THYMOMA

A Review and Reclassification *

Lalla Iverson, M.D.
From the Armed Forces Institute of Pathology, Washington 25, D.C.

The term thymoma with modifying nosologic designations has been applied to a host of mediastinal tumors of varying morphologic pattern. Elaborate classifications have been erected from relatively small series of cases. These classifications, in general, attempt to fit particular examples into embryologic or histogenetic categories. However, in neoplasia the thymus gland displays such freedom of expression that it conforms to none but the broadest of definitions.

The confusing literature will not be reviewed here, except to point out three general observations. First, there is agreement among some workers that the various histologic variants of the neoplastic gland are a composite of one tumor.[1,2] In accordance with this approach, the thymoma is then defined as a neoplasm in the anterior mediastinum, arising in the thymus gland and showing various mixtures of cells; it is usually benign in behavior, often encapsulated, and, in some cases, occurs in patients with myasthenia gravis. Second, it is now generally agreed that tumors such as malignant lymphomas, although sometimes originating in the lymphoid tissue of the thymus, should not be classified under the specific term thymoma. Third, until more is known about the potentialities of the thymus gland, it is best to withhold the specific designation from neoplasms of dubious origin when the only definite support for the diagnosis may be the mediastinal location of the tumor.

During the years 1950–52, as criteria for the diagnosis of certain mediastinal tumors in the Chest Tumor Registry were under revision, 50 cases from the files of the Armed Forces Institute of Pathology, diagnosed as thymoma, were studied. There were no examples which could be called thymic carcinoma; 8 of the cases classified under this designation were found to be neoplasms resembling seminoma or dysgerminoma. Five cases called thymoma were excluded because they represented reactive changes in groups of anterior mediastinal lymph nodes with alterations in the follicles which simulated Hassall's corpuscles. Ten cases were shown to be examples of Hodgkin's disease, lymphoma, and possible metastatic tumor. The remaining 27 tumors

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were identified as true thymomas. These were a more or less homogeneous group of localized neoplasms arising in the region of the thymus gland and composed of various mixtures of lymphocytes, pale spindle cells, cystic spaces, and large epithelial cells. In order to correlate these variations with the histologic changes of the non-neoplastic glands, thymus glands from 165 necropsy cases, ranging from premature infants to adults 70 years of age, were examined. For further information on the subject of normal growth patterns, histologic preparations of thymuses of embryos of 2 to 6 weeks were studied at the Carnegie Institution. This embryologic material was supplemented by thymus glands from fetuses aborted after gestation periods of 4 weeks to 3 months.

The purpose of this paper, based on the results of this study, is (1) to define thymoma as a single entity showing variations in morphologic pattern in relation to the presence or absence of clinical evidence of myasthenia gravis; (2) to define and differentiate the morphologic features of mediastinal seminoma, formerly called thymic carcinoma, and to define the criteria by which it is to be distinguished from true thymoma, and (3) to point out the anatomical differences between thymoma and reactive hyperplasia of mediastinal lymph nodes so that common errors in interpretation may be avoided.

In the preliminary review of the 27 neoplasms retained in this series as examples of thymoma, two consistent histologic patterns became apparent, and these were found to be related to the presence or absence of clinical evidence of myasthenia gravis. In the group with myasthenia gravis, epithelial cells were prominent. The remaining tumors showed a prominence of lymphocytes, spindle cells, or other structures resembling the stromal elements of the gland.

Thymomas Without Myasthenia Gravis

In 14 of the 27 cases, the patients had no symptoms suggestive of myasthenia gravis. The average age of the group was 50 years, and the range was from 24 to 71 years. The selection of material did not lend itself to correlation with race or sex of the patients. The clinical symptoms were those which might be anticipated from the presence of a slowly growing benign mediastinal mass. Although some tumors were removed immediately after roentgenologic diagnosis, others were observed for as long as 8 years before operation was performed, and one was an incidental finding at necropsy.

A representative case history follows:

A.F.I.P. Acc. 176626. A 28-year-old man experienced sudden onset of severe, steady pain in the right side of the chest, for which he was treated with penicillin. A

mediastinal tumor, seen on roentgenologic examination, was removed by thoracotomy. The tumor measured 4 by 5 by 7 cm., and was lobulated and encapsulated. A central cystic cavity was present in an otherwise firm tumor, which at first was considered to be a malignant lymphoma. Four years later the mass recurred and encroached upon the bronchi and vessels. Histologic preparations of a dissected portion then showed a neoplasm composed largely of pale spindle cells.

MORPHOLOGIC CHARACTERISTICS

On gross examination, the 14 tumors averaged from 8 to 10 cm. in diameter and the largest was 15 cm. All were circumscribed and more or less encapsulated. The tumors were generally soft, white or yellowish white, and sometimes contained cystic areas. The inner surface of the fibrous capsule tended to split and dip into the body of the mass, dividing the neoplasm into lobules. These fibrous septa were particularly prominent in those tumors with marked cystic alterations. The capsules were sometimes thickened by deposits of calcium and by collections of fat undergoing phagocytosis.

The histologic structure of the tumors was represented essentially by the stromal and cellular elements that are normally present in the thymus, but which, in the neoplasms, varied considerably in arrangement and quantity.

The tumors were best grouped according to the prevailing components: lymphocytes, spindle cells, and supportive structures. By so doing, it was possible to make interesting comparisons with the stages in enlargement and regression of the normal and abnormal non-neoplastic thymus glands seen incidentally at necropsy. It should be noted, however, that these stages could not be correlated chronologically with the duration or size of the tumor in a series so small.

Lymphocytic Proliferation

In thymomas of patients without myasthenia gravis and showing lymphocytic proliferation, the tumor was divided by fine cellular septa into large lobules consisting mostly of small round cells interspersed with occasional pale reticulo-endothelial cells (Fig. 1). Sometimes the septal divisions were so light that the gland seemed to be uniformly replaced by lymphocytes, and a diagnosis of lymphosarcoma was entertained. However, careful examination always showed a reticulum framework, more or less uninvaded, or unaltered, by the overflow of lymphocytes. There was little vascularity of the gland and correspondingly little fibrosis. Hassall's corpuscles were rare. When they occurred, most of them lay in a thin rim of thymic tissue, which might be located at the periphery of the tumor. In thymomas of this type, the lobular lymphoid hyperplasia was reminiscent of the appearance

of the thymus gland when it is at its largest after birth, or of the thymus gland in certain abnormal conditions such as anencephaly, hyperthyroidism, or hypoadrenalism (Fig. 2).

Spindle Cell Proliferation

In the tumors of patients without myasthenia gravis and showing spindle cell proliferation, the capsule was more dense than in those in which lymphoid cells predominated. The septa also were correspondingly prominent, dividing the lobules more definitely from one another. Small cystic spaces, which appeared to be lined by endothelial cells, lay within the fibrous septa and extended into the lobules. These were connected to the ramifying vessels and sinusoids which seemed to branch out from the septa into the lobules (Fig. 3).

The septa were rich in elongated spindle cells, extending into the periphery of the lobule with the penetrating vessels (Fig. 5). Similar changes occurred within the lobules. Whether by actual transformation of lymphocytes or by invasion of cells from the reticulum framework of the gland, the cells at the periphery of the lymphoid lobules became oval or elongated and the nuclei pale. Masses of these cells merged with the identical spindle-shaped cells in the vascular septa. The cells were uniform and did not reproduce by abnormal mitosis. They were most prominently displayed around blood vessels, but also were seen amassed in small clumps embedded in the lymphoid tissue.

Many lymphoid lobules might disappear altogether in the transformation, and in some cases the tumor seemed almost entirely replaced by the cystic, fibrous, and vascular network interlaced by the pale spindle cells peeling off from vascular spaces. Misinterpretation of the nature of the spaces lined with cells appearing to be endothelial cells, and of the pale spindle cells, has led to such confusing diagnoses as perithelioma, spindle-cell sarcoma, neurofibroma, or diffuse reticular thymic carcinoma.[3] Mediastinal paragangliomas also have been confused with thymomas showing these changes.

As in the thymoma with lymphoid proliferation, this process is reminiscent also of some of the changes in thymus glands. It is noted in the normal thymus gland that with increasing thickness of the capsule and of the septa, the lymphoid elements become less prominent. Usually, adipose tissue replaces the involuting lymphoid tissue. However, unusual regressive changes may occur in some individuals. In these, the small round cells are replaced by pale spindle cells, and the entire gland becomes atrophic and very vascular. Under these circumstances Hassall's corpuscles are rare or atypical.

These changes were seen most strikingly in a thymus gland, weighing between 2 and 3 gm., removed at necropsy from an 8-months-old child with scurvy. No lymphoid tissue remained in the atrophic cortex, which consisted of several finger-like extensions composed only of pale spindle cells threaded by vascular spaces. The medulla was restricted to the central portion of the tiny gland. The few Hassall's corpuscles remaining there were small, sometimes cystic, and associated with patent vessels (Fig. 4).

These alterations—vascularity, relative absence of Hassall's corpuscles, and replacement of lymphocytes by small spindle cells—suggest that the intermediate stage of thymomas unassociated with myasthenia gravis may be one of unusual regressive change in certain of the "stromal" and, possibly, epithelial components of the neoplasm, or of proliferation of these epithelial elements without maturation. This would explain the tumors characterized by small round cells distinguished from lymphocytes, as well as those composed of more obviously spindle forms.

Stromal, Endothelial, and Vascular Proliferation

In thymomas of patients without myasthenia gravis and showing stromal, endothelial, and vascular proliferation, the cystic areas predominated, and the solid cellular portions of the neoplasm were reduced to small islands scattered between the spaces lined with cells resembling endothelial cells (Fig. 6). The stroma might be hyaline or fibrous, and it was richly vascular. Lymphocytes or spindle cells were sometimes sprinkled along fibrous strands between the cysts. This appearance, in its extreme, suggested lymphangiomatous formations. Generally, however, these advanced changes were limited to a portion of the tumor, while the remaining lobules showed other stages such as lymphoid or spindle cell proliferation. These changes have been well described by Hubbell and Liebow,[4] who interpret the tumors as representing vascular neoplasia. However, numerous gradations among the subgroups were noted and it was apparent that even though one component might predominate, all elements participated in producing the characteristic histologic appearance of each neoplasm.

Thymomas Associated with Myasthenia Gravis

The average age of the 13 patients with thymomas associated with myasthenia gravis was 38 years. It is significant that these tumors were of relatively short duration, most of them being removed months after the first symptoms. The longest history was 7 years. In all cases

in which prostigmine was used, there was no demonstrable, consistent, histologic change in the size or appearance of the gland which could be correlated with quantity or duration of the therapy.

Although these tumors were sometimes diagnosed as "carcinoma" or "lympho-epithelioma,"[5] in no instance had metastasis occurred.

A representative case history follows:

A 41-year-old man was admitted as an emergency patient because of great difficulty in breathing and inability to sleep. Three months previously he had noticed weakness in the upper eyelids and generalized fatigability, followed by weakness of mandibular muscles and respiratory difficulty. Prostigmine produced considerable improvement. However, a relapse in symptoms occurred and by the time the patient was admitted it was necessary to reinforce breathing with a Drinker respirator. In spite of increased doses of prostigmine the patient became weaker. He was unable to raise phlegm, and gradually became less able to eat. Decline was rapid and he died 5 months after the onset of symptoms. At necropsy, a lobulated mass, 5.8 by 4 cm., was found anterior to the aortic arch in the superior mediastinum. The mass was hard and completely encapsulated. Several small cystic spaces were noted in its substance. There was no extension to surrounding structures.

MORPHOLOGIC CHARACTERISTICS

Grossly, thymomas associated with myasthenia gravis were usually circumscribed but might be lobulated. Occasionally, extensions protruded from the tumor and became separated by a pedicle from the parent mass. Usually the capsule remained intact. The tumors were soft. Unlike thymomas without associated myasthenia gravis, complex variations due to fibrous and cystic changes were infrequent, but did occur.

The most striking first impression of any microscopic field of the usual thymoma associated with myasthenia gravis was that of the loose association of lymphocytes and large watery pale cells in a succulent vascular bed. There was very little stroma and only faint reticulum to give body to the neoplasm. Thin-walled vessels coursed through all portions of the tumor in no particular arrangement (Fig. 7).

The relative proportions of lymphocytes and large epithelial-appearing cells varied from field to field and from tumor to tumor. The presence or absence of lymphocytes in this series was unrelated to symptoms in the patient. However, the large cells, when present, usually indicated that the patient had a history suggestive of myasthenia gravis. Cells of this type had a large, oval, watery nucleus, approximately 25 to 30 μ in diameter, and one or two very prominent nucleoli. The cytoplasm, when visible, might be clear or granular and the cell outlines oval, columnar, or polyhedral. In most examples, these cells were loosely mixed with lymphocytes but also in many areas occurred in small clumps throughout the tumor. In those examples in which lymphocytes were scarce, there was a tendency toward

greater organization of the type-cells. In large numbers they became confluent, and then almost syncytial in arrangement (Fig. 8). Usually, whether in small or large clumps, these cells were seen in intimate relationship with blood vessels, and when they lined up in cords around vascular spaces they tended to assume a more columnar shape (Fig. 9). With the periodic acid-Schiff stain, there may be noted finely dispersed red granules in the cytoplasm of the cells lining the vessels.[6]

In some areas the cytoplasm of the large cells became scant. The cells then assumed a more oval shape and might fall into concentric whorls resembling Hassall's corpuscles (Fig. 10). As more examples accrue, some of the unusual variations of tumors of this group may be found to be due to such changes in shape and in organization of the type-cell.

The relationship with blood vessels seems to be of particular significance. The innermost structure is generally a thin-walled capillary partly surrounded by a large crescentic lymphatic. In most examples the lymph vessel contained the usual circulating lymphocytes and monocytes, but in some the lumen was plugged with foamy macrophages which were noted also among the cells of the surrounding tumor. In some of the neoplasms the lymph vessel was no longer visible except as a faintly eosinophilic amorphous band in the customary relationship to the still patent capillary.

The fact that Hassall's corpuscles may be formed by epithelial cells suggests that these cells, not the lymphocytes, should be termed thymocytes. Further, their morphologic appearance when in relationship to blood vessels indicates the possibility of a period in the growth of the thymus during which an endocrine function may be maintained by the developing gland. In the thymuses removed from fetuses at necropsy there were scattered foam cells, a prominent medulla, and a relationship between Hassall's corpuscles and blood vessels; however, no cells similar to the type-cell of the thymoma in myasthenia gravis could be seen in these fetal glands or in those dissected from early embryos. More extensive embryologic studies will have to be undertaken before a direct relationship can be demonstrated, if any exists.

Comparison of Thymomas With and Without Associated Symptoms of Myasthenia Gravis

The symptoms produced by a slowly growing mass in the anterior mediastinum are common to thymomas with and without associated myasthenia gravis. In this series, the thymomas not associated with myasthenia occurred in an older age group. This may indicate that in the older age group they represent a phase of regression of

active tumors. However, in neither group was clinical correlation of the histologic appearance of the gland with prostigmine therapy, or with the progress of symptoms in the patient, adequate to permit conclusions on this point.

Because the thymoma in a patient without myasthenia gravis represents neoplasia predominantly of the stromal or non-functioning elements of the gland, this group contains more examples in which cyst formation and fibrosis are prominent. However, there is no clear-cut characteristic generally useful in gross differentiation.

The histologic differentiation of the two types depends upon basic understanding of the organization of each. The tumor associated with endocrine symptoms is recognized by the peculiar arrangement of large pale cells around thin-walled vessels and the loose association of these cells with lymphocytes in the "pulp" of the mass. This pattern and these cells in this form are not noted in thymomas in which one or another of the non-functioning elements separately enlarge and dominate the neoplasm. Instead, one may note replacement of the tumor by lymphocytes or by small pale spindle cells. Or, a more complex arrangement may result from the appearance of heavy fibrous septa which penetrate the bulk of the mass and divide it into lobules. It is probable that as time elapses the vascularity increases and formations resembling endothelium become more evident while the cellularity diminishes.

"Thymic Carcinoma" and Seminomatous Tumors of the Mediastinum

In 1946, Friedman and Moore,[7] in an extensive review of neoplasms of the testis, suggested an interrelationship between teratocarcinoma and other testicular tumors such as embryonal carcinoma, choriocarcinoma, and seminoma. Although this relationship is challenged by other workers,[8] the histologic criteria of choriocarcinoma and seminoma or dysgerminoma are more or less well defined, and their various sites of origin, in common with teratomas, are recognized. Since teratocarcinomas are known to arise in the mediastinum, it is not surprising to find reports of primary mediastinal choriocarcinoma,[9,10] or even the less well defined embryonal carcinoma. In view of these findings and the increasing numbers of reports of mediastinal teratoma, it is even more noteworthy that the only recorded examples of seminoma or dysgerminoma of the anterior mediastinum are the two reported by Friedman[11] as originating in the thymus.

In the present series of 50 anterior mediastinal tumors, those thymomas classified as benign and those called thymic carcinoma were

grouped separately. It was then readily appreciated that the histologic pattern of the two differed radically and that the tumors called thymic carcinoma were similar to seminoma or dysgerminoma. These conformed to some reported cases of thymic carcinoma of the granulomatous type.[12] Eight of the 50 cases, whether or not they seemed to originate in the thymus, were consequently reclassified as mediastinal seminoma and, together with three additional contributions from other sources, were studied as a group.

In this series of 11 examples of mediastinal seminoma, 9 of the patients were males with an average age of 24 years. Although the mass in 3 patients was discovered during routine x-ray surveys, in the majority roentgenograms were made because of pain or other symptoms referable to a slowly invasive mediastinal tumor. In one patient an Aschheim-Zondek test was positive, but there were no signs in the other patients by which the tumor could be distinguished clinically. None of them had weakness or paralysis suggestive of myasthenia gravis. X-ray therapy, when employed in 2 patients, caused remarkable shrinkage of the tumor. In some instances, however, both surgical and x-ray treatment was followed by recurrence or metastasis after a period of months or years.

There was widespread extrathoracic metastasis in one case studied at necropsy, but, in another, death was, more typically, the result of local invasion of the lungs and mediastinal structures. This tendency to local extension was demonstrated in two other individuals in whom the tumor was first diagnosed clinically by biopsy of cervical nodes. In one of these, the spinal cord became involved almost 2 years after the metastasis was discovered in the nodes of the neck.

A representative clinical history follows:

A.F.I.P. Acc. 164308. A 20-year-old white man was admitted to the hospital because a mediastinal tumor had been observed on x-ray examination during his separation from the Army. There were no previous symptoms other than asthma and frequent colds. The only contributory physical findings were directly related to the presence of the mass. Exploratory thoracotomy showed the tumor to be so attached to the inferior vena cava and innominate veins that it was considered inoperable. A small piece was removed for histologic examination. Postoperative x-ray therapy resulted in rapid shrinkage of the mass and during the subsequent 3 years the patient remained well except for cough and mild dyspnea. During that time roentgenograms showed no recurrence.

MORPHOLOGIC CHARACTERISTICS

Grossly, primary mediastinal seminomas were usually circumscribed and lobulated, but were not necessarily encapsulated. They might attain a size of 18 to 20 cm. or more. At operation they were described as spongy, soft, and grayish yellow. The stroma was not especially

dense. The tumors often were found to be attached to the surrounding great vessels and for this reason might be inoperable.

Microscopically, the tumor was honeycombed by thin fibrous and reticulum strands dividing it into acini in which clustered the neoplastic cells (Fig. 11). Lymphocytes were scattered throughout the vascular fibrous stroma which was boldly outlined by reticulum stains. This basic pattern was seen uniformly throughout the neoplasm.

The type-cell of the primary tumor was distinctive. It was large and irregularly rounded. The nucleus had coarsely clumped chromatin and was fairly uniform in size and in staining quality. Sometimes the cells formed almost a syncytium within the acini and in those instances their cytoplasm was clear and slightly swollen. In other tumors, they were seen to cluster loosely, and the cytoplasm then formed a dark band outlining the coarse nucleus. When this occurred, the lymphocytic infiltration in the septa was more prominent and varying degrees of reticulo-endothelial reaction, not correlated with x-ray therapy, might be noted (Fig. 12).

This reticulo-endothelial reaction seemed to originate in the stroma of the tumor. It consisted chiefly of a local proliferation of the histiocytes abutting on the acini. The cells were easily distinguished from the neoplastic cells by their pale nuclei and abundant eosinophilic cytoplasm. In the more extreme reactions many lymphocytes and plasma cells were seen; giant cells were noted (Fig. 12) and even birefringent particles could be demonstrated in their cytoplasm. Epithelioid tubercles might be formed. If the reaction was of sufficient proportion, the tumor cells might be overlooked (Fig. 13) and, depending on the types of reactive cells present, a diagnosis of Hodgkin's disease or sarcoidosis might result.

Definite inclusions indicative of a relation to teratoid tumors were noted occasionally in this series (Fig. 14). In one, several small foci of cells resembling trophoblastic elements were demonstrated; in another, glands; and in a third, nervous tissue and cartilage. Transitions to embryonal carcinoma were reported in a case not included with this series.[11]

Poorly differentiated mediastinal seminomas may be expected to occur and these may be distinguished only with great difficulty from some teratocarcinomas. In one example, the uniform large round cells composing the biopsy specimen strongly suggested a tumor of this general category but the diagnosis was confirmed only when trophoblastic structures were noted. In other cases, the first biopsy of the

metastasis or of the primary tumor was histologically characteristic of seminoma, but subsequent biopsies or necropsy preparations showed such poor differentiation that the tumor could not have been classified without reference to the previous material.

Comparison of Mediastinal Seminomas and Thymomas

In summary, the justification for reclassifying these neoplasms as mediastinal seminoma, rather than as thymic carcinoma, is based on clinical and anatomical similarity to testicular seminomas and ovarian dysgerminomas, as well as their dissimilarity to clearly recognizable thymomas. The mediastinal seminoma is relatively radiosensitive, tends to occur in younger age groups, and to extend locally. Like the testicular seminoma, it also may contain teratoid, trophoblastic, or other embryonal structures which are never seen in thymomas. A study of the embryos at the Carnegie Institution and of numerous glands removed from fetuses failed to reveal any embryologic or histologic connection between the thymus and this tumor.

Contrasted to the true thymoma, which comes to clinical notice because of a routine roentgenogram of the chest or because of myasthenic symptoms, the mediastinal seminoma is detected clinically because of its invasive properties, either through local extension or through metastasis to cervical and axillary lymph nodes. While the thymoma remains encapsulated, or at least circumscribed, except in unusual cases, the mediastinal seminoma in its gross appearance is much more irregular in its shape, extension, and size. Histologically, other striking differences are seen. The thymoma occurring in patients without myasthenia gravis, regardless of its classification, is divided into lobules by connective tissue septa of varying vascularity. The lobules are composed of indiscriminate mixtures of cells which are normally found in the thymus, arranged in no rigidly characteristic pattern. In contrast, the mediastinal seminoma has no large septal divisions. It is uniform throughout. It is basically arranged in acini separated by fine connective tissue septa. There are no sinusoids and no lymphoid follicles; there is no evidence of attempts at formation of Hassall's corpuscles, and none of the histologic features normally seen in the thymus, which often carry over into benign thymomas. Granulomatous reactions may be an intrinsic part of the seminoma (Figs. 12 and 13), but are rarely seen in the tumors defined here as thymomas, except when associated with fats. Lastly, those thymomas in patients with myasthenic symptoms are characterized by a type-cell which also contrasts with that of

the seminoma. In the thymoma, the type-cell has a large watery nucleus, prominent nucleolus, and ill defined cytoplasm. In the seminoma, the neoplastic cell is recognized by its round, dark nucleus with coarsely clumped chromatin, surrounded by a thin rim of sometimes granular cytoplasm. It should be emphasized that while these differential features are generally applicable, there are still some puzzling exceptions provocative of further study. Some tumors classifiable in this group arise in the thymus gland, and are involved by such a marked granulomatous reaction that the nature of the type-cell is obscured. None of these exceptional examples was associated with myasthenic symptoms in the patient, and it is hoped that study of a larger series will clarify their relationship, either to thymogenic tumors or to the teratoid group.

Localized Hyperplasia of Mediastinal Lymph Nodes

In this series, there were 5 cases in which the revised diagnosis of "reactive lymphoid hyperplasia" was made. Since the histologic appearance of the lesion was similar to that illustrated in other series of thymomas,[3,12] these cases are reviewed here for purposes of clarification. Numerous other examples may be gathered by screening a larger sample, but because of the similarity of all only a summary description is required.

The extreme importance of the proper diagnosis of this lesion lies in its differentiation from thymoma and prevention of unnecessary surgical and psychologic trauma to the patient.

The 5 cases selected for study concerned patients whose ages ranged from 22 to 45 years, and averaged 25 years. None of the lesions produced symptoms and all were discovered on routine fluoroscopy or roentgenologic examination. In one patient, the mass remained stationary for 6 years and was excised only after a cervical node became enlarged. The node and the mediastinal mass showed a similar reaction of lymphoid hyperplasia, and enlargement and hyaline alteration of the germinal centers.

A representative case history follows:

A.F.I.P. Acc. 523088. A 22-year-old man was operated upon because of an anterior mediastinal mass discovered by routine roentgenologic examination. The mass was located in the superior mediastinum, and was loosely adherent to the phrenic and vagus nerves at the arch of the aorta. The gross specimen weighed 67 gm. and was 8 by 5 by 3.5 cm. in size. It was roughly nodular, with shaggy adhesions on some portions of the encapsulated surface. The cut surface revealed fat caught between the nodules which were a contrasting gray. On histologic examination, the mass was believed to represent a thymoma. Microscopic examination of portions of the pleura and pericardium revealed mild diffuse inflammation of these structures.

MORPHOLOGIC CHARACTERISTICS

The tumors from the cases of "reactive lymphoid hyperplasia" showed no gross distinguishing characteristics. They were generally encapsulated, and attained a size of 15 cm. or more. It is noteworthy that they tended to vary in location and were described as comprising several nodules clumped together. The cut surfaces were usually grayish with little apparent stromal pattern.

In this group and in other similar examples, the prominent histologic features were the centers of the lymphoid follicle. These might be larger and more numerous than usual (Fig. 15). At first the hyaline alteration and the whorled arrangement of the hyalin might suggest thymus gland to the observer who knew that the mass was removed from the anterior mediastinum. The hyaline "rings" might completely transform the germinal center, or pale cells might still be visible. The pulp of the gland usually was unaltered, although at times there was a more pleomorphic response consisting of plasma cells, eosinophils, histiocytes, and even giant cells. Sinusoids also were frequently obscured by an obliterative reaction which was marked by hyaline thickening of the sinusoidal walls (Fig. 16). Pale slender reticulo-endothelial cells, however, might still indicate the course of the sinusoids which reticulin stains demonstrated plainly. Associated with these changes there was thickening of the nodal capsule and there might also be thickening of the small vessels embedded in the surrounding fibrous tissue.

In one case the presence of inflammatory cells in the node and the mild inflammation in the adherent pericardium indicated the possibility that an extrinsic inflammatory lesion was responsible for the localized reactive lymphadenitis. However, whether the lesion takes origin in a non-specific mediastinitis, in some form of chronic vascular obstruction, or from some other local reaction cannot be determined until a large series is studied as a separate entity.

COMPARISON OF HYPERPLASTIC MEDIASTINAL LYMPH NODES AND THYMOMAS

Except for the instances in which thymomas may be associated with myasthenic symptoms, there is little difference in the early clinical symptoms caused by the two lesions. Thymomas not associated with myasthenia gravis and localized enlargement of mediastinal lymph nodes are both characterized clinically by the appearance of a mass, usually detected by routine roentgenologic examination, occurring in a young person without symptoms. Signs of local extension may occur in

patients with thymomas, but since localized lymph node hyperplasia of the mediastinum is a non-neoplastic lesion, it remains encapsulated and restricted in its growth potential. More difficulty in gross differentiation may occur in those instances in which mediastinitis is associated with the lymphoid hyperplasia causing adhesions of the capsule.

The essential differences between the two lesions are histologic. The confusion with thymomas results from the hyaline change in the center of the lymphoid follicles superficially resembling Hassall's corpuscles. However, reticulum stains and numerous sections show the fundamental anatomical pattern of the mass to be that of a hyperplastic lymph node undergoing certain sclerosing alterations. Further, since the reaction is non-specific, it may be expected that the lesion, unlike thymomas, may be noted in lymph nodes in other regions. For example, nodes removed from a patient with bronchogenic carcinoma showed a similar reaction (Fig. 17). This may explain the puzzling reports of tumors believed to be thymomas occurring in unusual locations within the chest.

Discussion

The significance of these observations lies chiefly in their usefulness as a means of diagnosis and as a tool for further analysis of the tumors discussed.

There are several interesting problems introduced by this study.

(a) The Endocrine Nature of the Epithelial Cells Noted in Thymomas Removed from Patients with Myasthenia Gravis

As noted in this series, the regularity of organization of pale epithelial cells around vessels in thymomas from myasthenic individuals seems almost prophetic of the symptoms to be expected. A series much larger than 27 cases, however, must be studied in order to ascertain how strictly these observations may be applied. Castleman[6] has now verified the fact that these criteria are applicable in at least 75 per cent of the cases at the Mayo Clinic and in his own series. It would seem, therefore, that they can be offered safely, not as an absolute sign for histologic diagnosis of tumors in myasthenic individuals but, as in many other examples of endocrine tumors, as an indication of the nature and functioning state of the cells which are concerned.

It would be helpful to correlate the histologic changes in the tumor over a period of time with remissions of the patient, both those remissions which occur spontaneously and those which are produced artificially by prostigmine therapy. In this series, there is a difference in the average age between myasthenic and non-myasthenic patients with thymomas; the patients without symptoms comprised an older

age group. A very careful exploration of the past history of this group may reveal some symptoms heretofore believed unrelated to the tumor and a clue as to whether the pale spindle cells noted in the tumors removed from them are not, in reality, a primitive or resting stage of the functioning cells.

Some relationship between duration and histologic appearance is indicated in this series by the one case in which an interval of 4 years between biopsies showed a change from a predominantly lymphoid appearance to a tumor mostly composed of spindle cells. Hence, further study may profitably be directed, not toward cytologic classification of the tumors, but toward understanding the histologic alterations occurring in them over periods of time.

(b) The Term Thymic Carcinoma

The term thymic carcinoma has often been applied to ordinary thymomas in patients with myasthenia gravis or to tumors resembling seminomas. There may be tumors which properly can be designated thymic carcinoma; but eliminating those which are clearly thymomas of the classical type, it is probable that most thymic carcinomas, as in this study, are more closely related to seminomas than to thymomas. Of course, it is not unreasonable to suppose that epithelial cells of the thymus may become malignant under certain circumstances, and that, when they do, they need not necessarily engage in functional activity. Nevertheless, it is significant that there are no reported cases of distantly metastasizing thymomas in patients who have had myasthenia gravis.

(c) Origin of Mediastinal Seminomas

As already discussed, the clinical similarity and the histologic evidence of teratomatous transitions or inclusions in those cases designated thymic carcinoma relate them to teratomas rather than to thymomas. Because of this interrelationship, the problem of their origin is linked with the histogenesis of teratomas.

It has been observed that some seminomas arise in the thymus gland, particularly in the cystic thymus; but, as with parathyroid adenomas under similar circumstances, this is not adequate basis for enlisting the thymus itself as the histogenetic factor. Non-specificity is further indicated by the fact that seminomas and teratomas arise elsewhere while thymomas do not.

It is quite possible that the site of origin may be both thymus and mediastinum, but that the tissue of origin in either case is the same. This requires some speculation concerning the possibility of inclusions within the thymus. Using the work of Norris[13] as supportive evidence,

Schlumberger[14] postulated that the ectodermal inclusions together with degeneration of Hassall's corpuscles may initiate production of tridermal tumors. However, in reviewing the embryos on which Norris based his interpretation concerning the ectodermal inclusions within the descending thymus, I have noted considerable latitude for other concepts of the histogenesis of Hassall's corpuscles. In fact, confirmation of all possible theories requires more supportive observation. One may reason equally that germ cells wandering off from their usual path in the embryonic era may be included in an anomalous thymus and later give rise to these tumors, or that certain primitive cells under proper environmental conditions may show unusual potential toward germinal tumors.

(d) Use of the Term Seminoma

If the words seminoma or dysgerminoma are applied to analogous tumors arising in the mediastinum, it indicates the identity of one with the other. Friedman's[11] very pertinent term germinoma commits one to the wandering germ cell theory concerning their origin. Therefore, to avoid coinage of a new and imperfect designation, the term seminomatous tumor is tentatively suggested in order to call forth a prompt mental image of the general class of tumors while allowing for the probability that the location of the particular example, whether pineal gland, mediastinum, testis, or ovary, may have some differentiating influence, both histologically and clinically.

(e) Pathogenesis of Localized Hyperplasia of Mediastinal Lymph Nodes

The pathogenesis of localized hyperplasia of the mediastinal lymph nodes can be studied only after more examples have been properly separated from thymomas and analyzed in respect to associated clinical and histologic findings. As with non-specific lymph node reactions elsewhere, this localized mediastinal enlargement is probably a reaction to a variety of stimuli. In one case the cause of the enlargement was associated pleuritis and pericarditis. The prominent vascular sclerosis suggests also a congestive process, possibly due to obstruction or increased venous tension.

Conclusions

No metastasis occurred in a group of 27 thymomas. Thymomas, therefore, are considered to be generally non-metastasizing but locally extending tumors.

In this series, true thymomas are classified simply into two histologic subgroups related to the presence or absence of symptoms of myasthenia gravis in the patient. Each example is generally a composite of various elements, typical of the group, in varying proportions:

(a) Thymomas in patients without myasthenic symptoms are characterized by stages of lymphoid proliferation, spindle cell proliferation, or stromal proliferation.

(b) Thymomas in patients with myasthenia gravis are characterized by the appearance of large pale epithelial cells, loosely mixed with lymphocytes, and often arranged in cords or clusters around vessels.

The close correlation of the symptoms of myasthenia gravis with the appearance in the thymoma of epithelial cells around vessels suggests an endocrine function for the type-cell.

In this series, most of the cases previously diagnosed thymic carcinoma proved to be seminomatous tumors of the mediastinum. Eleven examples are discussed. They may be differentiated from thymomas by the histologic characteristics of the type cell, by the frequently accompanying granulomatous reaction, by their radiosensitivity, and by their evident malignancy.

Five cases of localized hyperplasia of mediastinal lymph nodes are reported. The lesion is a non-specific reaction, histologically benign, and characterized by alterations of the germinal centers simulating Hassall's corpuscles. It is frequently misdiagnosed as thymoma, both by surgeons and by pathologists.

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LEGENDS FOR FIGURES

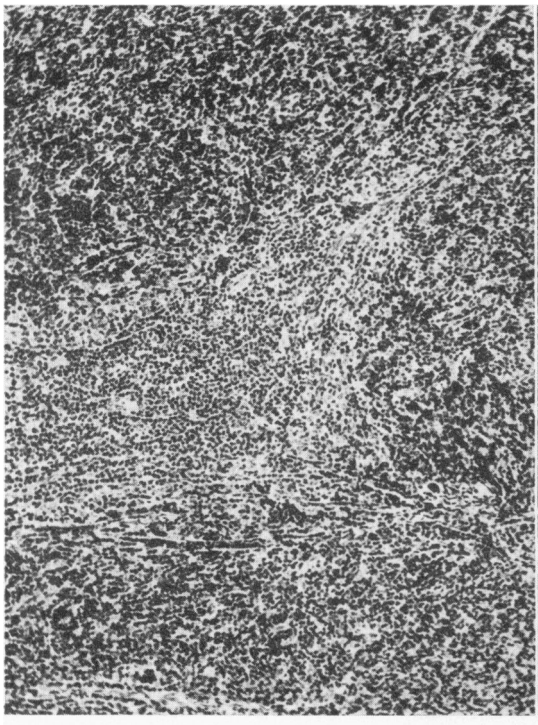
All sections were stained with hematoxylin and eosin unless otherwise stated.

FIG. 1. Armed Forces Institute of Pathology Accession No. 176626. Thymoma not associated with myasthenia gravis, showing lymphoid proliferation. The lobular arrangement and absence of Hassall's corpuscles may be noted. × 125.

FIG. 2. A.F.I.P. Acc. 186567. Thymus gland in an anencephalic infant showing predominance of lymphoid elements and paucity of Hassall's corpuscles. × 75.

FIG. 3. A.F.I.P. Acc. 298252. Thymoma not associated with myasthenia gravis, showing proliferation of spindle cells. Of note are the diminution in lymphoid lobules, absence of Hassall's corpuscles, and microcystic spaces within septa. × 75.

FIG. 4. A.F.I.P. Acc. 178650. Thymus gland from an infant with scurvy showing atrophy, replacement by spindle cells, vascularity of medulla, and atypical, scarce Hassall's corpuscles. × 125.



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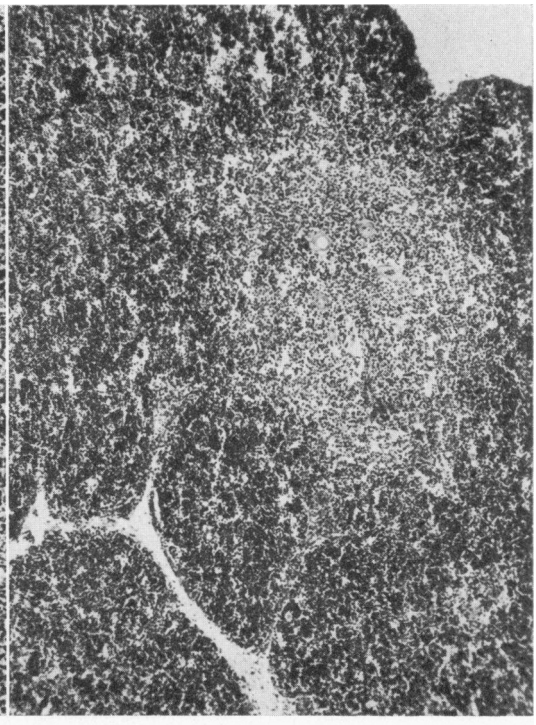

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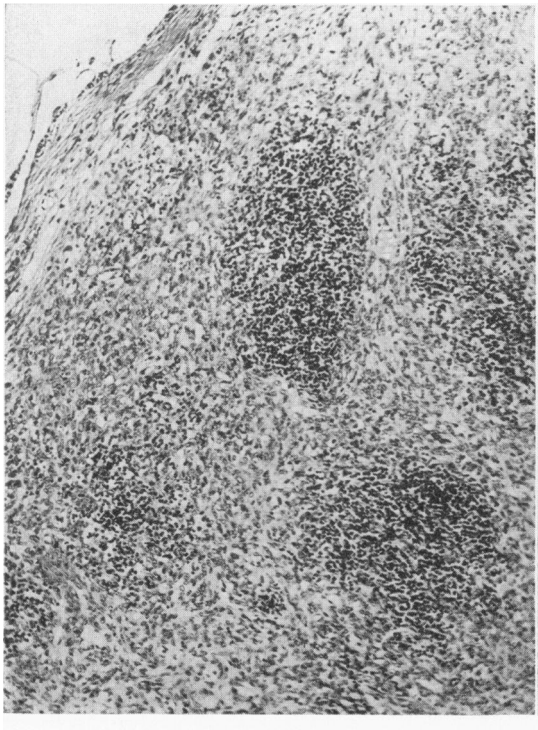

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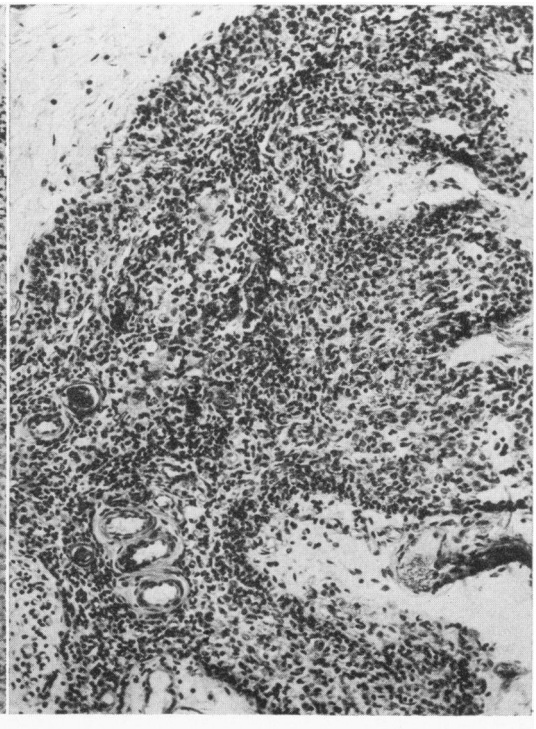

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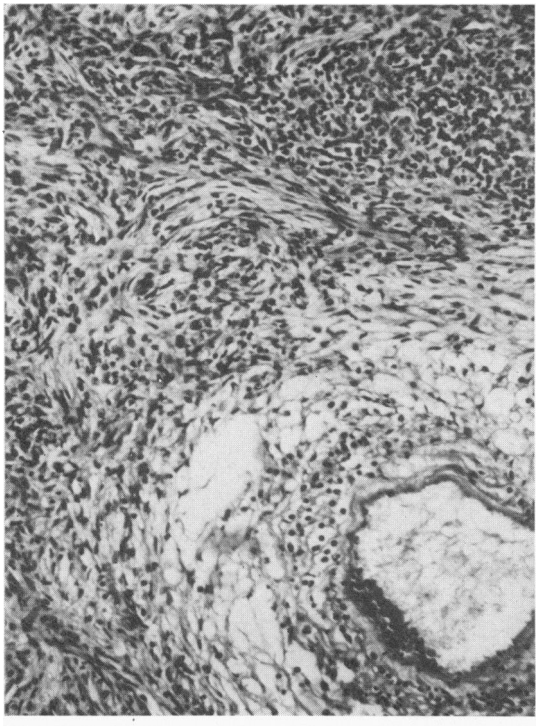

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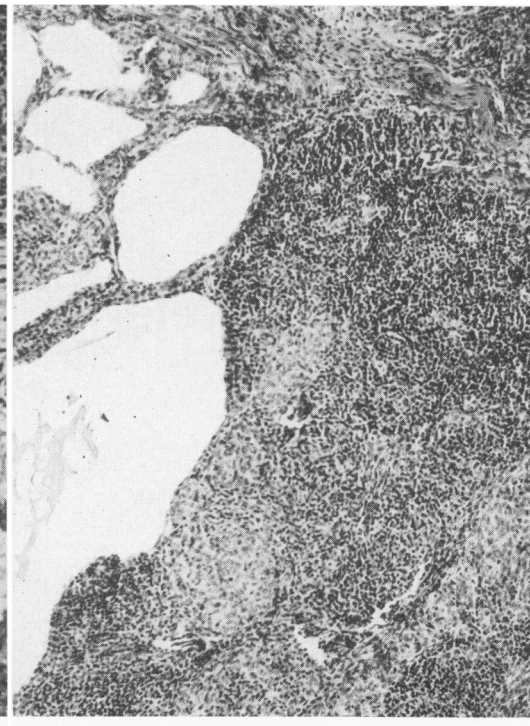

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FIG. 5. A.F.I.P. Acc. 338795. Thymoma not associated with myasthenia gravis. Interlobular septum showing proliferation of spindle cells and formation of cystic spaces. There is an intermixture of lymphocytes and spindle cells in the remaining lobule. × 178.

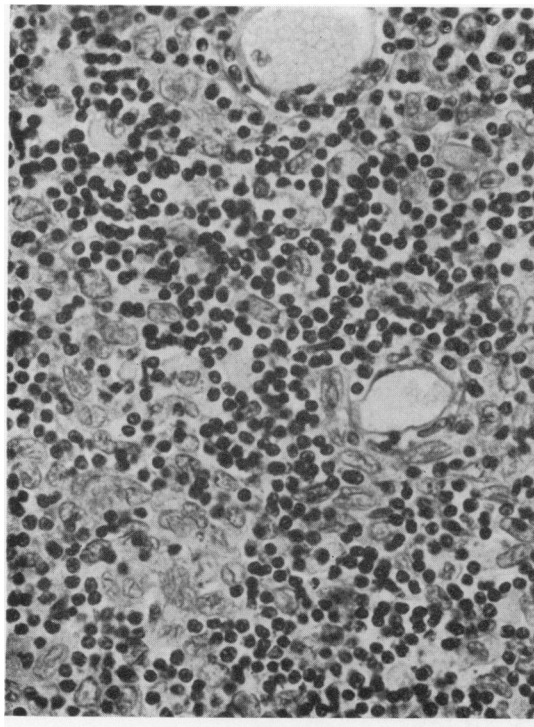
FIG. 6. A.F.I.P. Acc. 520728. Thymoma not associated with myasthenia gravis. Pale spindle cells dominate the lobule. Cystic spaces are associated with the pale spindle cells. Cellularity and vascularity of the tumor and increased fibrosis of the septum may be noted. × 100.

FIG. 7. A.F.I.P. Acc. 520726. Thymoma associated with myasthenia gravis. A characteristic field shows intermixture of large epithelium-like cells with lymphocytes, succulent pulp, and thin-walled vessels encircled by large pale cells. × 453.

FIG. 8. A.F.I.P. Acc. 541010. Thymoma associated with myasthenia gravis. The epithelial cells dominate this field and lymphocytes are limited to sinusoid-like channels. The epithelial cells form solid sheets around the vessels. A central capillary may be noted with a surrounding lymphatic. Periodic acid-Schiff's (PAS) stain. × 290.

FIG. 9. A.F.I.P. Acc. 541010. Thymoma associated with myasthenia gravis. A central capillary and lymphatic are surrounded by cords of epithelial cells in an endocrine-like pattern. PAS stain. × 405.

FIG. 10. A.F.I.P. Acc. 541010. Thymoma associated with myasthenia gravis. The epithelial cells exhibit a tendency to whorl formation and transitions to Hassall's corpuscles. At the periphery some are intermixed with lymphocytes in the more typical manner. × 450.



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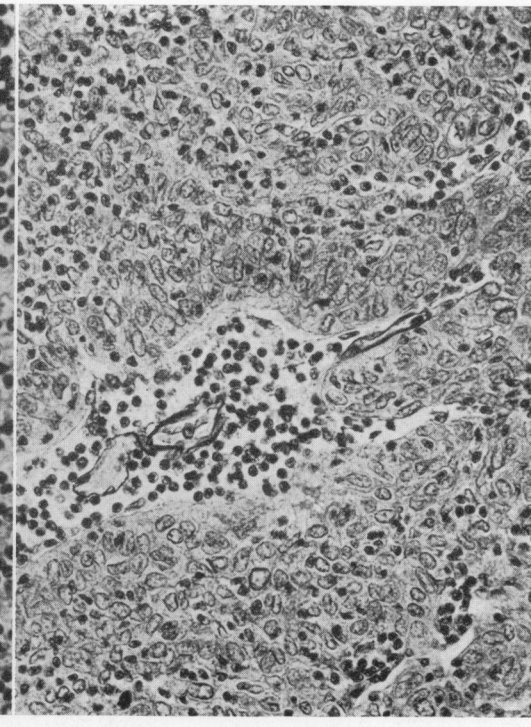

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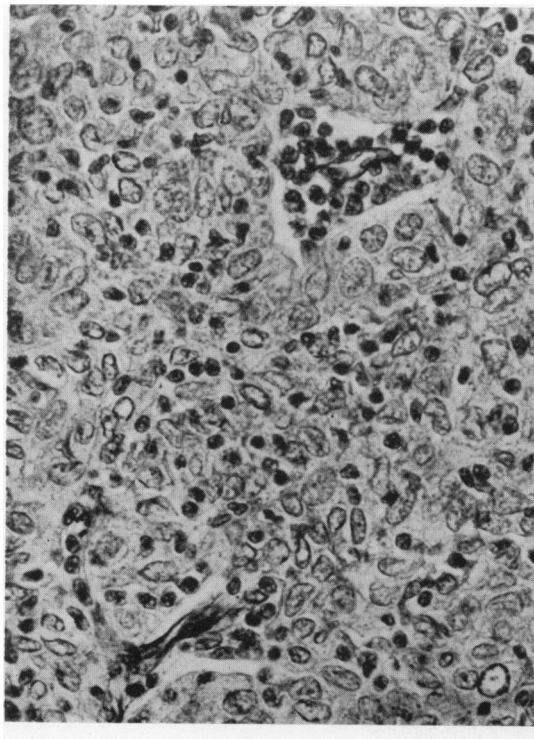

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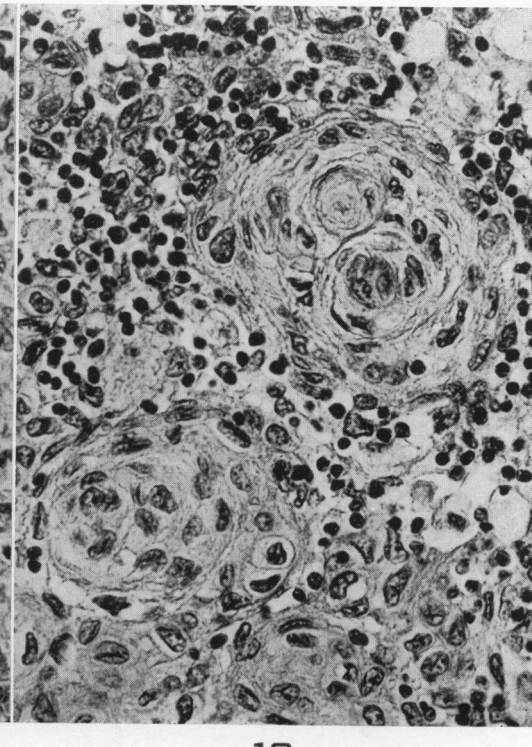

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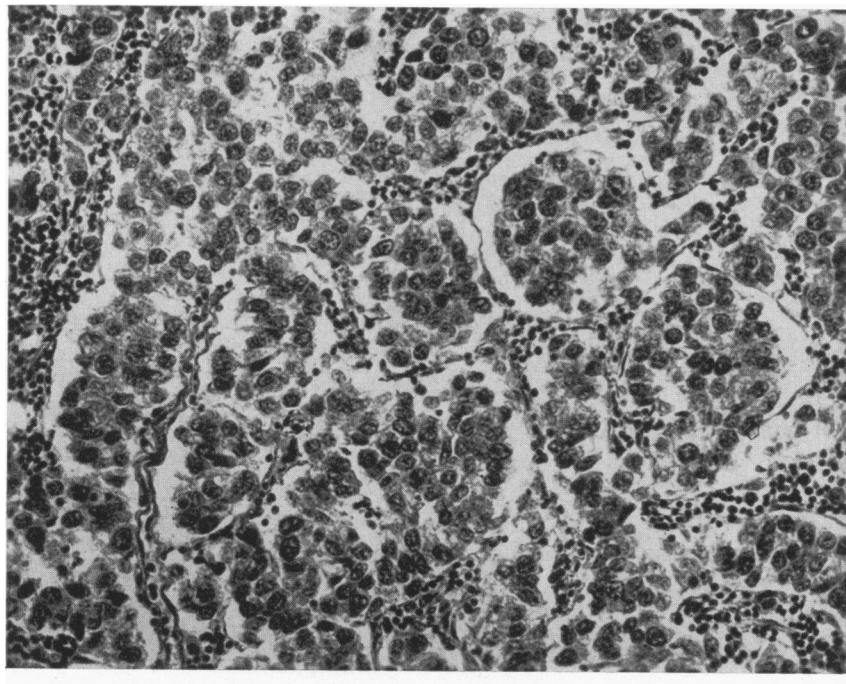

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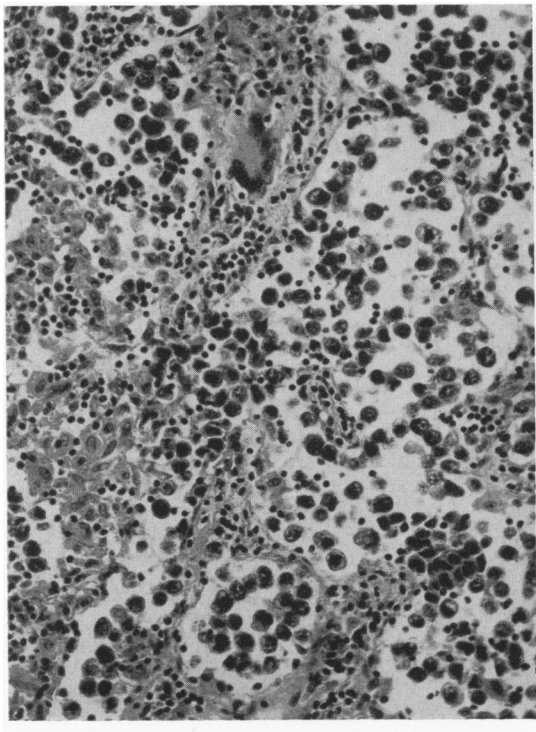
FIG. 11. A.F.I.P. Acc. 528347. Seminomatous tumor of mediastinum. Clusters of dark round cells within acini. Lymphocytes outline the fine connective tissue strands of the stroma. × 220.

FIG. 12. A.F.I.P. Acc. 320877. Seminomatous tumor of mediastinum. The neoplastic cells are loosely clumped within acini. The stroma is accentuated by reticuloendothelial reaction, giant cells, and increase in connective tissue. × 185.

FIG. 13. A.F.I.P. Acc. 167385. Seminomatous tumor of mediastinum. The granulomatous reaction may sometimes dominate the field and obscure the presence of the tumor. There are small cords of tumor cells within the vascular space. × 275.

FIG. 14. A.F.I.P. Acc. 528347. Seminomatous tumor of mediastinum. A teratoid inclusion, showing glands and intervening cells resembling poorly differentiated nervous tissue. This was adjacent to the main tumor which resembled that shown in Figure 11. × 105.



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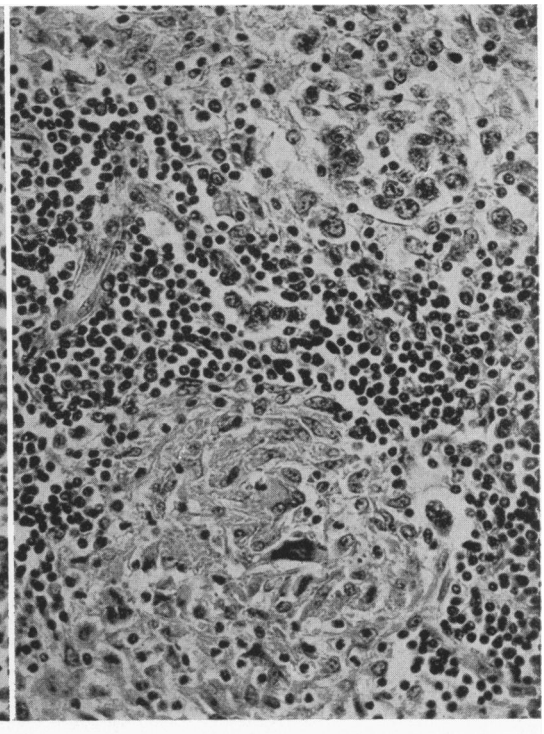

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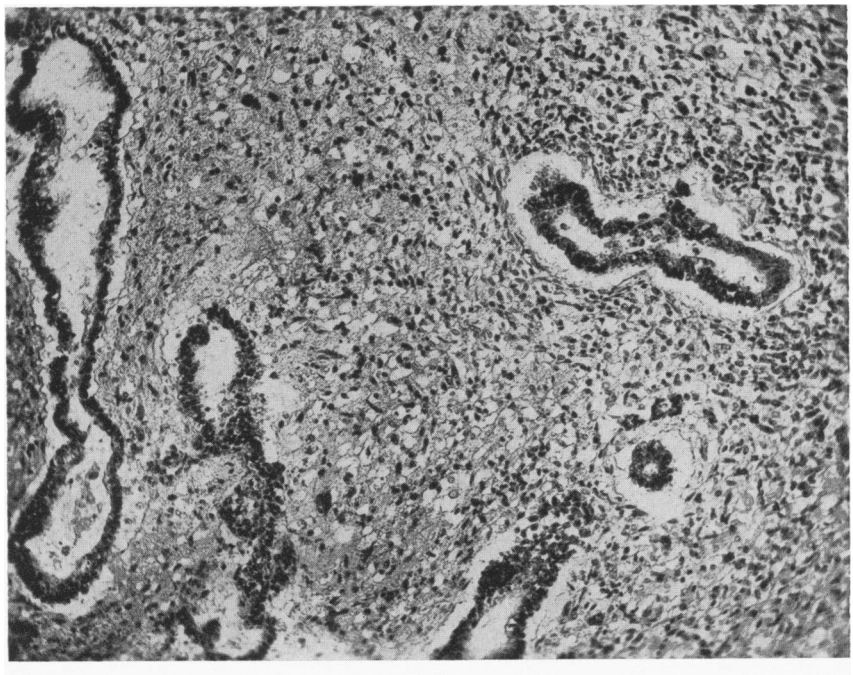

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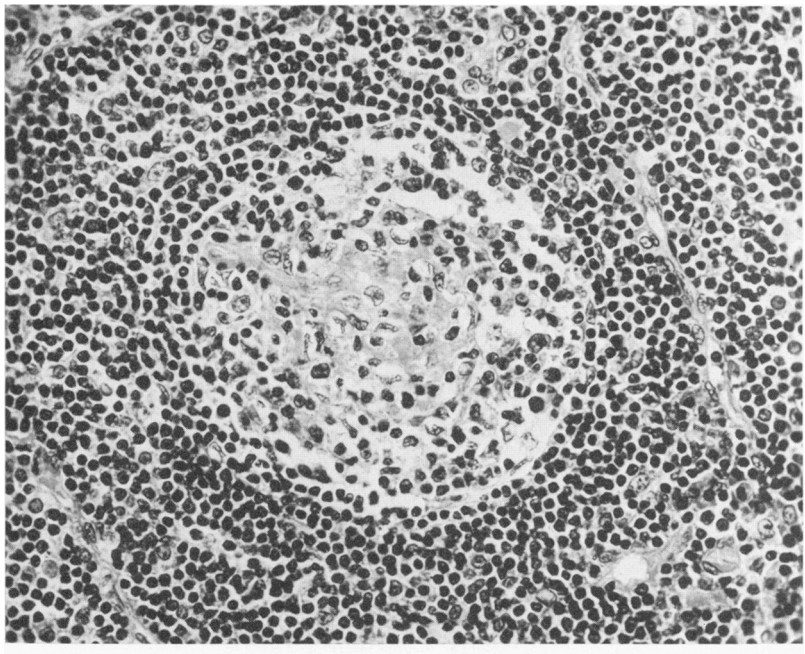
FIG. 15. A.F.I.P. Acc. 523088. Localized hyperplasia of a mediastinal lymph node, showing hyaline alteration of the germinal centers of the follicles. Inflammatory cells may sometimes be noted in the pulp. × 330.

FIG. 16. A.F.I.P. Acc. 484088. Localized hyperplasia of a mediastinal lymph node. Follicles are converted to hyaline masses superficially resembling Hassall's corpuscles. Sinusoids show similar alteration. Septa and lobular pattern of the thymoma are not seen. × 112.

FIG. 17. Reactive hyperplasia of tracheobronchial nodes in a patient with bronchogenic carcinoma. This non-specific reaction resembles that shown in Figure 16 in mediastinal nodes misdiagnosed as thymoma. × 112.



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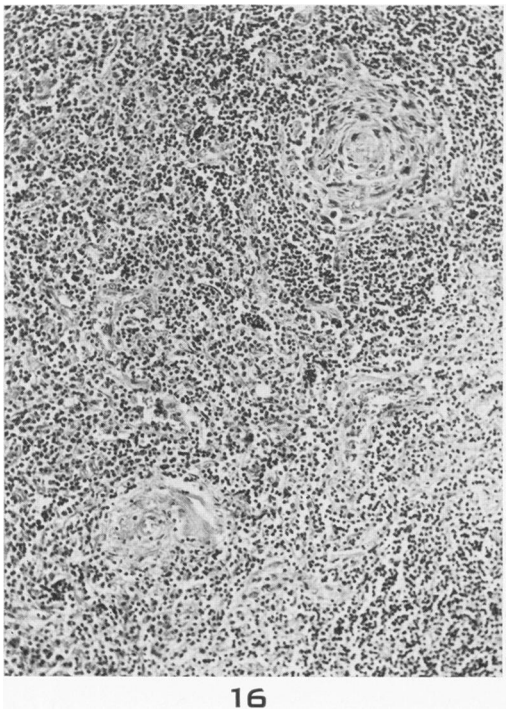

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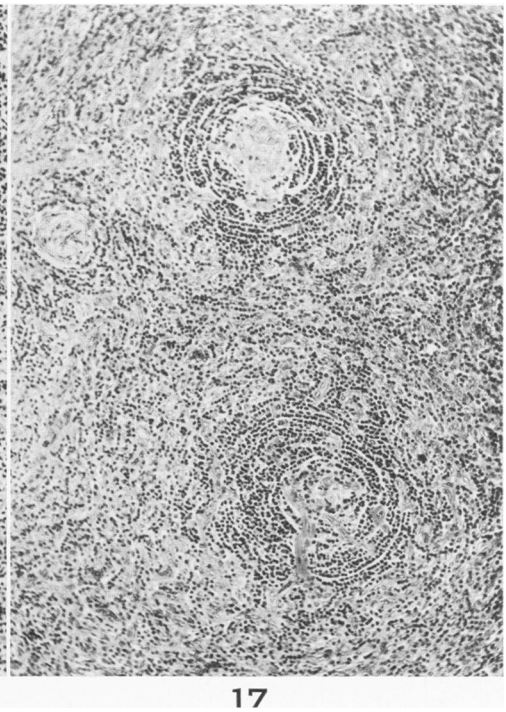

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