TUMORS OF THE THYMUS: PATHOLOGY, CLASSIFICATION AND REPORT OF CASES

HARRY M. MARGOLIS, M.D.

Pittsburgh, Pennsylvania

Tumors of the thymus have been of interest both to clinicians and pathologists. This is due partly to their rarity, but largely to the interesting problems they present when attempts are made to classify them on an anatomic basis. The difficulty is due mainly, of course, to lack of definitive conclusions concerning the histogenesis of the thymus. This fundamental difficulty is accentuated by the well known tendency of primary tumors of the thymus to present a variegated histologic appearance and extreme polymorphism of cellular structure.

In this consideration of primary thymic neoplasms I refer particularly to those which arise from the thymic parenchyma, in other words, from the cells of the reticulum, the small thymic cells, or so-called thymic lymphocytes, and the corpuscles of Hassall, assuming tentatively that all of these constituents of the thymic parenchyma are subject to neoplastic changes. In contradistinction to these, are those other primary tumors which arise from the cells of the stroma of the thymus. Such tumors may be in the nature of true lymphosarcomas, fibrosarcomas, myxosarcomas, or lipomas, which have been reported occasionally. As will be pointed out later, there should probably also be excluded from the group of tumors of the thymic parenchyma those true lymphosarcomas which apparently have their primary origin in the thymus and which subsequently are followed by a leukemic blood picture, the condition usually designated leukosarcoma (Sternberg). Finally, one may occasionally encounter a metastatic tumor within the substance of the thymus.

It is logical to begin a consideration of neoplasms of the thymus with a review of the theories that have been held with reference to the final sources of the small thymic cells, for the classification of thymic neoplasms is closely linked with the histogenesis of these thymic cells. Recently, I reviewed briefly the salient facts

1 Work done in the section on Pathologic Anatomy, The Mayo Clinic, while a Fellow in Medicine in The Mayo Foundation, Rochester, Minn.

2106
which have been adduced in this controversy. Two diametrically opposed views are still held. The studies of Maximow, Pinner, Hammar, Rudberg, Jonson and Danchakoff led them to conclude that the small thymic cells are morphologically and histogenetically related to the blood lymphocytes and that they are therefore of mesenchymal origin. More convincing evidence seems to have been adduced by Nusbaum and Prymak, Stöhr, Bell, Prenant, Dustin, and, more recently, by Gottesman and Jaffe and by Deanesly, indicating that the source of the small thymic cells is the entodermal thymic reticulum. At the present time the leaning toward one or the other hypothesis depends on the point of view of the individual observer, based on his interpretation of the studies that have been made by numerous observers. It is agreed, however, by most writers that final conclusions are not as yet warranted. It would, then, seem reasonable that a definitive classification of thymic tumors is equally unjustified.

A correct anatomic classification of thymic neoplasms presupposes unequivocal proof of the sources of the thymic cells from which these tumors arise. In the absence of conclusive knowledge regarding the histogenesis of all of the constituents of the thymus, attempts at detailed classification of tumors of its parenchyma must perforce lead to inaccuracies. It appears inconsistent to admit lack of knowledge of the histogenesis of the normal thymus and yet to proceed with a dogmatic subdivision of tumors of the thymic parenchyma into carcinomas and lymphosarcomas, implying an origin on the one hand from epithelial structures, and on the other from "lymphocytic" elements. When final conclusions concerning the origin of the various elements of the thymic parenchyma become available, such a classification may be shown to be entirely incorrect, in which case it would have served only to increase the overburdening confusion that already exists regarding many aspects of our knowledge of the thymus.

Any classification of tumors arising from the thymic parenchyma, if it is to serve a useful purpose, should imply clearly the lack of definite knowledge regarding their source, thus avoiding confusion and stimulating interest in studies which may throw further light on this problem. The generic term, thymoma, suggested first by Grandhomme, hints at the lack of more specific knowledge regarding the sources of such tumors, and is a most appropriate designation. It indicates only the primary source of the growth from the thymic parenchyma, at the same time
implying a lack of definite knowledge concerning the cellular elements from which the tumor has arisen.

It appears, too, that except for distinguishing between such tumors as frank fibrosarcomas and lipomas, attempts are usually not made to distinguish tumors of the thymus which may not have their origin in the parenchyma. I refer to such tumors as true lymphosarcomas, which may conceivably arise from the lymphocytic elements within the stroma of the gland, as contrasted with those so-called lymphosarcomas that are believed to be derivatives of the cortical cells of the thymus.

Because of this confusion concerning the entire subject of thymic neoplasms, it has seemed justifiable to undertake a review of the subject and to report the views obtained from the critical analysis of several tumors of the thymus observed in the Section on Pathologic Anatomy at The Mayo Clinic.

**Review of the Literature**

Bristowe, in 1854, described a tumor of the anterior and posterior mediastinum, occupying the site of the thymus, enclosing the lower end of the trachea and partially surrounding the heart. The microscopic features were inadequately described, making it impossible to determine whether this tumor was a thymoma or a true lymphosarcoma of the thymus. The patient was twenty-two years old and complained of dyspnea, with expiratory wheezing.

Cayley, in 1868, described a tumor in a woman aged thirty-six years, which had probably originated in the thymus. This patient had severe dyspnea, cough, and edema of the left upper extremity. There was infiltration of the pericardium, pleura, and lung, and involvement of the bronchial and mediastinal lymph nodes. The microscopic appearance of the primary tumor was not described, so that its identification is not possible.

Ambrosini, in 1894, reported a tumor of the thymus which had involved the lungs and pericardium. "Structurally the tumor was a carcinoma, essentially scirrhous in type."

Paviot and Gerest, in 1896, described a tumor of the thymus regarded by some as the first true epithelioma of the thymus. The patient was a woman aged fifty-two years, who complained of retrosternal pain, marked dyspnea, cough, and later change in voice and edema of the legs. There was evidence of a mediastinal tumor with dilatation of the thoracic veins. The patient died of asphyxia. At necropsy a large tumor was found in the
region of the thymus, and a metastatic nodule in one renal capsule. Sections of these tumors revealed a definitely epithelial type of structure with an abundant, poorly vascularized stroma. Besides the cords of epithelial cells, there were spherical bodies which were apparently derived from the epithelial cells. The authors stressed the significance of these corpuscles in the diagnosis of tumors of the thymus.

Thiroloix and Debré, in 1907, reported the occurrence of a mediastinal tumor which was undoubtedly of thymic origin. The patient was a man aged fifty-six years, who for two years had had substernal pain, and dyspnea which was more marked at night. Later, he lost weight and strength, and succumbed in an attack of asphyxia. At necropsy a large tumor was found in the thymic region. It was whitish and very firm. It infiltrated the borders of the lungs and was adherent to all the mediastinal structures, spreading downward and involving the pericardium and the auricles of the heart. Metastasis was not found. Microscopic examination revealed tumor cells which varied markedly both in size and shape. The cells were either polyhedral, oval, or spherical, and were arranged in solid cords. There were also scattered, small, concentric layers of cells with a tendency to central keratinization, giving the appearance of Hassall's corpuscles. The authors agreed with the suggestion of Grandhomme, that until more is known concerning the origin of most of the mediastinal tumors, the designation of thymoma for tumors which appear to be derived from the thymic parenchyma is probably most desirable.

Schridde, believing, as did Stöhr, in the epithelial nature of the thymus, was inclined to consider all tumors of the thymus as carcinomas. However, in view of the uncertainty of the origin of all the elements of the thymic parenchyma, he preferred to designate them malignant thymic tumors.

Rubaschow, in 1911, compiled a list of sixty-nine thymic tumors which had been reported in the literature to that time, though he admitted that, on account of the difficulty of ascertaining the source of certain mediastinal tumors, it was hard to determine the actual number. He favored the view that the thymic parenchyma is composed of epithelial and lymphocytic structures, and accordingly classified most thymic tumors either as carcinomas or as lymphosarcomas, basing such distinction on the morphologic characteristics of the tumor cells. According to such a classification, he found that most tumors of the thymus appeared as
lymphosarcomas, and only a small number presented the appearance of carcinomas. He considered the polymorphism of the cellular structure of thymic tumors. His own case was that of a man aged sixty-two years, who during life presented no signs referable to a thymic neoplasm. At necropsy a large tumor was found at the site of the thymus. Microscopically the tumor cells varied considerably in size and shape. Some of the cells were round; others were oval or polygonal. The cells were collected into solid groups or presented an alveolar arrangement. There was a supporting network of connective tissue and remnants of thymic tissue were seen.

Ewing, in 1916, reported three tumors of the thymus. He felt that thymic tumors fall into two main groups: (1) lymphosarcoma or thymoma, composed of a diffuse growth of round, polyhedral, and giant cells, and (2) carcinoma, arising from the reticulum cells. Yet in the same paper he stated: "The exact origin of the so-called lymphosarcomata of the thymus remains undetermined. My own study of several cases has led to the conclusion that the thymic round-cell tumors differ from other round-cell tumors of lymph-nodes, that the reticulum cell is here the chief or sole source of the tumor. If these conclusions are correct, the term thymoma deserves recognition."

One of Ewing's patients was a girl, aged nineteen years, whose illness began with a swelling of the left side of the neck. The acute febrile course in this case simulated that of an infectious process. At necropsy a very extensive tumor was noted, with the densest portion of the growth in the region of the thymus. On microscopic examination the tumor showed the general structure of a large-cell lymphosarcoma. Closer study revealed a medium-sized polyhedral cell or cubical cell of epithelial character. The nuclei were large and vesicular, the nucleoli were prominent, and the cytoplasm was opaque and acidophile.

In another case, that of a man aged thirty-two years, the initial symptoms were tenderness over the upper part of the sternum and enlargement of the axillary lymph nodes. Examination revealed evidence of a mediastinal tumor. The temperature ranged from 99° to 103° F. Under heavy roentgen ray treatment the tumor gradually regressed and the enlarged nodes disappeared. Biopsy of the sternal tumor showed a structure resembling Hodgkin's granuloma, with an excess of peculiar giant cells, which were large, rounded, or polyhedral, with light-staining
cytoplasm, multilobed nuclei which were hyperchromatic, or multiple vesicular nuclei, and strongly acidophile nucleoli. The derivation of the giant cells seemed traceable to more numerous, smaller, rounded or polyhedral epithelioid cells, which made up the bulk of the tissues.

The third case, that of a woman aged fifty-six years, presented many features similar to the second case. The microscopic picture was strikingly similar to that observed in the second case. "The tumor presented the general appearance of Hodgkin's granuloma with excess of peculiar giant cells and unusual fibrosis. On analysis from the standpoint of thymoma, characteristic features are revealed. The chief cells are not large lymphocytes, but cubical, cylindrical, polyhedral, elongated, and very irregular cells with vesicular nuclei and prominent nucleoli. Giant cells are very numerous and of all sizes. They may be traced to the proliferating cells of the reticulum. Mitoses are very scanty. This structure differs notably from lymphosarcoma or Hodgkin's granuloma. This history and the indefinite neoplastic properties suggest that the process, like Hodgkin's disease, was of infectious and inflammatory origin."

The descriptions of the cellular structures of thymic tumors, particularly those reported by Rubaschow and Ewing, indicate clearly how difficult it is, from the morphologic standpoint alone, to classify some of these tumors as carcinomas and others as lymphosarcomas. Indeed, it is a striking fact that in the same tumor, cells which morphologically are epithelial are found in association with cells which show considerable variation in form, at times assuming a superficial resemblance to cells seen in lymphosarcoma.

Bell, in 1917, also pointed out the fallacy of the prevailing classification of thymic neoplasms. He wrote of the so-called thymic lymphosarcoma as follows: "It does not seem justifiable to assume that tumor tissues of this type are of connective tissue origin. We know that malignant neuroblastomata often assume this (sarcomatous) appearance, and it is not uncommon to find the rapidly growing part of malignant epithelial tumors of the kidney composed of loosely arranged rounded cells. It is easily possible that tumors arising from the thymic epithelium may take on this appearance when growing rapidly. The type of cell in these tumors is probably a thymic epithelial cell. The term sarcoma will lose all its original significance if applied to tumors
of this character, and it seems equally inappropriate to call them carcinoma. The term thymoma seems most suitable."

The structure of the thymoma reported by Foot in 1920 was described as follows: "The tumor is made up of innumerable lymphocytoid cells which, at first glance, might be taken for microlymphocytes. Closer examination showed cells which were larger than lymphocytes, more polygonal in outline, with an acidophile cytoplasm, vesicular nuclei and nucleoli. There was also a dense network of connective tissue."

Symmers and Vance, in 1921, issued what they believed was the fourth report of a primary thymic epithelioma. On the assumption that the small thymic cells are lymphocytes of mesodermal origin, these authors pleaded for the subdivision of thymic neoplasms into "epitheliomas" and "lymphosarcomas." Yet the description of the microscopic structure of the epithelioma in their case is of a bizarre variety of cells, some of which approached lymphocytes in morphology.

Jacobson, in 1923, described a case of carcinoma of the thymus. The patient was a man aged forty-two years, who complained of pain and stiffness in the lower part of the back, sharp kyphosis in the lower thoracic region, and a slight afternoon rise in temperature. Metastatic carcinoma and tuberculosis of the spinal column were suspected. Later roentgenograms revealed mediastinal and pulmonary new growths. At necropsy a tumor of the thymus, with extensive metastasis to numerous organs, was found. Jacobson felt that the tumor was derived from the concentric corpuscles of Hassall. The cells of the reticulum did not play a recognizable part in making up the growth. "The degeneration phenomena in the cells of the tumor in the thymus and most of the metastases were very bizarre and might be said to be an exaggeration of the peculiar changes seen in the epithelium of normal thymus glands. There was also a tendency for the metastases to form structures resembling Hassall's corpuscles."

Largiadèr, in 1923, reported a carcinoma of the thymus composed largely of epithelial cells of various sizes, arranged in the form of columns, alveoli, and solid nests, and separated by a dense fibrous stroma. However, in other sections there was a different structure; namely, a diffuse growth of small cells and relatively scanty stroma, a structure which, if seen alone, might be interpreted as sarcoma. Largiadèr commented on the extraordinary polymorphous character of the growth of the tumor.
Knerringer and Priesel, in 1923, reported a tumor of the thymus in which the neoplastic tissue was composed of cells which were morphologically both epithelial and lymphocytic. This was described as "lympho-epithelioma thymi." Unless one assumes that the lymphocytic elements were only remnants of the thymus and not a part of the new growth, it would appear that the same type of tissue, under certain conditions, is capable of producing two morphologically distinct types of cell.

Nathan, in 1929, presented a similar thymic tumor, composed mainly of epithelial cells and, to a lesser extent, of small round cells which had a typical lymphocytic structure. Only the epithelial cells showed any tendency to infiltration. Nathan was under the impression that only the epithelial portion of this tumor was definitely neoplastic, and from the description it appears that the lymphocytic elements were probably the remnants of the normal thymic structure.

Foot and Harrington, in 1923, presented a detailed report on a case of thymoma; the patient was a child aged two years. The tumor was composed of cells which showed three types of growth: "a reticuloid, resembling the embryonic thymic reticulum; an epithelioid, resembling an adenocarcinoma or a medullary carcinoma, and a sarcomatoid, resembling a large, round-cell lymphosarcoma or fibrosarcoma."

Lemann and Smith, in 1926, described a case of "carcinoma" of the thymus; the patient was a man aged fifty-eight years. The clinical features in this case resembled closely those noted in Jacobson's case, the chief complaint being referable to the metastatic nodules in the spinal column. Practically no symptoms were produced directly by the primary growth until just before death.

Brannan, in 1926, described a "carcinoma" of the thymus which had occluded the superior vena cava and its tributaries. He pointed out that involvement of the large veins of the thorax occurs not infrequently, and that this had not been emphasized sufficiently.

Herriman and Rahte, reporting a case of thymoma, stressed particularly the difficulty that may be encountered in establishing a clinical diagnosis.

Friedlander and Foot, in 1925, reported a case of malignant small-cell thymoma with acute lymphoid leukemia. The patient was a woman aged thirty-eight years, whose chief complaint was
a painful swelling of the right leg. On examination she was found to have thrombophlebitis and acute lymphoid leukemia. Leukocytes numbered 140,000 in each cubic millimeter of blood, and the proportion of lymphocytes was 93 per cent. Later there were found an increase in retrosternal dulness, and enlargement of the liver and spleen. At necropsy a tumor of the thymus, with extensive metastasis, was found. The sections from the primary tumor showed it to be composed of cells which were essentially lymphoblasts and which contained innumerable mitotic figures. The cells of the circulating blood, of the lymphoid pulp of the nodes, and of the spleen were practically identical with the type cells of the thymic tumor. The conclusion of Friedlander and Foot was that they were "probably dealing with a lymphosarcoma of the thymic cortex, a small-cell malignant thymoma, and with a lymphoid leukemia directly connected with it and originating in the thymic cortex. . . . This case is also useful as supporting the theory of the mesenchymal origin of the lymphoid elements of the thymic cortex." I shall have occasion to refer to this case later when I shall attempt to indicate the necessity of making a distinction between thymoma and true lymphosarcoma of the thymus, of which this case may be an example.

Foot, in 1926, reported still another case of thymic tumor; the patient was a man aged forty-five years, whose chief complaint was shortness of breath, pain in the thorax, and cough. There was evidence of venous engorgement, and, despite intensive deep irradiation, the condition progressed and the patient died of profuse pulmonary hemorrhage. Histologically the tumor appeared to be of a definitely epithelial type; its cells corresponded to those of a loosely built alveolar carcinoma, but differed from them inasmuch as they were stellate, more like embryonal thymic reticulum cells, and also because they tended to form bodies that resembled thymic corpuscles more closely than the epithelial pearls of an epidermoid carcinoma.

Now it is significant that in the report of Foot and Harrington, mentioned above, the authors indicated the error of naming a tumor of the thymus with polymorphic tendencies "carcinoma." They also made the following assertion: "The term lymphosarcoma should not be used in connection with the lymphocytoïd type of malignant thymoma, until it is proved that it is indeed a neoplasm of the lymphatic system." However, as a consequence of the observations of Friedlander and Foot, Foot no longer believed
to be tenable the hypothesis of the unitary epiblastic origin of all the parenchymatous elements of the thymus. Consequently, in 1926, he expressed the reversal of his original views on the histogenesis of the small thymic cells in the statement: "That these lymphoid cells (small thymic cells) are really lymphocytes was clearly indicated, if not proved, by the thymic tumor reported by Friedlander and myself last winter (1925), in which the neoplasm was lymphoid in type and accompanied by an unmistakable lymphoid leukemia, without any noticeable involvement of the lymph nodes in general. Thus it seems very probable that the 'dualists' are warranted in their assumption that these are true lymphocytes and not differentiated entodermal cells." Whether this view is correct cannot be definitely asserted. Nevertheless, the evidence adduced by Friedlander and Foot seems insufficient for such a radical reversal of views on a topic so fundamental and so much disputed. There are, in fact, many positive data to indicate that the view opposite to that held by Foot can be supported equally well by a different interpretation of data derived from cases of leukemia and some types of leukosarcoma.

This review of the literature indicates the different attitudes taken by various observers concerning the nature and classification of thymic neoplasms. The attempt has not been made here to review all the reports of tumors of the thymus. Many clinical case reports are available in which the diagnosis has not been confirmed by pathologic studies, and many reports of cases of thymic neoplasm in which pathologic studies were made lack sufficient data for identification of the growth with certainty either as a thymoma or as sarcoma arising from cells within the stroma of the thymus.

Report of Cases

Case 1: A man, aged forty-nine years, came to the clinic because of pain in the thorax. This had begun about six months previously, but had not given him much distress until two months previous to his admission. The pain and a drawing sensation in the thorax occurred particularly if he lay on his left side. He generally felt better when he was up and about. He did not cough or expectorate. For two weeks he had had slight dyspnea and palpitation. He had lost approximately 25 pounds in weight in the previous seven months.

Examination revealed a somewhat undernourished man, whose weight was 139 pounds. The veins of the thorax and neck were somewhat dilated, and the patient became extremely cyanotic on bending forward.
There was evidence of a large mediastinal tumor. There was no expansile pulsation, no cardiac hypertrophy, and no evidence of bronchostenosis. The roentgenogram of the thorax revealed a rounded, somewhat lobulated tumor in the mediastinum, suggestive of malignant lymphoma. The blood count and urinalysis gave normal values. The Wassermann reaction of the blood was negative. A clinical diagnosis of mediastinal tumor was made. In view of the questionably malignant nature of the growth, surgical exploration was attempted.

The left pleural cavity was opened, and a lobulated, multilocular, cystic mass could be felt anterior to the pericardium and extending into the left thoracic cavity. The tumor was firmly attached to the pericardium, to the ascending aorta, and to the right pulmonary artery, and extended under the arch of the aorta, filling the anterior and superior mediastinum and extending to the pleura of the right lung, to which it was adherent (Fig. 1). The tumor contained a number of multilocular cysts.
cysts. Most of it was excised. For several days the patient's condition was desperate and he died on the seventh day after operation.

At necropsy, performed one hour post mortem, there were found 20 c.c. of sanguinopurulent material in the left pleural sac and some purulent exudate over the internal surface of the left thoracic wall. The left lung was completely collapsed, and its anterior surface was covered by a fibrinous exudate and was studded with several small tumor nodules. In the anterior mediastinum, in the region of the thymus, was the remnant of the tumor. This was an irregular, pear-shaped mass, of firm consistence, measuring 7 cm., 3 cm., and 4.5 cm. in various diameters. The upper part of the mass was continuous with tissue that was apparently the thymus. This mass surrounded the great vessels and extended backward, partially enveloping the trachea, but without causing compression of it. Tumor tissue covered some of the anterior surface of the pericardium. The cut surface of the tumor was white, and revealed anthracotic lymph nodes which had become surrounded by the tumor without being invaded by it. There were regions of old hemorrhage.

Sections of the tissues other than those involved by the tumor revealed nothing that is of significance in this report. The tumor tissue within

**FIG. 2. CASE 1: SECTION OF THYMIC TUMOR**

Nests and cords of tumor tissue within an abundant stroma of fibrous tissue. Hematoxylin and eosin. × 100.
the thymus was generally disposed in the form of solid nests or irregular columns which were composed of cells varying in size from 12 to 30 microns in length and from 10 to 15 microns in width (Fig. 2). These cells also varied considerably in shape: some were nearly spherical; most of them were polygonal or ovoid. The cytoplasm, which was relatively scanty compared with the large nucleus, was slightly acidophilic. The nuclei were very large and vesicular and contained a fine, deeply staining chromatin network which was most abundant near the periphery. One or more nucleoli were present in most of the well stained nuclei. In general appearance these markedly resembled epithelial or modified reticular cells (Fig. 3). Among these there were other cells in which the nuclei were either pyknotic or from which the chromatin had practically disappeared. These nests or cords of tumor tissue were embedded in a stroma composed of fibrous tissue which in some parts was rather cellular, and in others was a dense, fibrous tissue containing numerous blood vessels. The cells in the centers of some islets of tumor tissue were the sites of degenerative phenomena; some nuclei were pyknotic, whereas most of the central cells gave evidence of marked swelling of the cytoplasm, which stained intensely with eosin, revealing a more homogeneous, hyalin-like appearance, the nuclei assuming a vacuolated appearance due to the nearly complete disappearance of the
chromatin. In other islets the cells immediately peripheral to the central degenerating ones were much flattened and tended to be arranged concentrically, these islets assuming the typical appearance of corpuscles of Hassall (Fig. 4). Other, larger nests of tumor tissue gave evidence of far more advanced degeneration of the central tumor cells. These nests were, for the most part, converted into a homogeneous mass which stained with eosin, and in which remained scattered remnants of tumor tissue or merely the outlines of tumor cells. Such islets presented the appearance of irregular cysts, the walls of which were composed of several layers of tumor cells, the remains of the peripheral portion of the

![Figure 4. Case 1: Section of thymoma showing rather typical corpuscles of Hassall derived from the tumor cells.](image)

Hematoxylin and eosin. × 375

original islet. In still other regions there was a greater abundance of intercellular substance in which there were, in addition to the fibroblasts and modified reticular cells, some lymphocytes. Regions of the pleura which were invaded by the tumor presented evidence of fibrosis, with lymphocytes and newly formed blood vessels, as well as small collections of tumor cells.

The anatomic diagnosis was as follows: recent partial excision of thymoma; collapse of left lung and pleuritis (left), and former gastro-enterostomy.

Case 2: A man, aged fifty-five years, came to the clinic on account of a carcinoma of the rectum. He also complained that for one and a
half years he had had some difficulty in swallowing; that at times considerable effort had been required to get solid food into the stomach. The patient died on the fourth day following operation for carcinoma of the rectum. On discussing with the patient's wife the abnormalities found at necropsy, it was learned that for years, ever since childhood, the patient had had difficulty in talking at times and sudden attacks of shortness of breath.

The necropsy was performed twelve hours post mortem. In the anterior and superior mediastinum there was encountered a firm mass, which was related posteriorly to the anterior surface of the heart, and which was adherent to a portion of the pericardium. It extended also to the arch of the aorta and to the innominate artery, to which the mass also was attached. Continuity with the thyroid gland could not be demonstrated. The mass also extended to the right and was adherent to the right lung. On section, the mass presented a central white portion with radiating strands of tissue which enclosed small reddish lobules. There was no evidence of tumor tissue in any other organ.

The sections of the thymic tumor presented irregularly sized lobules of tumor tissue, which corresponded fairly well with the general arrangement of the ordinary thymic lobule in a normal thymus. These lobules were divided by septa of dense fibrous tissue. The lobules were composed almost entirely of tumor tissue, with but a scanty number of cells morphologically like the small thymic cells or lymphocytes.

The type cell of which the tumor was composed presented a rather characteristic structure which contrasted strikingly with the cells which comprised the rectal tumor. There was, however, considerable variation in the morphologic appearance of some of the cells of the thymic tumor and a striking variation in the arrangement of these cells in the various sections of the same tumor. The cells were generally arranged in long, irregular, anastomosing cords, or in solid nests, or as fairly large cystic spaces. The cords of cells were often so arranged as to produce the appearance of a distinct reticulum, whereas at times an irregular alveolar arrangement was suggested. Among these reticular cells there were scattered a variable number of small round cells, with deeply staining nuclei, which were morphologically identical with lymphocytes or with the cortical cells of the thymus. The cells of the tumor showed either a perfect resemblance to the thymic reticulum cell, or, as will be more evident later, a most striking resemblance to the cells lining the cystic spaces that sometimes are encountered within the normal thymus. The cells, exclusive of those lining the cystic spaces, varied considerably in size, averaging from 6 or 7 microns to 12 or 15 microns in length; they presented usually an ovoid form, although frequently the cell was rounded or polyhedral in shape. The nuclei were either ovoid or rounded, corresponding in general with the form of the cell, and were surrounded by a variable amount of faintly acidophilic cytoplasm. The nucleus was vesicular in appearance, containing a very small amount of chromatin distributed as minute granules. Small nucleoli were often, but not invariably, present. Mitotic figures were not observed.
The stroma was extremely scanty in amount, and there were few blood vessels. In numerous foci some of the tumor cells were densely aggregated in the form of small, concentrically arranged bodies, the cells of which gave evidence of degenerative changes in their nuclei and of marked swelling and beginning hyalinization of their cytoplasm, producing rather typical corpuscles of Hassall (Fig. 5). In other sections the central mass of cells within a nest of tumor tissue had undergone more marked necrosis, leaving a nearly homogeneous, acidophilic mass in which there were faintly discernible the outlines of the former cells. This appeared to be identical with the necrosis observed in the center of tumor nests in Case 1. Where the arrangement in the form of cysts was most pronounced, the cells composing them were of the tall, columnar type, with a long, somewhat fusiform nucleus poor in chromatin (Fig. 6). Cilia were not observed. Although, as a rule, these cystic spaces were lined with but a single layer of cells, there were some in which the lining epithelium was two or three layers deep, and in which the cells at the base had a more cuboidal form. Some of these cysts contained small lymphocytes and the remains of degenerated cells. Staining with mucicarmine did not reveal the presence of mucus, and the sections stained by the van Gieson method revealed only dense fibrous septa between the lobules of tumor tissue.
The anatomic diagnosis was as follows: recent colostomy and resection of rectum for mucoid carcinoma; retroperitoneal pelvic cellulitis; purulent pleuritis (right), and thymoma.

Case 3: A boy, aged three years, was brought to the clinic complaining of cough and wheezing respiration. He had been born at full term, had had measles, mumps, chickenpox, and pertussis. Two months previous to admission a dry cough developed, and, about one month later, wheezing on inspiration and a rattling noise on breathing. There was some dyspnea. At intervals during the day the breathing became labored. On lying down, the child experienced spells of choking. The patient's home physician found evidence of a mediastinal tumor and roentgen-ray treatment was given.

On examination at the clinic the patient presented the appearance of a healthy, active boy. The tonsils were large and the pharynx was mildly inflamed. The cervical, axillary and inguinal lymph nodes were somewhat enlarged. There was dulness over the mediastinum, extending beyond both lateral margins of the sternum. There were harsh breath sounds over the entire thorax, and some loud, crepitant, and whistling râles. Urinalysis and a complete blood count gave normal results, and the Wassermann reaction of the blood was negative. A roentgenogram of the thorax revealed a large mediastinal tumor. A diagnosis of tumor of the thymus, with evidence of respiratory obstruction, was made. Two days after admission difficulty in breathing suddenly developed and the child died within a few minutes.
At necropsy, performed six and a half hours post mortem, distended superficial veins were found over the right side of the thorax. On opening the thoracic cavity, a large, firm, yellowish-white tumor, measuring 9.5 cm., 7 cm., and 12 cm. in various diameters, was found in the anterior mediastinum, in the region of the thymus. The surface of the mass was rather smooth and regular. It was attached posteriorly to the anterior surface of the pericardium, which it covered entirely, and it extended upward, infiltrating the superior mediastinum and surrounding the great vessels, which were not, however, visibly compressed. The trachea was compressed by the tumor which surrounded it. The mass also extended laterally to the pleura on both sides; it was more firmly attached, however, to the right lung (Fig. 7). The surface of the cut section of the tumor was homogeneous and yellowish-white. Most of the mediastinal lymph nodes were considerably enlarged and were incorporated in the growth. These nodes presented, grossly, the same appearance as the thymic tumor; yet some of them remained discrete and could be outlined distinctly within the main tumor.

The inner surface of the parietal pleura, particularly over the intercostal spaces, presented numerous, yellowish-white, flattened elevations, which were firm and appeared to be metastatic nodules. Large portions of the surface of the right lung and smaller portions of the surface of the left lung presented the same yellowish-white appearance as the thymic
tumor, due to the tumor spreading, sheet-like, over the surface of the pleura, dipping into the interlobar fissures, and extending for a variable depth into the parenchyma of the lungs. This involvement was most marked along the anterior borders of both lungs, and particularly over the base of the right lower lobe. Several small, discrete nodules were present on the surface of the right lower lobe. These appeared to be the result of metastasis rather than being due to direct extension from the thymic tumor.

The left kidney weighed 52 gm., and the right kidney, 50 gm. When the capsule of the right kidney was stripped, there were seen within the dark, reddish-brown cortex, several discrete, soft, yellowish-white nodules, ranging in size from several millimeters to a centimeter in diameter (Fig. 8). These appeared to be metastatic nodules. Otherwise, examination of the kidneys did not reveal notable gross abnormalities. The spleen weighed 55 gm., and was normal in appearance except for the marked prominence and the great abundance of lymphoid follicles. There was hyperplasia of most of the lymph nodes, particularly of those in the mesentery. There also was evidence of lymphoid hyperplasia in the intestinal tract. The results of other observations which were recorded were essentially negative.

Sections of the thymic tumor contained one area in which several lobules of the thymic parenchyma still maintained the normal proportions
of cortex and medulla; within the medulla there were a number of corpuscles of Hassall. Most of the small thymic cells in the cortex of these lobules presented the normal appearance. But there were scattered among these cortical cells many others in which the nuclei were larger and contained a smaller amount of chromatin, and large nucleoli, and many cells which contained mitotic figures. These cells were scattered diffusely among the apparently mature cortical cells of the thymus, from which they were readily distinguished. In every essential respect these cells could be interpreted either as immature lymphoblasts, or, what are morphologically comparable to them, immature cortical thymic cells.

Fig. 9. Case 3: Section of thymoma showing the morphologic characteristics of the constituent cells, some of which contain mitotic figures.

Hematoxylin and eosin. × 900

TUMORS OF THE THYMUS
Separated from these thymic lobules by the normal trabeculae were some regions which still maintained the general outline of the thymic lobule, and there were other, larger regions, represented by diffuse, dense collections of cells, in which the normal trabeculae were no longer discernible. Such regions were filled with spherical or somewhat irregularly rounded cells, the diameter of which was 6 to 8 microns. The nuclei were so large as nearly to fill the cell and to leave but a narrow rim of faintly basophilic cytoplasm. This description holds for tumor cells except those in which there were large mitotic figures; in these the cytoplasm stained more deeply with eosin. The nuclei in some cells contained large amounts of deeply staining chromatin, whereas in most of the cells the nuclei appeared more vesicular and the chromatin was arranged in the form of a thin network. One or more nucleoli were present in most of these nuclei. There were innumerable mitotic figures throughout the section (Fig. 9). Here and there within this cellular tissue was a corpuscle of Hassall which presented either a hyaline appearance or was partially calcified. Within the sections of tumor these corpuscles appeared to represent the only remnant of the original thymic tissue. Nowhere was there apparent any tendency on the part of the tumor cells to produce bodies resembling corpuscles of Hassall. The stroma was extremely scanty in amount and contained few vascular channels.

A section of one of the mediastinal lymph nodes presented the histologic appearance identical with that of the thymic tumor. Here, too, mitotic figures were extremely numerous. Corpuscles of Hassall were not observed. The lymphoid follicles were not discernible. This contrasted strikingly with the histologic appearance of lymph nodes from other regions, as, for example, from the meso-appendix, in which were numerous prominent germinal centers and in which the reticulum was prominent. The spleen, too, presented marked prominence of the cells of its reticulum and numerous germinal centers, but no evidence of tumor cells such as were observed in the thymus and in the mediastinal lymph nodes.

The section of a nodule in the parietal pleura revealed dense infiltration with tumor cells identical with those of the thymic tumor. The section of a nodule in the lung presented cells of the same type as were observed in the thymic tumor. These cells extended into the tissue just beneath the pleura and infiltrated the alveolar walls. There were present small foci in which the tumor cells were very closely aggregated, producing an appearance suggestive of minute lymphoid follicles. The metastatic nodule in the kidney was composed of the typical tumor cells which had infiltrated the parenchyma, leaving but remnants of degenerating tubular epithelium and an occasional glomerulus. In the periphery of the tumor nodule, the cells gradually faded off in density, leaving a fairly distinct line of demarcation between the edge of the tumor and the surrounding renal tissue.

The anatomic diagnosis was as follows: thymoma with extension and metastasis to the lungs, pericardium, wall of the thorax, kidney and lymph nodes, and compression of the trachea.
Comment: In view of the histologic appearance of the thymic tumor observed in Case 2, it seems worth while to describe very briefly several cases in which there were found, in the course of routine histologic studies of the thymus, epithelial cysts or alveoli associated with small nests of poorly differentiated reticulum cells, varying somewhat morphologically from the cells of the surrounding thymic reticulum. There is much to suggest that these abnormal structures within a relatively normal thymus may be closely linked with the subsequent development of some form of thymoma.

Case 4: A man, aged fifty-seven years, came to the clinic on account of recurrent epigastric distress, typical of peptic ulcer, which symptoms he had had intermittently for twenty years. He died of severe hemorrhage from a bleeding vessel in the bed of the ulcer.

At necropsy, performed three and a half hours post mortem, the gross pathologic changes were confined essentially to the stomach and duodenum. In the stomach the large ulcer and evidence of hemorrhage were found, and there was a healed ulcer in the duodenum. Grossly, the thymus appeared to be almost entirely replaced by fat.

Microscopic observations of the tissues exclusive of the thymus
disclosed nothing relevant to the present consideration. The thymus had undergone advanced involution; it was composed, for the most part, of fatty-areolar, connective tissue in which were embedded islets of thymic parenchyma of varying sizes. In these islets there was marked prominence of the cells of the reticulum, and nearly complete absence of the small thymic cells. Within these islets of parenchyma, also, were occasional corpuscles of Hassall. Within one of the islets there were a number of groups of distinctly epithelial cells, which contrasted strikingly with the reticulum of the thymus. These cells exhibited, for the most part, an alveolar arrangement (Fig. 10). The alveoli were composed usually of a single layer of rather tall columnar cells, the scanty cytoplasm of which was faintly acidophilic, and the nuclei of which were ovoid and vesicular in appearance, containing but small amounts of chromatin distributed in the form of minute granules. Some alveoli were composed of a double layer of cells, so arranged that the more peripheral cells, which were cuboidal in shape, alternated with irregularly columnar, pyriform cells, which occupied a position nearer the lumen of the cyst. Cilia were not definitely demonstrable in the cells lining these alveoli. Each alveolus was clearly demarcated by a layer of long, much flattened cells, apparently of the thymic reticulum. In places the epithelial cells were arranged rather in the form of irregular cords or solid nests. Nowhere was there apparent the slightest tendency to cellular proliferation or invasion of the surrounding tissues. In some of the cords the epithelial cells were flattened, and merged almost imperceptibly with the reticulum of the thymus.

The anatomic diagnosis was recent gastro-enterostomy for gastric ulcer; gastric hemorrhage; healed duodenal ulcer, and thymoma.

Case 5: A man, aged seventy years, came to the clinic on account of symptoms of hyperthyroidism which he had had for two years. Subtotal thyroidectomy was performed for adenomatous goiter with hyperthyroidism. On the eighth postoperative day the patient died of edema of the lungs and bronchopneumonia.

At necropsy, performed two hours post mortem, the thymus weighed 10 gm. and was embedded in a very large amount of fibrous tissue. The other pathologic features were not relevant.

The thymic tissue presented a paucity of small thymic cells and islets of hyperplastic medulla in which the thymic reticulum was very prominent and contained numerous corpuscles of Hassall in varying stages of degeneration. There was a considerable increase in the amount of fibrous tissue. In one region, embedded within the parenchyma, were several nests and cords of epithelial cells, which stood out in sharp contrast with the thymic reticulum (Fig. 11). These cells were morphologically identical with those comprising the alveoli in Case 4. The arrangement of the cells in this case tended, however, more toward the formation of solid nests or irregular cords; the tendency toward an alveolar arrangement was only faintly discernible. Here, too, the epithelial nests were usually definitely demarcated from the surrounding thymic reticulum by one or two layers of very thin, long, spindle-shaped cells, which appeared to be flattened reticulum cells. The epithelial
cells showed no tendency to active proliferation or toward invasion of
the surrounding thymic reticulum.

The anatomic diagnosis was recent thyroidectomy for adenomatous
hypertrophy of the thyroid gland; edema of the glottis; edema of the
lungs with bronchopneumonia, and thymoma.

Case 6: A woman, aged fifty-two years, came to the clinic with
symptoms and neurologic signs indicative of a tumor of the brain in the
region of the optic chiasm. There were no other significant data. The
patient died the day after operation.

At necropsy, performed seven hours post mortem, the thymus
appeared to be largely replaced by fat. Microscopic examination of
sections of the thymus revealed evidence of considerable involution;
the thymic tissue consisted of small islets embedded in large amounts of
connective tissue. The cortical cells were diminished in number, and
there were few corpuscles of Hassall. Within one of the islets of thymic
parenchyma were numerous small cystic bodies lined by single layers of
cuboidal or columnar cells identical with those comprising the alveoli
observed in Cases 4 and 5, except that the low cuboidal type of cell was
somewhat more in evidence. In association with these alveoli, and lying scattered among them, were irregular cords of cells having the same general morphologic appearance as the cells composing the alveoli. There was, however, considerable variation in the form of the cells of these cords; some were cuboidal, whereas most of them were somewhat polygonal or ovoid, and tended to resemble the reticular cell of the thymus. Evidences of active proliferation of these cells or of invasion of the surrounding tissue were entirely absent.

The anatomic diagnosis was recent partial excision of pituitary carcinoma, and thymoma.

Comment

It is evident that certain tumors of the thymus, such, for example, as were found in Cases 1 and 2, bear very close morphologic resemblance to carcinomas, and, arising as they probably do from the reticulum, they might justifiably be classified as carcinomas of the thymus. At present this carries with it, however, the implication that there exist other tumors of the thymic parenchyma from which carcinomas must be distinguished. Thus, in the literature there has appeared the conception that certain tumors of the thymus, the histologic appearance of which differs from that clearly indicative of carcinoma, are totally different histogenetically also, and that, therefore, such tumors deserve a different designation. The term lymphosarcoma of the thymus consequently has been employed to include that group of tumors the histologic appearance of which, frequently bizarre, indicates a predominant tendency toward the production of a more diffuse growth of round cells and a lesser tendency for an epithelial type of growth to take place. Yet, tumors of the thymus which are predominantly sarcomatous in appearance, when studied in detail, usually are found to be extremely polymorphous in the character of their constituent cells. Some of the cells, indeed, are very similar to those observed in tumors which are clearly carcinomatous.

That alone has often engendered doubt as to the actual sarcomatous nature of such neoplasms, and, as already stated, Ewing has concluded, in regard to thymic round-cell tumors that the reticulum is here the chief or sole source of the tumor. If this view is correct, such tumors deserve the appellation of carcinoma equally as much as frankly carcinomatous appearing tumors of the thymus. However, it is not surprising that in the realm of thymic neoplasms, a tumor with a histologic appearance even
slightly suggestive of sarcoma may be interpreted as such, whereas a sarcomatous appearing tumor in the breast or stomach might be considered as possibly denoting a high degree of malignancy and consequently a lesser tendency to differentiation of the tumor cells. At least the attempt to determine the carcinomatous or sarcomatous nature of such a tumor as that of the stomach would not suffer from the insinuation that its parenchyma may have a dual histogenetic basis, one entodermal, the other mesenchymal.

Here, it is possible to note the striking interplay of facts relating to the histogenesis of the thymus and its lesions, especially neoplasms. The differentiation of thymic neoplasms into carcinoma and lymphosarcoma usually has involved the acceptance, or at least the implication, of the view that the thymic parenchyma does have a dual histogenetic basis. And when sufficient evidence for such a view was considered lacking, the occurrence of a lymphosarcoma in the thymus suggested itself as proof of the mesenchymal origin of a part of its parenchyma. Both of these views have obvious shortcomings and both have the tendency to contribute to the confusion that abounds in many phases of knowledge of the thymus.

As an example of the difficulties sometimes encountered in the classification of certain thymic tumors, a case observed by Bedford
may be cited, in which sections of the thymic and metastatic tumors were available to the present writer for study. The polymorphism of the cellular types and the arrangement of the cells were most bizarre when various sections were examined. Although the predominating cellular type was epithelial, or like the reticulum cell of the thymus, and although the arrangement was often that of distinct alveoli and solid nests containing corpuscles of Hassall, and lying in an abundant stroma, there were sections of the primary and metastatic growths in which large round cells and a sarcomatous type of growth were so evident as strongly to suggest sarcoma when those sections alone were viewed. Yet one could not evade the conclusion that the various cellular types represented a morphologic variation of the primary cells from which the tumor arose (Fig. 12). Such an example, as well as many cases reported in the literature as sarcoma of the thymus, lead one to accept the conclusion expressed by Ewing: "On close analysis the round-cell tumors of the thymus are found to differ in structure from the round-cell tumors of lymph nodes. The lymphocytes are scanty. The chief cell showing mitosis is often polyhedral, with acidophile cytoplasm, vesicular nucleus and well developed nucleoli... The marked fibrosis suggests the desmoplastic property of carcinoma."

Correct classification of tumors of the thymus, which have a morphologic resemblance to lymphosarcoma, involves the consideration of several factors. Does the tumor in question arise from the parenchymatous or from the interstitial elements of the thymus? In tumors suspected of arising from the parenchyma, an attempt must be made to assign their origin to the cortical cells of the thymus or to the cells of its reticulum. Should this be possible, what shall be the attitude toward the prevailing opinions regarding the histogenesis of these components of the thymus? Lastly, one must determine the accuracy of morphologic criteria alone in the differentiation of neoplasms into carcinomas and sarcomas.

As regards the origin of certain tumors of the thymus from its connective-tissue stroma, Ewing wrote: "Although it has been commonly assumed that various spindle-cell or alveolar or perivascular tumors arise from the connective tissue stroma of the thymus, this origin has never been fully traced, and there are strong grounds for concluding that the so-called spindle-cell sarcomas and endotheliomas are varieties of thymoma."
It may also be suspected that certain tumors of the thymus which have characteristic features of lymphosarcoma, and which frequently are assumed to arise from the cortical cells, may, indeed, arise from elements within the stroma of the thymus. A true lymphosarcoma originating in the thymus, and proved to be derived from the cortical cells of its parenchyma, occurring in association with lymphatic leukemia, would be strongly confirmatory of the view that the small thymic cells are of true lymphocytic nature. Such a conclusion concerning the lymphocytic (mesenchymal) nature of the small thymic cells actually was arrived at by Friedlander and Foot. One cannot, however, agree that in their case the origin of the lymphosarcoma was traced indisputably to the cortical cells of the thymus. Origin of that tumor from lymphocytic elements in the stroma of the thymus is not impossible and must be considered.

In a previous study in which I attempted to determine the relationship of the thymus to lymphatic hyperplasia associated with various forms of lymphatic leukemia, it was observed that in lymphatic leukemia participation of the thymus in the general lymphoid hyperplasia was strikingly absent. The evidence indicated, also, that the lymphosarcomatous type of thymic tumor found in association with leukemia, in the condition of leukosarcoma, appeared to be due not to hyperplasia of the cortical cells of the thymus, but to infiltration of lymphocytes or to local hyperplasia of lymphocytic elements, comparable, and usually quantitatively proportional, to the degree of similar infiltration of other non-lymphatic organs. Although it must be conceded that in those cases of leukosarcoma on which that study was based there was not any evidence of the primary source of the condition in the thymus, this does not lessen the significance of the suggestion that the occurrence of a true lymphosarcoma in the thymus, whether or not such a tumor is followed by leukemia, does not establish the lymphocytic nature of the gland unless the origin of the lymphosarcoma can be traced to the parenchymatous elements of the thymus and not to lymphocytic elements in its stroma.

In a review of the subject of leukosarcoma, by Flashman and Leopold, in which analysis of the probable primary site of the invasive tumor was attempted, it was found that of 107 cases recorded in the literature, the primary source of the tumors was not always in lymphatic organs, although, as would be expected,
the majority of them were traced to such a source. There remain, however, some cases of leukosarcoma in which the primary source of the tumor appears to be in a non-lymphatic organ, as, for example, the breasts, the dura mater, the prostate gland, or the ovaries. Certainly the origin of a lymphosarcoma in a non-lymphatic organ is not impossible and has been observed frequently. Is, then, the origin of a thymic lymphosarcoma not compatible still with a purely epithelial origin of the thymic parenchyma? In other words, may not primary lymphosarcoma of the thymus arise from lymphocytic elements outside the parenchyma, just as such tumors arise occasionally from the lymphocytic elements of organs in which the epithelial nature of the parenchyma is obvious?

One may not, however, deny the possible origin of some tumors of the thymus from the cortical cells. And in view of the morphologic resemblance of the normal cortical cell of the thymus to true lymphocytes, it is conceivable that such tumors may present a histologic appearance that is indistinguishable from that of true lymphosarcoma. The appearance of such tumors might warrant the diagnosis of lymphosarcoma from the histologic standpoint, but this designation of tumors suspected of arising in the thymic cortex implies committal to the view that the cortical cells are of mesenchymal nature, a view which is not entirely substantiated by existing facts.

If one maintains, then, the attitude that the source of the small thymic cells is not yet definitely known, one is compelled to defer the final classification of this group of tumors. The logical compromise would seem to be to designate such tumors thymomas, pending solution of the problem of the histogenesis of the small thymic cells. Such tumors, then, would be proved to be either lymphosarcomas or modified epitheliomas. Probably, however, there will always remain some round-cell tumors of the thymus the origin of which from the cortical cells or from the stroma of the thymus may not be ascertainable. Such tumors will still deserve the designation of thymoma, until other criteria for their identification become available.

In Case 3 of this series, the lymphosarcomatous appearance of the tumor, both grossly and histologically, is evident. Again one must question its origin from the cortical cells of the thymus or from lymphocytic elements in the stroma, and this question can hardly be answered with finality. The observation of diffusely
scattered neoplastic cells, many with mitotic figures, within the
cortex of thymic lobules that still are only slightly invaded by
the tumor, hints at an origin of these cells from proliferation of
the cortical cells which they resemble so closely. Although the
possibility still exists that these cells represent the result of an
infiltrative process, the cells actually arising in the stroma of other
portions of the gland, the evidence, on the whole, seems more in
favor of the cortical origin of this tumor, which must be designated
a thymoma for reasons that have already been considered.

It becomes evident that, although it is impossible to conclude
with certainty regarding the histogenetic source of all thymomas,
the inclination is to suspect a possible unitary origin of all
parenchymatous tumors of the thymus from one embryologically
distinct source, the entodermal component of the thymus. Such
a view is in accord with my belief, based on embryologic and
histogenetic observations of others, as well as on observations
already quoted, that all the elements of the thymic parenchyma,
including the small cortical cells, are probably of entodermal
origin, the cortical cells representing merely a morphologic vari­
aton of the parent cells. There are indeed many observations
indicating that morphologic variation among cells can be induced
readily by changes in their environment. Uhlenhuth, among
others, has demonstrated that marked variations in the form of
epithelial cells may be induced by their cultivation in various
media. Thus, the epithelial cell was shown to undergo transfor­
mation into a spindle-shaped cell, resembling connective-tissue
cells, when grown in certain media, while it might assume a rounded
appearance when grown in a medium of different consistence.
Such observations make one feel that little reliance can be placed
on morphologic criteria alone in the recognition and differentiation
of neoplasms. This becomes increasingly evident as one studies
the more malignant types of carcinoma and sarcoma, in which
the lack of differentiation of the cells, consequent to their rapid
growth, almost precludes the possibility of constant identification
from histologic examination of the tissue alone.

Because of these facts, it would seem more correct to group
all tumors, the source of which is clearly the parenchymatous
tissue of the thymus, as thymomas. The designation sarcoma
should be reserved for those tumors which are proved to arise
from elements in the stroma of the gland, and these might be
differentiated further, according to the type cell, into lympho-
sarcoma, fibrosarcoma, etc. It is only in this manner that a
distinction can be made between true lymphosarcomas of the
thymus and those "sarcomatous appearing" tumors of the thymic
parenchyma which are regarded by some observers as derivatives
of the "lymphocytes" of the thymic cortex and by others as
modified epithelial tumors derived either from the entodermal
reticulum or from the small thymic cells, which may also be of
entodermal origin.

Under these circumstances the designation, thymoma, must
include a group of tumors, which, admittedly, shows considerable
variation in histologic appearance, a variation ranging from the
typical carcinoform structure to a structure approaching or
actually identical with the appearance of lymphosarcoma. As has
been indicated, tumors of the thymic parenchyma, frequently
classified by their investigators as carcinoma, lymphosarcoma, or
thymoma, are in fact described as partaking of the structure of
both carcinoma and lymphosarcoma when various sections of the
same tumor are studied. In some instances, too, there is evident
a definite transition, morphologically, between the carcinoform
and the more lymphosarcomatous-appearing tissue. Whether this
polymorphism of structure of various thymomas is the expression
of a unitary origin from a tissue which is susceptible of marked
morphologic variation, or whether it is the result of a superficial
morphologic resemblance between different types of tumor of the
thymic parenchyma of entirely different histogenetic origin,
remains to be decided in the future. Until the unitary or dual
histogenetic origin of the thymic parenchyma has been determined,
any pronouncement on the subject is a matter of conjecture.

I have cited examples of what appear to be thymic rests in
the form of cysts or solid nests of reticular cells found accidentally
in routine studies of the thymus (Cases 4, 5 and 6). It has been
the impression of Robertson that these rests are analogous to
thymomas which remain dormant in the absence of that stimulus
which incites malignant hyperplasia. Much support is loaned to
this hypothesis by the observation of the thymoma in Case 2,
in which the morphologic resemblance of the cells, and their
arrangement in the form of cysts and in the form of an imperfect
reticulum, mirror so strikingly the appearance of these so-called
thymic rests. Such a view suggests that the designation thymoma
with latent potentialities for malignant proliferation, as suggested
by Robertson, is most appropriate for these epithelial rests within
an otherwise normal thymus. Their relation to malignant thymomas may be analogous to that which seems to exist between the so-called benign polyps and the carcinomas that develop in the colon, a relationship admirably set forth by Robertson.

In view of the recent revival of the controversy relating to the nature and the histogenesis of the corpuscles of Hassall, it seems worth while to consider briefly certain facts which this study offers bearing on this question. It may be recalled that the interpretation of Cornil and Ranvier that the corpuscles of Hassall represent the result of endothelial proliferation in blood vessels was later elaborated by Afanassiew, who also held that these corpuscles arose from the proliferation of endothelial cells within capillaries. Hammar later showed that the corpuscles of Hassall are essentially a part of the reticular epithelium, and this view was supported by the work of Jaffe and Plavska, Bell and others. The view that the corpuscles of Hassall represent involution forms of the original thymic tubules (ducts of Remak), as expressed by Marine and others, never has received full acceptance.

More recently, Jordan and Horsley, as a result of a comparative study of corpuscles of Hassall in the thymus and of similar corpuscles which they observed in involuting subcutaneous and abdominal lymph nodes of the rabbit, concluded that the corpuscles of Hassall "represent mainly and essentially segments of occlusion in capillaries and precapillary arterioles following endothelial cell hypertrophy." Later Dearth brought further support to the view of the epithelial nature of the thymic corpuscles, and Kingsbury, in considering their nature, also arrived at the conclusion that they arise from the cytoreticulum, the original epithelium, and that they are an expression of the differential growth of such an epithelium as modified by the unique conditions there prevailing; in other words, that the Hassall corpuscles are expressions of (1) growth in a confined space, a result of absence of a free surface, and (2) of a disjunctive growth differentiation due to the extreme reticulation that the epithelium has undergone. Kingsbury compared the degeneration changes in thymic corpuscles with the changes observed in epithelial pearls; he pointed out the tendency to the occurrence of central necrosis and liquefaction in both instances, and the occasional presence of lipoid material, concluding that both represent a growth transformation with no free surface of desquamation.
It appears from evidence presented by many observers that whatever part may be played by such phenomena as endothelial proliferation or by degenerative changes in the original thymic tubules in the production of structures resembling corpuscles of Hassall, their origin in most instances, if not in all, probably can be ascribed to changes in the reticular epithelium of the thymus. Support is given to this view by the occurrence of typical corpuscles of Hassall in some thymic tumors, and, singularly, in those tumors in which the epithelial nature of the neoplasm is most evident. Much significance may be attached to this observation in pathologic tissue, for by virtue of its neoplastic character it can readily be distinguished from certain anatomic structures that may exist in the midst of the normal thymic reticulum from which a given thymic corpuscle is suspected to arise. Study of corpuscles observed characteristically toward the center of islets of tumor tissue in which vascular channels were entirely absent, suggests the simple degenerative nature of these corpuscles, the result of “hyalinization” or “keratinization” of the more centrally situated tumor cells. This degenerative process, moreover, has the tendency to progress, as is indicated by the occurrence of complete necrosis of the central tumor cells, by their liquefaction, and by the production of cystic bodies in the larger islets of tumor tissue. This was without doubt the mechanism which was productive of the larger cysts which were grossly observable in one of the tumors here described, at the time of operation. If, then, such primary tumors of the thymus as show the morphologic resemblance to carcinoma may be presumed to arise from the reticulum of the thymus, and such a presumption seems justified on the basis of the established epithelial nature of the thymic reticulum, the development of corpuscles of Hassall unquestionably from the constituent cells of such tumors is strongly suggestive of an analogous origin of such corpuscles in the normal thymus, from its epithelial reticulum cells.

It is of interest that in the thymoma in which the origin of the tumor from the cortical cells seems probable (Case 3), the formation of Hassall’s corpuscles from tumor cells was entirely wanting. Those few, scattered corpuscles which were observed in that tumor, by their advanced degeneration and by the absence of any intimate relationship between them and the tumor cells, suggest that they are merely remains of the thymic tissue within which the tumor developed. This view is
strengthened by the total absence of formation of corpuscles in
the metastatic nodules of this tumor, as contrasted with the
presence of typical corpuscles of Hassall even in the metastatic
tumor nodules in the thymoma observed by Bedford, and in
others recorded in the literature.

**SUMMARY AND CONCLUSIONS**

A review of the literature indicates the relative rarity of
primary thymic tumors. A rigid pathologic classification of
tumors of the thymic parenchyma is not possible at present,
because of the lack of definite knowledge concerning the histo­
genesis of all the elements of the thymic parenchyma, and because
of the marked polymorphism of the cells which constitute most of
such tumors. For this reason, the designation of thymoma for
all tumors derived from the parenchyma of the organ seems more
satisfactory than their classification as carcinomas and lympho­
sarcomas.

Careful study of tumors of the thymus, of the type often
designated lymphosarcoma, suggests that the sarcomatous appear­
ance of the tissue may represent only a morphologic varia­
tion of a type cell derived from the thymic reticulum. For the
present the designation of sarcoma, including lymphosarcoma of
the thymus, should be reserved for those tumors apparently derived
from elements within the stroma of the thymus.

The occasional finding of epithelial ducts or circumscribed
islets of epithelial or modified reticular cells within an otherwise
normal thymus, and the similarity between the histologic appear­
an ce of such bodies and one tumor of the thymus observed by
the writer, suggests that there may exist some relationship between
them. It appears that these structures, probably embryonal
rests, may be looked on as thymomas with potentialities for the
development of malignant hyperplasia under certain conditions.
This was suggested by Robertson and receives support from data
already quoted and indirectly from the conception of the relation­
ship that probably exists between benign and malignant tumors
which occur elsewhere, as for example, between polyps and
carcinomas of the colon.

The observation of typical corpuscles of Hassall resulting from
degeneration of epithelial cells of tumors apparently derived from
the thymic reticulum, suggests an analogous mode of formation
of these thymic corpuscles in the normal thymus, as a result of
degenerative phenomena within the thymic reticulum.
Bibliography


AMBROSINI, G.: De l’épithélioma du thymus, quoted by Brannan.


BRISTOWE: Cancer of the kidneys, upon the pleura and mediastina, Tr. Path. Soc. London 5: 185, 1854.


CORNIL AND RANVIER: Quoted by Bell.


DUSTIN, A. P.: Quoted by Deanesly.


GRANDHOMME: Quoted by Thiroloix and Debré.

HAMMAR, J. A.: Zur Kenntnis der Teleostierthymus, Arch. f. mikr. Anat. 73: 1, 1908; The new views as to the morphology of the
thymus gland and their bearing on the problem of the function of the thymus, Endocrinology, 5: 543, 731, 1921.


Paviot, J., and Gerest: Un cas d'épithélioma primitif du thymus, Arch. de méd. expér. et d'anat. path. 8: 606, 1896.


Prenant: Quoted by Bell.

Robertson, H. E.: Personal communication to the author.


