unknown etiological agent.

In a study of several such cases (13), we came to the conclusion that the end picture of fibrosis seen in Riedel's struma, and not infrequently associated with myxedematous symptoms, was invariably preceded by the histological features of struma lympho-
matosa. This does not, of course, exclude the possibility that Hashimoto's disease may occur without the subsequent development of Riedel's struma, but in our opinion it is strongly suggestive of the usual sequence of events. On the other hand, it raises a very interesting and as yet moot point, whether or not a struma lymphomatosa may undergo malignant degeneration and develop into a lymphosarcoma. We are forced to admit that the potential lymphoid cells are present in large numbers, and that architecturally they are arranged very much as lymphoid structures elsewhere, as, for example, in Peyer's patches of the small intestine, where lymphosarcomata are by no means uncommon.

We also have other possible analogies in the sarcomatous degeneration of inflammatory processes, of which Hodgkin's disease is the most striking example. On both theoretical and on morphologic grounds it seems entirely reasonable to assume that this lymphomatous degeneration may take place, and that certain of these small round-cell tumors of the diffuse type may truly be classed as lymphosarcomata. On the other hand, their clinical behavior, their occurrence in individuals usually in the late fifties, their radioresistance, their vascular invasion similar to that of other thyroid malignancies, the appearance morphologically of their metastases locally and in distant organs, their rapid course, their almost invariable fatality, all bespeak an epithelial origin like that of the vast majority of malignant neoplasms of the thyroid.

In a few instances it is impossible for us to establish an adenomatous origin for these tumors, and accordingly we cannot exclude the possibility of their lymphosarcomatous nature. We cannot but agree that theoretically such tumors might arise in the thyroid gland. We feel, however, that all the evidence points away from such a theory, as we have attempted to demonstrate, and we are still inclined to agree with Ewing (5) that no completely acceptable mesothelial tumor of the thyroid has yet been reported.

From the pathologist's standpoint we would like again to emphasize the fact that, whether or not all these small round-cell tumors and the spindle-cell type of giant-cell tumor of the thyroid are epithelial or mesothelial in origin, clinically they behave identically and must be given an almost completely bad prognosis. The important thing for the pathologist is, first, to recognize the material submitted to him for examination as of thyroid origin, and secondly, to be able to differentiate a malignant small round-cell tumor from its benign counterparts—the struma lymphomatosa, Hashimoto's disease, Riedel's struma group—whatever their relationship. In this latter group we have ordinarily an entirely benign condition which usually runs a self-limited course. In the former we have a rapidly progressive, fatal disease.
In this discussion of the diffuse type of small round-cell tumors of the thyroid we have taken up the theoretical sixth division of our classification. We have no cases which we are willing to place, without qualification, in this division. As we have already intimated, one, at least, of our spindle-cell tumors might be considered by many pathologists as a fibrosarcoma. Similarly three or four of the small round-cell type might be grouped as lymphosarcomata. As with many other aspects of medicine and pathology, there is more or less of a cycle of thought, what one might perhaps call the fashion of the day. Originally there were almost as many sarcomata of the thyroid reported as there were carcinomata. Not many years ago the use of the term sarcoma as a diagnosis for thyroid tumors nearly disappeared from the literature; to-day, we find the pendulum swinging back a little toward the sarcoma side. Perhaps ultimately we may have more accurate means of diagnosis and let the pendulum come to rest. In the meantime, it is such controversial points that help make the field of pathology so peculiarly stimulating.

**Clinical Diagnosis**

From the clinical side the diagnosis of thyroid malignancy is even more difficult than it is pathologically. In early cases, especially those originating in an adenoma, there are no clinical features to suggest the diagnosis. Balfour reports that at the Mayo Clinic in only 18 per cent could a positive preoperative diagnosis be made clinically. As Pemberton states, symptoms by which a diagnosis can be made are usually not present until the growth has invaded the capsule. Then the lesion presents as a hard, irregular, nodular, fixed mass. It is often associated with hoarseness, even aphonia, dyspnea, dysphagia, and loss of weight. By this time the tumor is too advanced for surgical intervention. In only one-third of the cases diagnosed as malignant at the Mayo Clinic was this even attempted. Increase in size of an existing goitre is usually the first feature to attract the attention of the patient. This growth is always progressive, with no periods of regression.

The differential diagnosis must consider chronic thyroiditis, Riedel's struma, tuberculosis, syphilis, and hemorrhage into a cystic adenoma. The history and careful physical examination will usually clear up any doubt. Occasional uncertainties occur, however, due to the extreme firmness and fixation of the gland and the compression and deviation of the trachea.

**Treatment**

The treatment of carcinoma of the thyroid, as has been noted, is distinctly unsatisfactory in the light of our present knowledge
and methods. Carcinoma in and confined to an adenoma may be considered independently, and it is this feature upon which emphasis can be laid, since it offers conditions favorable for treatment. It is evident that an adenoma, especially in middle life, which shows clinical evidence of rapid growth must be regarded as potentially malignant. The proper procedure in these cases is resection of such portions of the gland as contain adenomata. Multiple adenomata in general demand resection: solitary adenomata may be enucleated. These procedures are referred to here, since they may be regarded as prophylactic measures to insure against malignancy.

Considering the relative infrequency of cancer of the thyroid, it seems unwise to alarm a patient by the suggestion of malignant potentialities. While the removal of adenomata should be urged, the probabilities of the development of toxic symptoms are usually a sufficient argument to obtain consent to operation.

In presumptive carcinoma of the thyroid in which operative removal seems impossible, it has always seemed wise to us to have the patient submit to biopsy, if only to establish the type of tumor, so that some idea of prognosis or even of treatment might be obtained. Complete extirpation of the gland is theoretically the proper procedure, but it is never actually indicated because in cases of limited extent the measure is too radical, and in advanced cases it is useless.

Irradiation is a measure which has been too little used, in view of the unsatisfactory results of surgery in the advanced cases. In the less malignant cases a combination of surgery and radiation is advisable, although the use of radiation is somewhat limited by the radioresistance of most carcinomata of the thyroid. In the diffuse inoperable cases it seems the only procedure to employ, and to be used in massive dosage, if at all. No half-way measures in thyroid malignancy are of any avail, as many surgeons and pathologists have learned to their sorrow.

**Conclusions and Summary**

1. A clinico-pathological analysis of 54 cases of thyroid malignancy is reported. This represents an incidence of 2.5 per cent of all surgical thyroid cases. A discussion of the age and sex incidence follows.

2. The origin of thyroid malignancies from pre-existing adenomata is stressed, 92.6 per cent of the cases in this series presenting this feature.

3. A pathological classification of thyroid tumors is presented which attempts to correlate the clinical and pathological features of the condition with a view to prognosis.
4. The statistical study of the various classified groups is taken up, showing the progressive degrees of malignancy, the mortality varying from less than 30 per cent in group I to nearly 100 per cent in groups IV and V.

5. A discussion of the clinical diagnosis and treatment follows, showing that surgery is of little avail once the tumor has invaded the capsule of the adenoma or the parenchyma. Irradiation seems to be the most logical approach to the problem in the light of our present knowledge.

**Case Reports**

**Case 1:** A female of fifty-six, with six children, had a mass in the left side of her neck for nine years. At operation, an adherent mass the size of an orange was removed. This was an infiltrating papillary adenocarcinoma. The patient died the day of operation.

**Case 2:** A female of thirty-three was operated on for a papillary adenocarcinoma which was adherent to the trachea. There were signs of recurrence twelve years later.

**Case 3:** A female of sixty, with seven children, had bilateral masses in the neck for over ten years, with rapid increase in size for the three months preceding admission. At operation, two cystic tumors were removed, each approximately 6 cm. in diameter. These were adherent to the thyroid isthmus. Microscopically, they were old papillary cystadenomata showing malignant degeneration.

**Case 4:** A male of thirty-seven had a lump in the neck for a year before admission. At operation, a lobulated mass $5 \times 4 \times 2$ cm. was removed from the left side of the neck. Microscopically, it was a papillary adenocarcinoma, aberrant in location, and invading lymph nodes. The patient died six years later of an entirely dissociated tumor, a liposarcoma of the pericardium.

**Case 5:** A male of sixty-one had a mass in the neck above the sternum for eleven years. At operation, two masses approximately 10 cm. in diameter, which were attached to the surrounding tissue, were removed. Microscopically, these were papillary adenocarcinoma. Death occurred three months later, from metastases.

**Case 6:** A woman of forty noticed a swelling of the neck nine years before, coincident with the birth of a third child. The mass showed marked increase in size for a year. At operation, a diffusely enlarged thyroid gland which was adherent posteriorly was found, and material was removed for biopsy. Microscopically, this showed a malignant adenoma with papillary cystic changes. The patient was alive one year after operation.

**Case 7:** A woman of forty-nine had a history of swelling of the neck of ten years' duration. At operation a mass was removed from the right side of the neck, $9 \times 8 \times 5$ cm. in size, along with the cervical lymph nodes. The tumor was adherent to the skin and the sternoceleidomastoid. A second operation was done four months later for local recurrence and a mass $10 \times 8 \times 8$ cm. in size was removed. Microscopically, there was a predominantly papillary adenocarcinomatous picture. In spite of a subsequent carcinoma of the breast, the patient was alive and well five and a half years after the thyroid operation.

**Case 8:** A woman of thirty-nine had swelling of the thyroid for one year. At operation, a firm, adherent mass $5 \times 3 \times 3$ cm. in size was removed from the right lobe. The microscopic picture was that of papillary adenocarcinoma of low-grade malignancy. Three years and ten months after operation examination of the neck was negative; there were no masses.
CASE 9: A man of fifty had symptoms of one month's duration. He had had an abscess of the thyroid seventeen years previously. At operation, a mass of tissue aggregating 5 cm. in all diameters was removed; the microscopic appearance was that of papillary adenocarcinoma. Death occurred the day of operation.

CASE 10: A woman of sixty-one had a tumor of the thyroid of three months' duration. At operation, a mass 4.5 cm. in diameter was removed. Microscopic examination showed a low-grade papillary adenocarcinoma infiltrating the capsule and muscle.

CASE 11: A male of forty-five whose history showed no indication of thyroid disease died of metastases of a thyroid carcinoma. At autopsy, a tumor 2.5 x 2 x 1 cm. in the right lobe of the thyroid was found, with metastases to lung, liver, and kidney.

CASE 12: A woman of forty-four had a history of thyroid enlargement for three months, with an antecedent history of carcinoma of the breast. At operation, a mass 5 x 3 x 3 cm. in size was removed from the left lobe of the thyroid. This presented the microscopic picture of a moderately papillary type of adenocarcinoma of average malignancy.

CASE 13: A woman of fifty-six had symptoms of thyroid enlargement of three years' duration. At operation, an encapsulated tumor 6 cm. in diameter was removed. This, microscopically, showed a papillary adenocarcinoma of low-grade malignancy. The patient was well five months after operation.

CASE 14: A woman of twenty had a rapidly growing mass in the neck, of three months' duration. At operation, a tumor 6 x 4 x 2 cm. was removed. Microscopically, this appeared to be an adenocarcinoma with some papillary tendency and definite invasion through the capsule. The patient was well a few months later but was lost track of.

CASE 15: A woman of thirty-eight had a history of enlargement of the thyroid of fifteen years' duration with recent acceleration of growth. At operation, a tumor mass 7.5 x 5 x 4.5 cm. in size was removed. Microscopically, the picture is one of adenocarcinoma with papillary proliferation.

CASE 16: A man of forty-seven had had symptoms, apparently consisting chiefly of a lump in the neck, of twenty years' duration. At operation, there was a fairly hard mass of tissue 7 x 5.5 x 3.5 cm. in size. Microscopical sections showed increased cellularity, the cells being largely grouped in small acini. The capsule and the vessel walls in several places were infiltrated by the tumor process. Eight months after operation the patient had gained 18 pounds; his temperament was more stable; the wound well healed; pulse 84; no tremor. He was working hard as a laborer.

CASE 17: A woman of sixty-one had had a large mass in the right side of her neck for eight months. Her basal metabolism was 19 per cent above normal. At operation, two cystadenomas, 9 x 6 and 3 cm. in diameter respectively, were found. Grossly these were described as "grumous," while microscopically there were many large acidophilic cells arranged in an "embryonal" rather than "fetal" manner. There was no invasion. Ten months after operation no lumps were palpable in the neck; there was no recurrence.

CASE 18: A man of thirty-six complained that his neck had enlarged for four months, increasingly so during the preceding two weeks. A piece of tissue 3 cm. in diameter, largely cystic in character but in part calcified, was removed at operation. Microscopically, the alveolar arrangement suggested a peritheliomatous picture. There was a good deal of necrosis. Death occurred six months after operation.

CASE 19: A woman of fifty-nine had enlargement of the neck for nine years, with pressure symptoms and accelerated growth for three years. At operation, a lobe of thyroid 6.5 x 7 x 10 cm. in size was removed. This consisted largely of brown fibrous tissue. Microscopically, there was a vesicular arrangement with some masses of round cells. Death occurred thirty-nine months after operation.
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Case 20: A woman of fifty-eight had had a mass in the thyroid for twenty years, enlarging more recently. The operative specimen was 6 x 4.5 x 3 cm. in size. Microscopically, the picture was that of malignant adenoma, indicating "fetal" origin, although parts were papillary. The acinar structure was relatively well preserved, but definite intravascular invasion was present. Fifteen months later there were local recurrences, which were again removed.

Case 21: A woman of thirty-seven had a mass in the neck, of five years' duration. A larger mass the size of a chicken's egg and a smaller substernal nodule were removed at operation. It showed, microscopically, carcinoma of a fetal adenoma origin with rather unusually small cells. Forty-two months later there was a recurrence, and several large masses of thyroid tissue and some involved lymph nodes were removed. The microscopical picture was similar to that seen previously. Four years and three months after operation there was no sign of recurrence.

Case 22: A woman of fifty had had a tumor in the neck for many years. At operation, a small node was removed from the neck and showed metastatic carcinoma. Death occurred two weeks later of empyema. At autopsy there was a mass the size of a man's fist near the thyroid and a smaller mass in the thyroid. Microscopically the tumor was fetal adenoma with some spindle formation of the cells.

Case 23: A man of fifty-two had had a mass in the thyroid for six years, with recently more rapid enlargement. A mass of stony hard tissue 8 x 6.5 x 4 cm. in size was removed. Microscopically, it showed fetal adenoma with fairly well preserved acini but some formation of spindle cells and some infiltration of the capsule. The patient was receiving x-ray treatment and was alive and well seventeen months later.

Case 24: A woman of thirty-nine had had symptoms of nervousness for five years, with a tumor mass probably of over a year's duration. At operation, a hard mass 6 x 3 x 2 cm. in size was removed. Microscopically, the picture is that of carcinoma developing from a fetal adenoma.

Case 25: A woman of thirty-seven had noticed a mass in her neck for fifteen years. At operation, an encapsulated soft globular mass 7 cm. in diameter was found. Microscopically, the sections showed a very cellular tumor of fetal adenoma origin with most of the cells arranged in large sheets. There are some papillary areas. The patient died thirty-nine months after operation, having had symptoms indicating vertebral metastases.

Case 26: A woman of forty-one, who had had seven children, had a swelling of the right side of the neck for five years. At operation, an adherent mass 9 x 7 x 5 cm. in size was removed from the neck. This showed the picture of a carcinoma of the thyroid of fetal adenoma origin. Metastases to the neck, axilla, and lung arose, and death occurred forty-five months after the operation.

Case 27: A man of forty-five had had a mass in his neck for nine years. At operation, an encapsulated but fairly adherent globular mass 8 cm. in diameter was removed. This showed a picture of fetal adenoma "structurally malignant" (Ewing). Ten years and nine months after operation there was a small cystic mass on the left side of the neck in the region of the left lobe of the thyroid; the liver was enlarged and hard, and there were jaundice and some ascites.

Case 28: A woman of sixty-four had had an enlargement of the neck for twelve years. Radium seeds had been implanted three years previously. The basal metabolism was elevated 30 per cent; respiration labored. At operation, an almost completely encapsulated mass 14 x 11 x 18 cm. in size was removed. There were some calcified areas. Microscopically, the picture is that of an alveolar and papillary adenocarcinoma of fetal adenoma type. Death occurred three years and two months after operation.
CASE 29: A woman of forty-three had been operated on at another hospital four years previously for a thyroid condition. At operation at our hospital, a mass 2.2 x 1.5 x 1.2 cm. in size and several smaller masses were removed. Microscopically, there was a mass of rather small cells which represented a thyroid carcinoma of fetal adenoma origin. A year and a half afterward the patient was admitted to another institution, reason unknown.

CASE 30: A woman of thirty-nine had an enlargement of the neck of two years' duration. At operation, an encapsulated mass 4 x 2 x 3 cm. in size was found. Microscopically, the picture was that of thyroid carcinoma of the type arising from a fetal adenoma.

CASE 31: A man of fifty-six had enlargement of the neck of seven years' duration. At operation, an ovoid mass 7.5 x 4.5 x 4.5 cm. in size was removed. Microscopically, the picture is that of thyroid carcinoma of malignant adenoma origin. Three months after operation the mass seemed a little smaller but stony hard and fixed more than before. The trachea was almost straight; there was no change in weight. Social Service Report, one year later: swelling larger; condition fair.

CASE 32: A woman of fifty-seven had an enlargement of the neck of thirty-five years' duration. At operation, two small masses, each less than 1 cm. in all diameters, were found. Microscopically, they showed a carcinoma of fetal adenoma origin but largely composed of spindle cells.

CASE 33: A woman of forty-eight had had a very hard mass in the lower portion of the left thyroid lobe for three months. At operation, two masses were removed, the larger the size of a bantam's egg. Microscopical examination showed the picture of a thyroid carcinoma taking origin from a fetal adenoma. The patient was apparently well eight months later.

CASE 34: A woman of forty-six had noticed a hard mass of apparently rather shorter duration. At operation, a mass 4 x 5 x 2 cm. in size was removed. This was carcinoma of the type arising from fetal adenoma on microscopical examination. A small recurrence was removed two months later.

CASE 35: A woman of forty had a thyroid mass of unknown duration. At autopsy a very cellular tumor, the cells largely of spindle type, was found in the thyroid. There were massive metastases in the 4100 gm. liver, and smaller ones in both adrenals and the retroperitoneal lymph nodes. No involvement of the lungs or bones was found.

CASE 36: A woman of fifty-three had noticed a mass in her neck for the preceding thirty years, growing more rapidly recently so that it extended from the jaw to the sternum, laterally to the trapezius muscles. At operation, the mass was found to consist largely of a cyst, but a cellular carcinoma of fetal adenoma type was found microscopically. The patient died six days later. No autopsy.

CASE 37: A woman of seventy had noticed a swelling in the thyroid region for two weeks or a little longer. At operation, a soft mass 6 x 5 x 4.5 cm. in size was removed. Microscopically, the picture is that of an unusually cellular type of thyroid carcinoma, grade III, of fetal adenoma origin.

CASE 38: A woman of sixty-two had a history of four years' progressive enlargement of the neck. At operation, irregular pieces of tissue were found, some resembling brain in consistence. Microscopically, the tissue consisted largely of a mass of round cells, but was thought to be of fetal adenoma origin. Death occurred four days after operation, from "shock."

CASE 39: A man of fifty had had a goitre for sixteen years, which became hard four months before admission. There had been a dry cough for eight months and dyspnea for four months. The left lobe was removed and infiltrated lymph nodes were found. The mass was 9 x 7 x 6 cm. in size, the bulk of it calcified. The microscopical picture showed an epidermoid carcinoma with extreme anaplasia. The patient had x-ray treatment but died five months after operation.
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CASE 40: A woman of forty-nine had a goitre of many years' duration, which had grown more rapidly and been painful for one month. At operation, a partially encapsulated mass 12 cm. long and filled with soft crumbly necrotic material was removed. Section showed a giant-cell carcinoma of the thyroid. Death occurred within two days after operation.

CASE 41: A man whose age was not given had an enlargement of the thyroid of six years' duration. At operation, both lobes were enlarged and several nodules, each about 2.5 cm. in diameter, were found. Microscopically, a giant-cell carcinoma was found to infiltrate the thyroid. A diffuse recurrence ensued and the patient died three months after operation.

CASE 42: A woman whose age is not stated had a mass 5.5 x 4.5 x 4.5 cm. in size removed from her thyroid. This was partly cystic. It showed the microscopical picture of giant-cell carcinoma. Death occurred from recurrence two months later.

CASE 43: A woman of sixty-five had had a gradually increasing goitre for thirty-five years. At operation, a mass 17 x 3 x 8 cm. in size was removed. This showed the picture of a giant-cell carcinoma. The patient died before leaving the hospital, twenty-four days after operation.

CASE 44: A woman of about sixty-five had had an enlargement of the neck for twenty-five years, which was much accelerated for two months. A large mass partly adherent to the skin was removed at operation. The microscopical picture was that of a giant-cell carcinoma. Death occurred two months after operation.

CASE 45: A man of fifty-one had had enlargement of the neck for one year, more rapid for two months. An encapsulated mass 10.5 x 7 x 3 cm. in size was removed from the thyroid region. The microscopical section showed round and polygonal cells with some acinar arrangement. Death occurred six months after operation.

CASE 46: A man of twenty-nine had had a mass in the neck for some time, and hoarseness for six months. At operation, an irregular mass 7 x 5 x 4 cm. in size was removed. The microscopical picture, although suggestive of Hashimoto's disease or a lymphosarcoma, seems clearly to be a round-cell carcinoma.

CASE 47: A man of fifty-two complained that her neck had been enlarging for two years, recently more rapidly. At operation, a mass 10 x 7.5 x 5.5 cm. in size was removed. It showed a picture which has been variously interpreted but which we believe to represent a small-cell carcinoma. Death occurred four hours postoperatively.

CASE 51: A woman of sixty-two had symptoms of unknown duration. Intubation and partial thyroidectomy were performed. There were two masses, the larger 6.6 cm. in its greatest dimension. The microscopical picture was round-cell carcinoma. Death occurred two days later.

CASE 52: A woman of sixty-two had been nervous for a long time and had enlargement of the neck for four months. A mass the size of a lemon was removed at operation. Microscopically, the picture is that of a round-cell carcinoma with many mitoses. Death occurred four months after the operation.

CASE 53: An "elderly" woman had had an enlargement of the neck for several
years, recently growing more rapidly. A mass 7 cm. in size was removed at operation. It showed a picture diagnosed by some as Hashimoto's disease but which we believe to represent a round-cell carcinoma. The patient was alive four and a half years later.

Case 54: A woman of forty-eight had symptoms of enlargement of the neck of six months' duration. A mass 6 x 5 x 4 cm. in size was removed at operation. Microscopically, it showed a picture interpreted by some as a struma lymphomatosa or Hashimoto's disease, but which we believe to be a round-cell carcinoma.

BIBLIOGRAPHY