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THYMIC TUMOURS AND MYASTHENIA GRAVIS

A RADIOLOGICAL INVESTIGATION

BY

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## P R E A M B L E

It is now fifty years since Weigert first described the association of myasthenia gravis and thymic tumour, but during the ensuing fifty years remarkably little progress has been made in the relation of a tumour of the thymic gland to myasthenia.

No hormone or internal secretion has been isolated so far, and, whilst there would appear to be an association merely from the frequency of the association, and to some extent from the results of Keynes's experience in the operative treatment of myasthenia, it is only in recent years that the operative treatment has been undertaken on an extensive scale with the result that a fairly true picture of the incidence of tumour of the thymus in this condition has been obtained.

Before the report by Blalock in 1941 of the operative treatment of myasthenia gravis by extirpation of the thymic gland, only sporadic reports of myasthenia associated with tumour had appeared in the literature, and as these tended to be the main type of myasthenic case described, a false impression of their incidence was given.

The purpose, therefore, of this thesis is to clarify the position regarding the incidence of the association and to discuss the most satisfactory manner in which these tumours may be demonstrated from the radiological standpoint, as this is the only way in which these tumours may be demonstrated without operation. It will not be argued, however, that the diagnosis can

be made unequivocally, though this point will be discussed in greater detail later in the survey.

#### INCIDENCE OF TUMOURS OF THE THYMUS

In 1917 Bell collected fifty-six cases of myasthenia from the literature in which operation or autopsy had been carried out, and in ten of those (18%) a tumour was found. As will be seen, this is a rather high percentage, and is probably due to a certain selection of cases reported. Then in 1936, Norris collected reports of eighty cases of autopsy in patients with myasthenia gravis, and found pathological changes (not necessarily tumour) in thirty-five (45%).

In the same year, Lievre tabulated sixty-seven cases, and found that of these twenty-four had tumours (36%).

Blalock and associates were able to collect from the literature 110 cases of autopsy up to 1939 on patients suffering from myasthenia, and thirty-one were reported as having tumours. It is probable, however, that patients with tumours were reported in the literature in preference to those with no such dramatic findings at autopsy, and so a false impression of their incidence was given.

Heuer and Andrus (1940) collected 230 cases of so-called thymomas, but many were sarcomata, carcinomata, teratomata etc. and so were in reality not true thymic tumours at all.

Duany and Castellanos (1943) collected 100 cases of tumours of the thymus associated with leukaemia, but here also the thymic involvement is likely to have been secondary to the mediastinal lymph glands.

Many other reports of single or small numbers of so-called thymic tumours, often referred to as malignant thymoma, have been recorded in the literature, but, as many of these have no real pathological support and as they are not considered to be of relevance to the main purpose of this thesis, they have not been quoted individually.

Up to 1948, 296 thymomas had been reported in the literature, of which 255 were said to be malignant. Reid and Marcus state that in this survey benign thymomas occurred more frequently in myasthenia gravis, and from the facts which will emerge later this point is verified to the extent of casting considerable doubt on the source of these tumours which have produced blood-borne metastases and which have hitherto been regarded as thymic in origin.

McEachern (1943) states that X-Ray demonstration of thymic tumour is rare in myasthenic patients. It is true that in the average X-Ray Department thymic tumours are indeed rare, but in those centres to which patients with myasthenia tend to gravitate it is not uncommon to demonstrate a tumour in the thymic region. It is necessary to point out that, to obtain a true radiological incidence, every patient with myasthenia must necessarily be submitted to X-Ray examination.

The erroneous indications of incidence are seen from McEachern's report of two tumours found in four post-mortem examinations of myasthenics.

Veits stated that only one tumour was demonstrated by X-Rays in eighty-five myasthenic patients.

Good in 1947 reviewed the X-Ray films of 100 myasthenics

examined at the Mayo Clinic, and found seventeen tumours in his series.

Keynes's (1950) figure for incidence of tumour in his series of over 200 myasthenics operated upon is approximately 12%, and so it seems likely that the most accurate figure is about 15% as quoted by Seybold, Clagett, McDonald and Good (1950) when reporting forty-five thymic tumours found at operation. It should be stressed that, of these forty-five patients, eleven were non-myasthenic. It is important, therefore, to realise that thymic tumours occur in non-myasthenics, and, as will be pointed out later, may seem to lead in certain instances to the onset of myasthenia. It is to be noted that this later series from the Mayo Clinic gives an incidence of tumours of 15% for thirty-four tumours, as compared with Good's figure of 17% for the examination of 100 patients, and the former figure approximates more closely to Keynes's figure of 12% in this country. The incidence would therefore appear to be between 12% and 15%.

So far as can be ascertained, no anterior mediastinal tumour has been reported of other than thymic origin in myasthenic patients. This is of vital importance when presented with a tumour of the anterior mediastinum in a myasthenic subject; nevertheless, exceptions will no doubt yet be encountered.

Interesting features with regard to incidence of tumours arise from the observations of Seybold et alia who found that:-

1. 15% of myasthenics have thymomas.
2. 76% of patients with a thymoma have myasthenia.
3. 50% of patients with myasthenia come before they are forty years of age.

Castleman and Norris (1949) found that only 14.5% of tumour cases occur before the age of thirty and none before twenty; whereas of non-tumour cases, 35% occur before thirty and 16% before twenty years.

Thymomas seem thus to be commonest between thirty and sixty years, and non-tumour myasthenia between fifteen and thirty-five.

Seybold et alia record that of the eleven patients with non-myasthenic tumours, none subsequently developed myasthenia after removal of the tumour during the period observed until the time of their report.

It is interesting, however, that several of the tumours reported in myasthenics have obviously been present much longer than the myasthenia. It is possible, therefore, that these patients would sooner or later have developed myasthenia. This is a most intriguing question, and one to which it will be very difficult to find an answer, unless some internal secretion can be isolated and a suitable test evolved for thymic efficiency.

In my own experience, only one non-myasthenic tumour has been encountered, and Seybold et alia do not record how they found eleven. Presumably they were disclosed as anterior mediastinal tumours by examination of the patients attending the Clinic for routine check-up purposes, a type of examination which forms a large proportion of the work of the Mayo Clinic.

## P A T H O L O G Y

There has been great diversity and disparity in the nomenclature and classification of tumours of the thymus.

Willis and Seybold et alia state that many types of anterior mediastinal tumours other than thymic have been classified as thymic in origin, and, judging by the descriptions, sections and clinical histories of many cases, it appears that this is probable.

Tumours so described include teratomas, which are probably the commonest of the anterior mediastinal tumours. Many secondary tumours in anterior mediastinal lymph glands have probably been included, and Seybold states that oat-celled bronchogenic tumour, which is probably the commonest tumour to involve the thymus secondarily, has been frequently mid-diagnosed.

A feature of many of the tumours probably erroneously diagnosed is that they have been malignant and metastasising, and one of the remarkable features of the thymoma is the complete absence of distant metastases. It is the general experience of all those who have had to deal with thymic tumours in myasthenic patients that only local mediastinal or pleural deposits occur with these tumours and that they cannot be regarded as true malignant neoplasms.

It is now fairly widely agreed that the tumour of the thymus as seen in myasthenic patients should be called simply a thymoma. This is an interesting return to a suggestion made in 1900 by Meggendorfer for all types of thymic tumour.



Before discussing thymic tumour, I think it is timely and apposite to consider the thymus without tumour (Fig.A). It has been stated that when the thymus is considered in myasthenia gravis, one must not be too concerned with the actual size of the gland, but that the real criterion of abnormality is in the microscopic appearances, i.e. in the germinal centre formation in the medulla, and these centres were found in 75% of the cases reported by Castleman and Norris. They are not usually found in normal thymuses, and they state that an involuted thymus containing germinal centres is an almost certain indication of myasthenia gravis. They state also that without doubt the changes in the thymus are the most conspicuous and impressive lesion which has so far been identified with myasthenia gravis.

The tumour is composed in the main of two elements - the epithelial and the lymphocytic. From the differing degrees of these elements in the tumour, Castleman and Norris classified the tumours into three types:-

- (1) Epithelial elements preponderate.
- (2) Epithelial and lymphocytic elements in equal amounts.
- (3) Mostly lymphocytic.

They therefore regard the varying proportions of these elements as having given rise to the many different names under which such tumours have been reported.

The Hassall's corpuscles which are so typical of normal thymic tissue are absent in most thymomas.

Seybold et alia give the common features of thymomas as follows:- 1. a dense capsule, 2. fibrous trabeculae, 3. palisading of cells about cystic spaces, 4. foci of necrosis,

ILLUSTRATIONS

FIG. A

Macroscopically normal thymus removed from patient suffering from myasthenia gravis. Note the presence of the body and superior and inferior cornua of the gland.

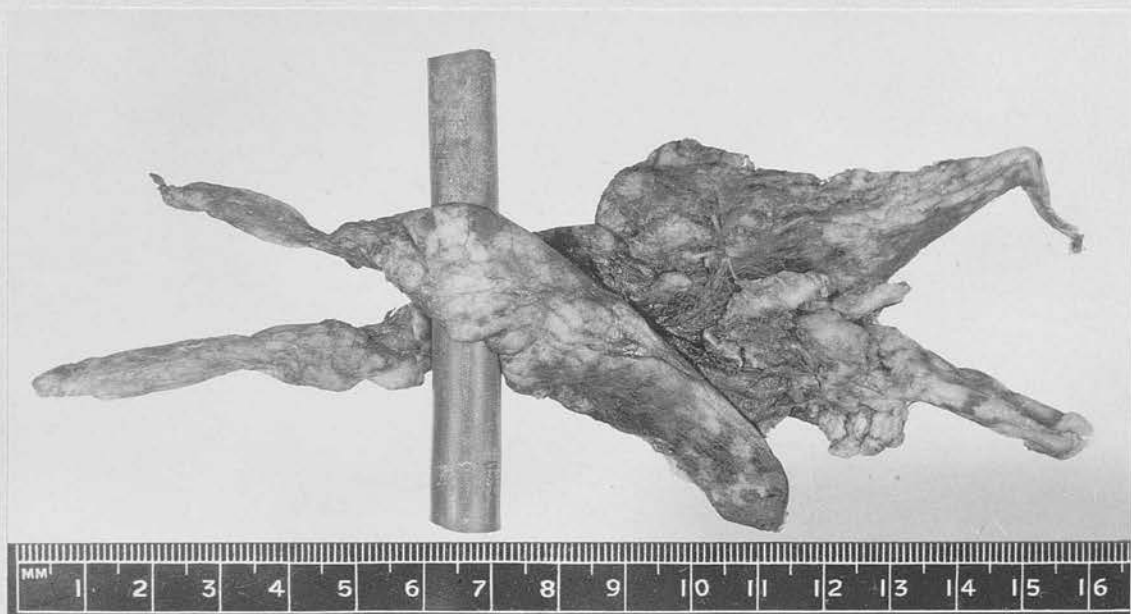


FIG. A

5. cysts, 6. calcification.

They are not necessarily all seen together.

They consider the thymoma to be a true neoplasm, circumscribed, expansive and encapsulated. They consider the tumour benign, but admit that from 5% to 10% may be malignant locally in view of the occurrence of pre-operative implants, and to support their opinion of low malignancy is the rare occurrence of mitotic figures.

The tumour is firm, round or oval, and often lobulated. The parenchyma is soft and greyish-yellow. Liquefactive cystic areas are fairly often seen, and occasionally areas of calcification are encountered, mostly situated near to or in the capsule.

It is generally regarded that the larger the tumour, the longer the symptoms have been present, but this has not always been my impression, as will be seen when case histories and radiographs are described.

Castleman and Norris state that ectopic areas of thymic tissue may be found in the mediastinum, and one of the cases described by Seybold et alia where the tumour proved to lie in the mid and posterior portions of the superior mediastinum may have arisen in this way, i.e. from an ectopic piece of thymic tissue. It may well be as Castleman and Norris point out that patients with tumour-like histories may have an ectopic tumour, which may not be found at operation. The tumour, however, should not remain undiscovered if adequate radiological investigation is carried out. In my series, no tumour has been found which would suggest ectopic origin.

McBurney, Clagett and McDonald have recently reported a case of a tumour in the right middle lobe in a patient suffering from myasthenia gravis, and stated that this tumour had all the features

of a thymoma. No other case of an intrapulmonary thymoma has so far been described, and all the evidence seems to point to this being a genuine case, as the tumour was removed and was available for detailed study.

Derow, Schlesinger and Persky have also reported what seems to be the first authentic case of an intrapulmonary metastasis from an anterior mediastinal thymoma, apparently resulting from ulceration of the primary tumour into the bronchus, with inhalation spread to the parenchyma.

#### CLINICAL ASPECTS

It is not the purpose of this thesis to embark on a clinical discussion of myasthenia gravis, but there are certain features with regard to the tumour patients which require emphasis.

As indicated in the section of incidence, the tumour age group is older than the non-tumour group, only 14.5% of tumour cases occurring before the age of thirty, whereas 35% of non-tumour cases occur before thirty, and even 16% before the age of twenty.

Certain authors give some variation in sex incidence, but Seybold et alia in their relatively large series of forty-five cases found no real disproportion between the sexes.

There has been general agreement that a tumour cannot be clinically diagnosed except perhaps in a rare case of mediastinal obstruction or pleural effusion, but it has been suggested by Seybold et alia that the presence of chest pain in myasthenia may well denote the presence of pleural disseminations and therefore, by inference, the presence of a thymic tumour.

ILLUSTRATIONS

FIG. B

Small dense shadow seen in the anterior mediastinum on tomograph  
This was regarded as being a small thymic tumour but on section proved  
to be a hard fibrotic lymph gland lying alongside the thymus.





FIG. B

## RADIOLOGICAL FEATURES

In 1948 a patient was X-Rayed in my Department to see if a mediastinal tumour was present. One of my colleagues reported on the examination and stated that there was no tumour present. The patient was operated on by Mr. Keynes a few days later, and a tumour was found. I was asked to scrutinise the films to check on the previous report, but, even having seen the tumour demonstrated at the time of operation, I was still unable to locate it on the films.

This was the reason for the revision of my technique, and for a greater interest in the problem of demonstrating these tumours. It is the custom of Mr. Keynes to have all tumours irradiated prior to operation being carried out. Most patients improve over a period of about three months after irradiation of the tumour, and some who, by reason of their poor physical condition have not been regarded at the time as fit subjects for thymectomy, improve sufficiently to be operated upon when carefully supervised by a medical colleague throughout the pre-operative, operative and post-operative phases.

It therefore became incumbent on us to make the pre-operative diagnosis as accurate as possible, and, so far, the method adopted has resulted in no mistakes of omission being made, although one very small "tumour" demonstrated proved to be a small fibrotic mediastinal gland which lay in close proximity to the thymus (Fig.B).

It is a fallacy to assume that the thymus is hypertrophied in myasthenia gravis, as many are atrophic, and there may be a very small thymus with a large tumour arising from one of the lobes (Case 10 Fig.4)

Whilst Seybold et alia have been able to give detailed pathological reports of the appearances of the thymus in tumour patients, it has not been our fortune to be able to do so, as most of the thymic cells are severely damaged by the course of irradiation before removal has been carried out. Microscopic detail cannot, therefore, be complete in this survey, but as this is primarily a radiological research, it is hoped that it is not considered necessary; pathological reports are, however, included where available.

In general terms, it may be said from this investigation that, as in many other conditions, there are no pathognomic features in these tumours, but there are certain aspects which tend to recur: (1) lobulation of a tumour in the anterior mediastinum is always extremely suggestive of a tumour of thymic origin; (2) a flat, plaque-like tumour difficult to dissociate from the other mediastinal structures without the aid of tomography - on which we lay a great emphasis - is another suggestive feature; (3) no tumour of any obvious size, found in a myasthenic patient, has yet been proved to be other than thymic in origin; this is most important, as any tumour found in the anterior mediastinum in a myasthenic subject can safely be assumed to be a thymic tumour.

Good of the Mayo Clinic, who appears to be the only other radiologist to have seen a comparable series of these tumours, relies on stereoscopic postero-anterior chest films, a lateral film, and careful fluoroscopic examination of the patient, but we have no doubt whatever that the tomographic method of demonstration is, in general, an indispensable addition to the investigation of the mediastinum.

Tomography helps to define the tumour much more clearly when used in both the antero-posterior and lateral positions, and so it is of great value to (1) the radiotherapist, who wants to know the dimensions of the mass, so that from shape, position and size, centering and dosage may be accurately calculated; (2) the surgeon, as the extent, and even the degree of adhesion to the surrounding structures may be demonstrated, and so enable a decision to be made regarding operability. Keynes is a most enthusiastic supporter of our contention of the value of this additional method of investigation and demonstration.

It is hoped that this point will be made abundantly clear in the cases illustrated.

It has been suggested by Hampton that Aortography might prove helpful in demonstrating that flat tumours may be differentiated from aneurysm of the ascending aorta, but by the use of tomography we have not so far found it necessary to resort to this more involved technique.

As all anterior mediastinal tumours are almost certainly thymic in origin when found in myasthenic patients, the only real difficulty arises in patients without myasthenia, as thymic tumours do occur in non-myasthenic subjects, albeit infrequently. I have only one such example in my series.

It is interesting to speculate on the possibility of the eventual development of myasthenia in such patients, and no authentic case has so far been recorded.

Nevertheless, it is obvious in view of the relatively short history of the clinical manifestations in some of the patients, that some of the large tumours which on section have been a

mixture of fibrous tissue, calcification and cystic changes, have been present before the onset of myasthenia. Attention will be drawn to this point in the individual cases. This point has also been raised by Castleman and Norris in connection with one of their cases.

The routine method of examination consists of the following:-

- (1) Careful fluoroscopic examination.
- (2) Postero-anterior, full lateral and localised lateral anterior mediastinal films.
- (3) Tomographic series of films. The series depends on the appearances in the full-size films. If a tumour is seen, the sections are so arranged that the mass is fully explored at 1 cm. distance between the sections. If nothing is seen on the large films, five tomographic films are taken of the anterior mediastinum, with the patient lying in the lateral position. A mid-line film is taken, and two on each side of the mid plane at 1 and 2 cms. respectively from the mid-line, as small tumours are often hidden behind the sternum in the postero-anterior film, and may be difficult to see in a thickset or fat patient in the plain lateral view.

The tumours tend, in general, to fall into four groups:-

- (1) The small round tumour, often centrally situated.
- (2) The flat, plaque-like tumour, which may be central, but is rather more frequently placed over the antero-lateral aspect of the aortic arch or pulmonary artery, the most difficult type to demonstrate.
- (3) The larger, lobulated tumour, which tends to extend over one or other hilum in addition to occupying the retro-sternal area.
- (4) The metastasising type of tumour, which may already have

seeded on the pericardium or pleura or seeds as a result of the operation and gives rise to deposits on the pleura. It may also recur extensively in the anterior mediastinum. This can be readily understood, as these tumours are frequently very adherent to pericardium and pleura, requiring very careful dissection, in spite of which the pleura is often opened accidentally.

#### GROUP I. ROUND TUMOURS.

##### CASE I. H.W. (M) AGED 52.

History. Has complained of diplopia for thirteen months and of weakness of grip and of the legs, which was worse at the end of the day. Moderate acceleration of symptoms, and addition of dysphagia during the last three months.

Examination. Fair condition. Diplopia and dysphagia. Moderate ptosis of eyelids and weakness of masseters. Palatal movements poor. Generalised limb weakness.

X-Ray examination. 6. 5. 48. A circumscribed rounded tumour was demonstrated in the anterior mediastinum.

The edge of the tumour was only just visible on the postero-anterior film.

X-Ray therapy in two series over twenty-one days led to almost complete disappearance of the tumour as seen by X-Ray examination, dated 25. 6. 48.

On 9. 9. 48. the tumour was removed by Mr. Keynes. It was said to be a reticulo-sarcoma, but would now probably be designated simply a thymoma.

I L L U S T R A T I O N S

CASE 1. H.W.

1. 6. 5. 48. Tumour just visible on right side of mediastinum at level of posterior end of eighth rib.
2. 6. 5. 48. Easily seen in lateral view and exceptionally well shown by reason of presence of emphysema.
3. 12. 6. 48. Tomographic film taken a few weeks later to show effect of X-Ray therapy.
4. 25. 6. 48. Almost total disappearance of tumour.



CASE 1



FIG. 1



FIG. 2



FIG. 3

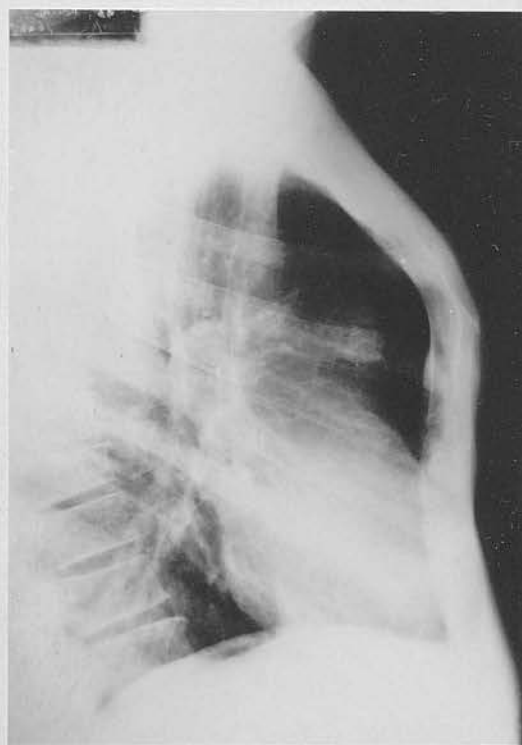


FIG. 4

CASE II. E.B. (F) AGED 53.

History. Known to have myasthenia for four and a half years. Had good response to Prostigmine for two years. Then she developed thyrotoxicosis, which was treated by Thiourasil.

Examination. Weakness of muscles of back, shoulders and hands. Also had slurred speech.

X-Ray examination. 11. 6. 50. The tumour was just visible to one side of the sternum, but much better demonstrated by tomography in the lateral plane.

After radiotherapy, 20. 7. 50., the tumour was much less well-defined, owing to inflammatory reaction surrounding the tumour.

TYPE II. LOBULATED TUMOURS.

Some tumours show obvious lobulation and are larger in the vertical axis. They are usually well-defined but may be poorly defined on their posterior surface where they are intimately associated with the aorta and pulmonary artery. They are often obscured to a large extent by the sternum, but may be situated mainly towards one side, in which case they have to be defined apart from the aorta or pulmonary artery. The following cases illustrate this type of tumour.

CASE 3. G.P. (M) AGED 31.

Admitted. 27. 10. 46.

History. Since May 1946 has noticed difficulty in swallowing and fluids coming back through the nose. Then drooping of the left eyelid and nasal speech occurred. Weakness of jaw, arms and legs.

ILLUSTRATIONS

CASE 2. E.B.

1. 16. 6. 50. Tumour not visible in P.A. film.
2. 16. 6. 50. Rather ill-defined in plain lateral film.
3. 16. 6. 50. Well-defined in lateral tomograph.
4. 20. 7. 50. Some loss of definition, resulting from course of X-Ray therapy, which has produced a surrounding inflammatory reaction.

CASE 2.



FIG. 1

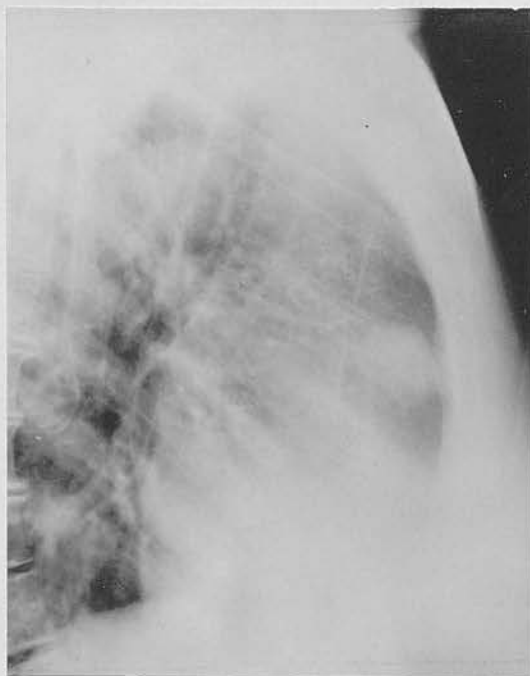


FIG. 2



FIG. 3



FIG. 4

I L L U S T R A T I O N S

CASE 2. E.B.

(cont)

5. Post-mortem section showing cystic mass in the anterior mediastinum. . . .

CASE 2

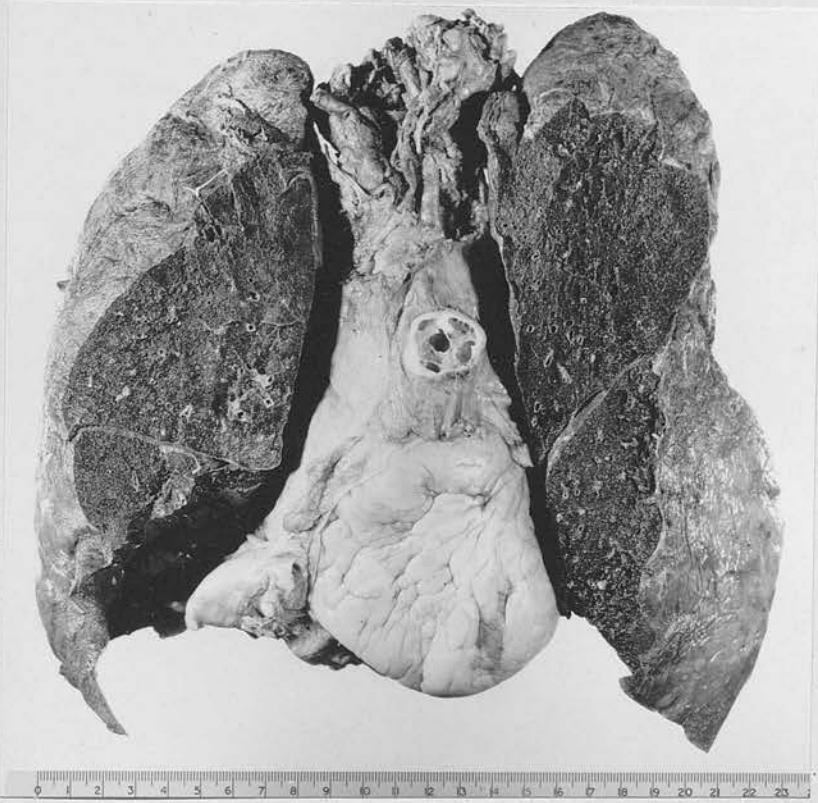


FIG. 5



ILLUSTRATIONS

CASE 3. G.P.

1. 28. 10. 46. Large tumour projecting from the cardiac area into the right side of the chest. The contour of the tumour conforms closely to an enlarged right cardiac border.
2. 28. 10. 46. Oblique view showing a large tumour mass overlying the upper part of the cardiac shadow.
3. 16. 7. 47. Large lobulated tumour removed at operation. Note presence of cystic changes - a common occurrence in these tumours. The tumour consisted of two large ovoid masses as seen in this photograph.

N.B. This patient was X-Rayed before the new technique was evolved.

CASE 3



FIG. 1



FIG. 2

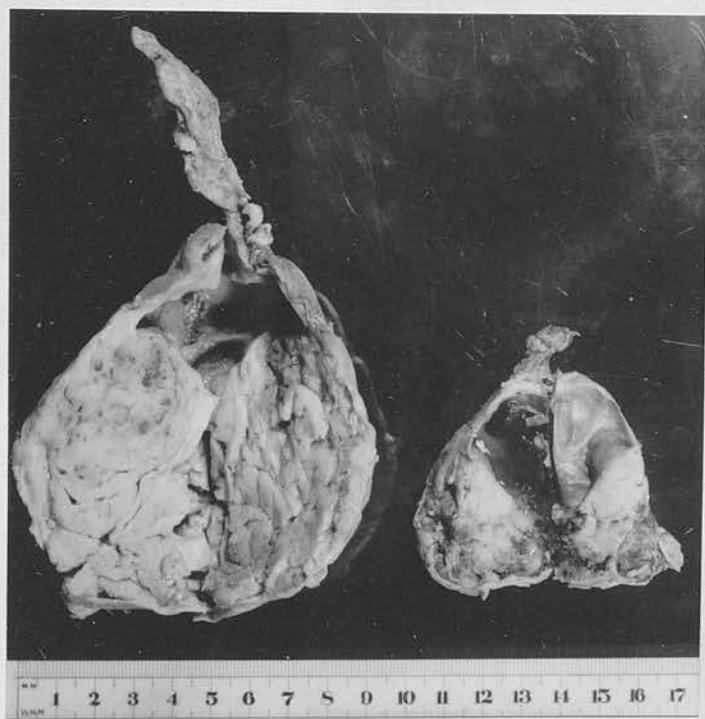


FIG. 3

X-Ray examination, 28. 10. 46., showed a large rounded mass overlying the right border of the heart, but mainly in the anterior mediastinum.

The tumour was removed on 30. 10. 46., and consisted of two ovoid masses of tissue 12 cms. and 5 cms. respectively in diameter. Section showed cystic spaces and certain haemorrhagic areas. The microscopic appearance of epithelial elements and pale-staining cells pointed to thymic origin.

The patient died soon after the operation.

The short history and large tumour with cystic spaces suggest that here again the tumour has been present before the onset of symptoms.

Pathological Report. The specimen consists of two ovoid masses of tissue. The larger of these is 12 cms. in the greater diameter and 7 cms. in the lesser diameter. The surface is smooth and had a horn, measuring 7 cms. in length, attached to its upper pole. The cut surface shows a cystic space, 2 cms. in diameter, at the upper pole, which contains some brownish material. The remainder of the tumour consists of pale, softish, rather degenerate-looking tissue, in which a few small haemorrhagic areas can be seen.

The smaller portion of tissue measures 5 cms. in the greater diameter and 3.5 cms. in the lesser. There is a cystic space 2 cms. in diameter, which contains some blood clot and blood-stained fluid. The appearance of the solid part of the tumour is in every way similar to that of the larger piece.

A small portion of friable tissue has been sent separately.

Sections taken from three blocks of tissue show similar

appearances. The tumour consists of a cellular mass in which little lymphoid tissue can be seen. Most of the cells are pale-staining, with only a moderate amount of chromatin, and in some places they are arranged to form epithelial spaces. Some of these pieces contain red blood cells, while others contain lymphocytes. In some places, structures which resemble Hassall's corpuscles are present. The amount of supporting tissue is small and no reticulin fibres can be distinguished.

While this tumour presents certain difficulties in diagnosis, the epithelial elements and the primitive Hassall's corpuscles suggest that it may be a true new growth of the thymus.

CASE 4. A.K. (M) AGED 38.

History. 22. 2. 49. Weakness of lower jaw and dysphonia.

Three months ago the patient had a sore throat, followed by weakness of voice. This latter feature steadily increased and was accompanied by weakness of the lower jaw and nasal regurgitation of fluids. In the last three months, he had weakness of arms and legs. No eye signs.

Examination. Slight bilateral ptosis. Weakness of masseters and other facial muscles. Palatal movements poor.

Gross weakness of trunk muscles. All motor signs much worse at the end of the day.

X-Ray examination. 17. 2. 49. Revealed a fairly large lobulated tumour in the anterior mediastinum, which was much more clearly defined by tomography in the lateral position on 18.5.49.. The tumour was removed and was found to be adherent to the right pleura, pericardium and to aorta, and slightly adherent to the left pleura. It was about  $1\frac{3}{4}$ " in length.

ILLUSTRATIONS

CASE 4. A.K.

1. 17. 2. 49. Tumour not really well-defined in P.A. film. Small projection over left hilum.
2. 17. 2. 49. Tumour visible in lateral film but rather ill-defined.
3. 17. 2. 49. Whole contour of tumour clearly delineated by lateral tomograph.

CASE 4



FIG. 1

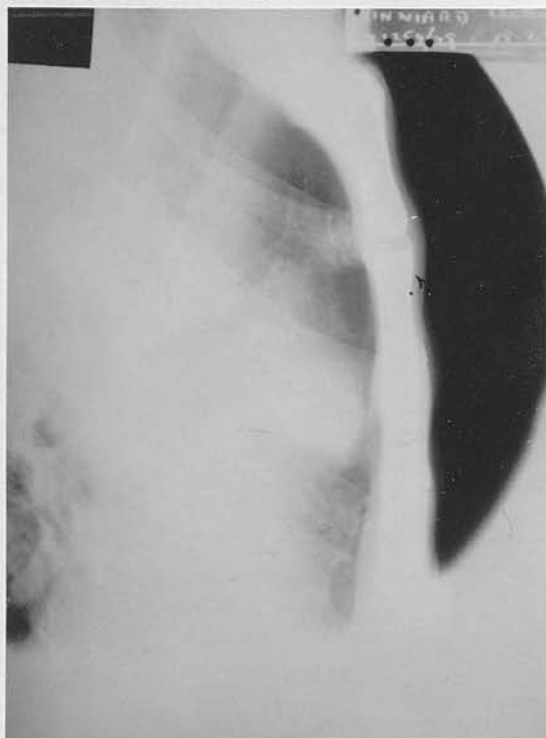


FIG. 2



FIG. 3



I L L U S T R A T I O N S . . .

CASE 4. A.K.

(cont)

4 and 5.

24. 3. 49. Reduction in size and definition of  
tumour on completion of course of X-Ray therapy.

CASE 4.

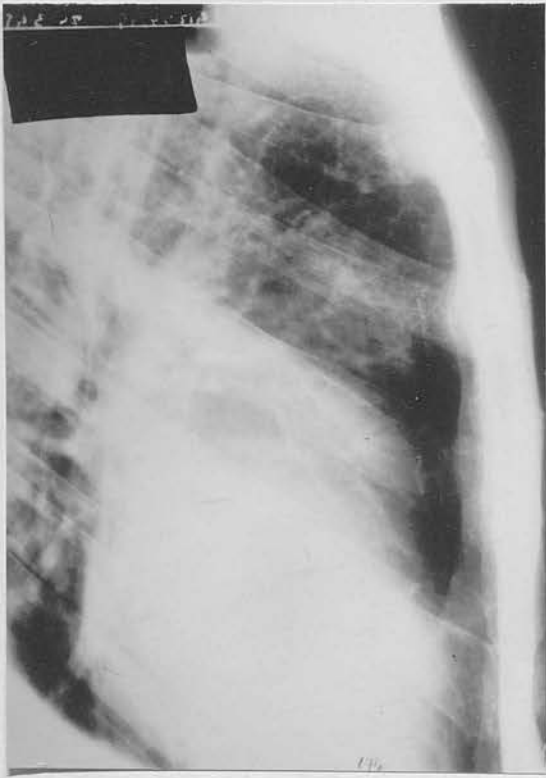


FIG. 4



FIG. 5

Pathological Report.

Macroscopic description. The specimen consists of a thymus gland, weighing 20.5 gms., the two horns of which show a normal appearance. The main body of the thymus appears yellow in colour, and on section is seen to be composed of two cystic cavities measuring 2.5 x 2 cms. in diameter respectively. The walls of these cavities lie adjacent to one another, and are composed of thick, white fibrous material. The smaller of the two spaces contains some pinkish material on the inner aspect of its wall, and a smaller amount is seen on the inner aspect of the larger. The wall of the larger cavity shows a yellowish discolouration suggestive of fatty material.

Histological report. Section from one of the thymic horns shows congested connective tissue in which lymphoid follicles and a few groups of proliferating reticular cells can be seen.

Sections from three portions of the main body of the specimen show some portions of a lymphoepithelioma. The lymphoid tissue appears to have been largely destroyed, and most of the remaining neoplastic material is epithelial. There are some areas of necrosis, in addition to broad bands of acellular fibrous tissue, some of which are encapsulating the tumour. Frozen section shows one part of the fibrous wall to contain fatty material, some of which is doubly refractile.

Conclusion. The appearances are those of a lymphoepithelioma of the thymus, which shows histological evidence of post-irradiational necrosis and fibrosis.

CASE 5. N.T. (F) AGED 40

History. 22. 2. 50. One year ago had difficulty in eating

I L L U S T R A T I O N S

CASE 5. N.T.

1. 7. 3. 50. Tumour visible in left hilar region.
2. 7. 3. 50. Tumour seen but rather poorly defined in lateral view.
3. 7. 3. 50. The mass is more clearly defined in the lateral tomograph.
4. 18. 7. 50. Postero-anterior film showing shrinkage of tumour following course of X-Ray therapy.

CASE 5



FIG. 1



FIG. 2



FIG. 3



FIG. 4

ILLUSTRATIONS

CASE 5. N.T.

(cont.)



5. 23. 7, 50. Post-operative film showing mediastinal haemorrhage and effusion.

6. 21. 7. 50. The tumour removed at operation on 20. 7. 50. Note degree of lobulation.

CASE 5

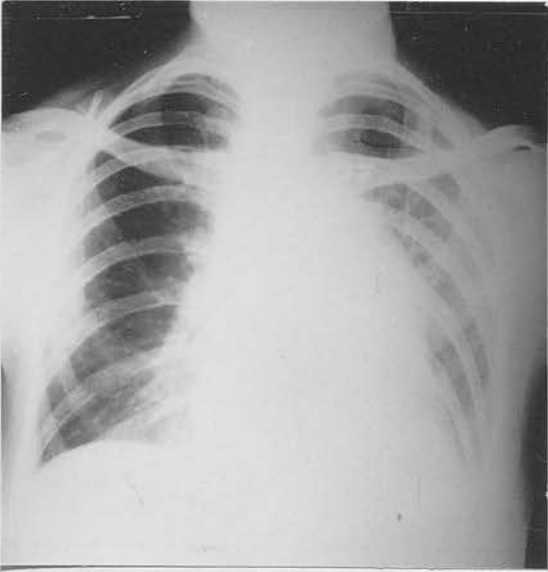


FIG. 5

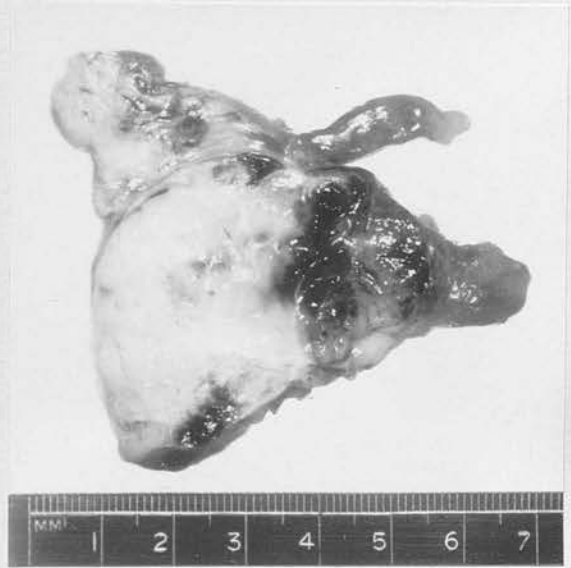


FIG. 6

and talking, which lasted for five weeks. She was then well until six months ago, when she had a sudden return of dysphagia with weakness of arms and back.

Now she has no diplopia or dysphagia. Speech normal. Easily tired with weakness of back. She has difficulty in getting out of bed.

Examination. Slight bilateral ptosis. Marked weakness of arms and legs, and unable to raise herself from the prone position.

X-Ray examination. 7. 3. 50. Showed a large tumour in the anterior mediastinum, not well shown in the frontal or postero-anterior view, but well demonstrated in the lateral view, and especially by tomography.

Pathological Report.

Macroscopic description. The specimen consists of a thymus gland weighing 27.5 gms. One lobe of the gland is markedly enlarged by tumour, measuring 3.5 x 1.5 cms. On section, the tumour is moderately well encapsulated, soft in consistency, and of greyish-white appearance. A few fibrous trabeculae and areas of recent haemorrhage are identified in the tumour substance.

Histological report. Sections show the tumour to be composed of areas of cellular tissue separated by a number of broad collagenous bands. The cellular material consists of a number of cells resembling lymphocytes, together with rather prominent thymic reticular cells, many of which show swollen and abnormal forms. Although mature Hassall's corpuscles are not present, a moderate number can be seen in process of formation.

The appearances show that the tumour is composed of all thymic elements, and it should, therefore, be classed as a thymoma.

CASE 6. M.B. (F).

History. 17. 7. 47. For two years has complained of weakness of arms, jaw and eyes. General feeling of tiredness. Vision usually blurred at the end of the day. Has had diplopia for six months and the condition has progressed. Responded to Prostigmine.

Examination. Revealed weakness of myasthenic type, which involved the face, neck and arms.

X-Ray examination. 21. 7. 47. Revealed a mass to the left and just above the heart shadow in the anterior mediastinum. This patient had been X-Rayed before tomography had been adopted as a routine part of the investigation.

Operation. 3. 9. 47. A lobulated tumour about  $3\frac{1}{2}$  ins x  $2\frac{1}{2}$  ins. was found and removed. Pathological Report not available.

CASE 7. G.S. (M) AGED 48.

History. 24. 4. 51. For five years has been subject to attacks of asthma and bronchitis with inspiratory dyspnoea.

For two years, has had variable pain in and weakness of the jaw muscles, which has been increasing recently.

Was diagnosed as myasthenia in Dartford Hospital, and was treated with Prostigmine.

Examination. At this time no weakness was observed.

X-Ray examination. 16. 4. 51. Showed a large right upper mediastinal tumour, which extended back to the right bronchus and produced slight posterior displacement. The tumour appeared to extend across the mid-line, and over-shadowed the arch of the aorta, probably due to lobular extension to the left.

Following a course of X-Ray therapy, the tumour showed

I L L U S T R A T I O N S

CASE 6. M.B.

1. 24. 7. 47. Postero-anterior film. Tumour visible in left hilar region.
2. 30. 7. 47. Oval mass in anterior mediastinum.
- 3.& 4. 22. 8. 47. Showed reduction of tumour following course of X-Ray therapy.

N.B. This patient was seen before tomography was adopted as a routine procedure.

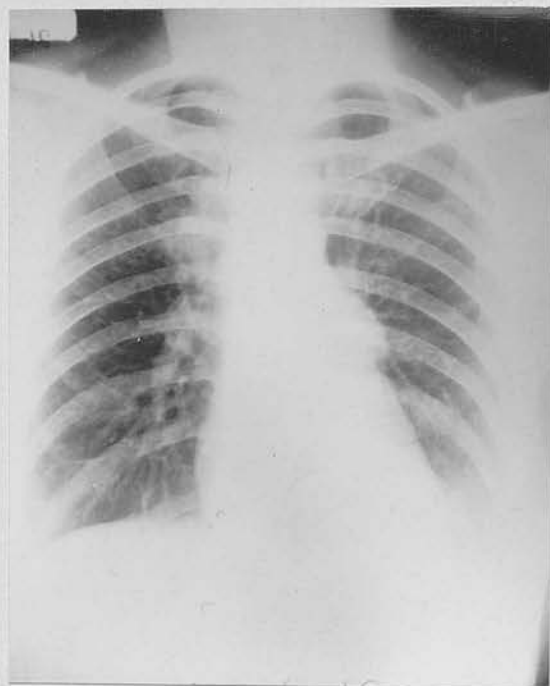


FIG. 1

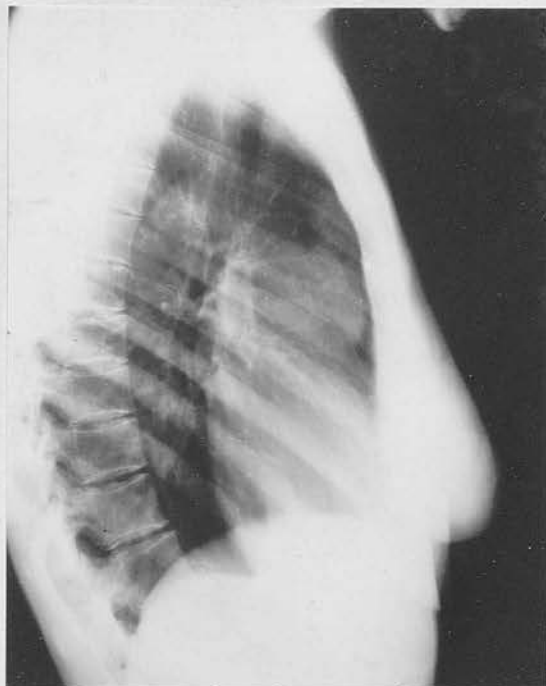


FIG. 2

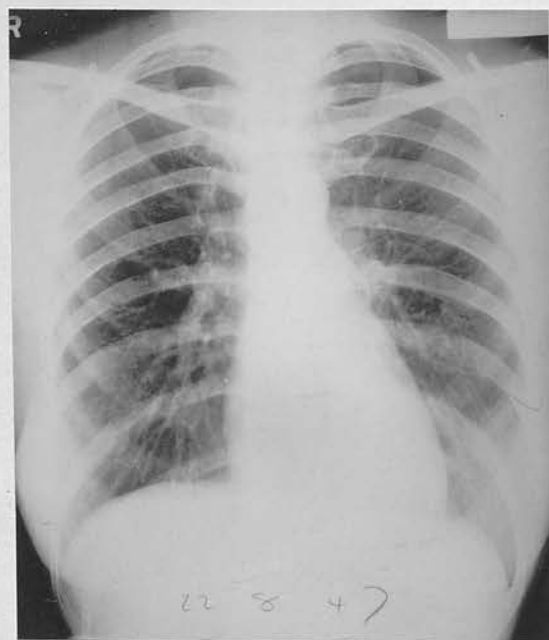


FIG. 3

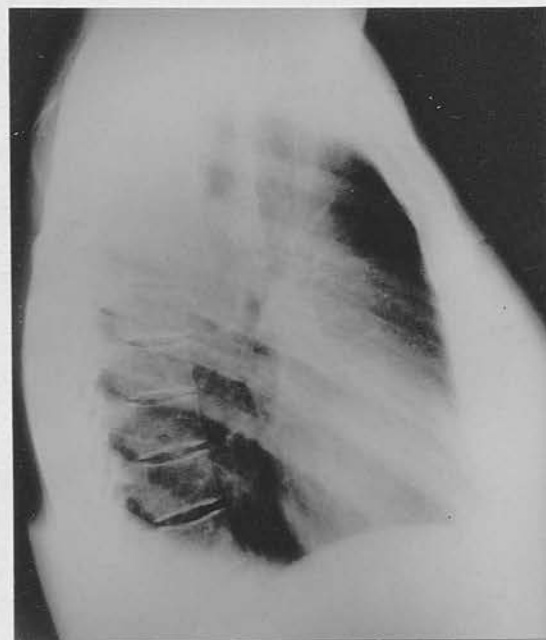


FIG. 4

ILLUSTRATIONS . . . . .

CASE 7. G.S. . . . . .



1. 16. 4. 51. Postero-anterior film shows mass projecting from right side of mediastinum.
2. 16. 4. 51. Large rather ill-defined mass seen in the lateral view.
3. 16. 4. 51. Tumour well-defined by antero-posterior tomography.
4. 4. 6. 51. Reduction in size seen following course of deep X-Ray therapy.



FIG. 1



FIG. 2



FIG. 3

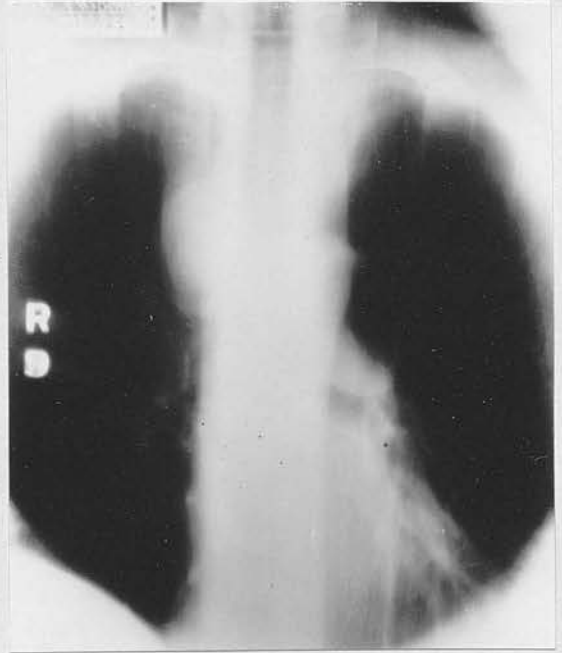


FIG. 4

considerable diminution in size, and the patient stated he was feeling much better.

CASE 8. G.G. (M) AGED 69.

History. 30. 11. 50. Undue tiredness for two years.

In July 1950 he was able to play two rounds of golf per day.

In September 1950 he could play only one round per day.

In mid-October he could play only 9 holes per day.

By the end of October he could not play any golf at all.

This indicates the rapid advance of the disease and the deterioration in the patient's condition.

Examination. All movements weak. Could not sit up from lying position without assistance.

X-Ray examination. 29. 11. 50. Revealed a large, lobulated tumour in the anterior mediastinum, but extending posteriorly on the right side to the main bronchus. There were signs of calcification in the tumour, which from its size and the presence of calcification was obviously of some standing, and was probably present before the onset of symptoms.

The patient's condition deteriorated rapidly and he died during the course of radiotherapy.

Pathological Report.

Post-mortem findings. Autopsy for removal of thymic tumour only. Situated in the anterior mediastinum is a fairly well demarcated tumour measuring 9 x 3 x 2 cms. The medial edge of the lower part of the upper lobe of the right lung is adherent to and covers most of the tumour. On section, the tumour is seen to be composed of an upper area, soft in consistency and brownish in colour. The lower portion by contrast is whitish and firm and shows a

ILLUSTRATIONS

CASE 8. G.G.

1. 29. 11. 50. Postero-anterior film showing large lobulated right mediastinal mass.
2. 29. 11. 50. Lateral film showing large lobulated but ill-defined mass with signs of calcification.
3. 30. 11. 50. Large upper posterior lobule well defined by tomography at 8 cms.
4. 30. 11. 50. Tomograph at 6 cms. displays the areas of calcification.

CASE 8.



FIG. 1

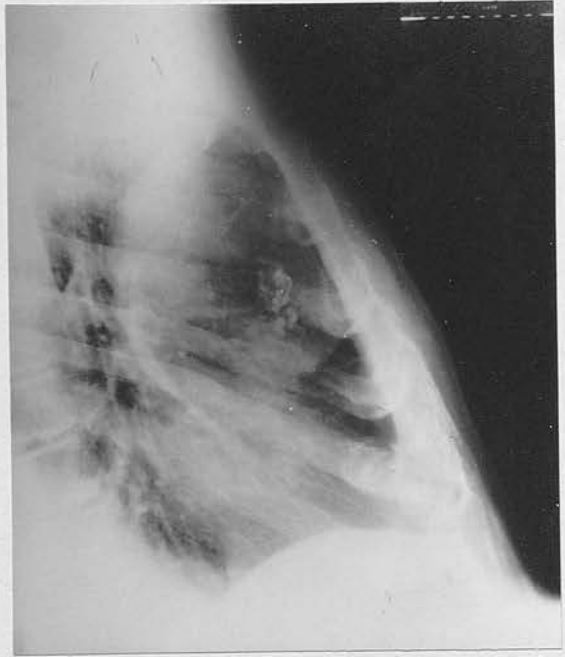


FIG. 2



FIG. 3



FIG. 4

ILLUSTRATIONS

CASE 8. G.G.

(cont.)

- 5 & 6. 30. 11. 50. Lateral tomographs displaying the upper posterior and anterior inferior lobules. The tumour extends back as far as the right main bronchus. Calcification well displayed.
7. 7. 1. 51. Post-mortem specimen showing size of tumour and relation to somewhat collapsed right lung.





FIG. 5



FIG. 6



FIG. 7

central area of calcification. Laterally the tumour is fairly adherent to the lung, but no definite invasion can be seen. Posteriorly and inferiorly, it is firmly adherent to the pericardium, the parietal layer of which shows some thickening on its inner surface. The macroscopic appearances do not suggest that the pericardium has actually become invaded by neoplasm.

Histology. Thymus. Sections of thymus show the tumour to be composed of cellular areas enclosed by strands of coarse acellular fibrous tissue. The cellular areas contain small elongated units which appear to be of connective tissue origin, and probably represent a process of organisation following destruction of the neoplasm by irradiation.

Microscopic areas of apparent new growth can occasionally be seen, and the appearances suggest a lymphoepithelioma, though this can only be a tentative diagnosis.

CASE 9. G.F. (F) AGED 37.

History. 27. 6. 47. Complained of drooping of eyelids, tiredness, difficulty with walking and with speech. Had been well until three months previously. Voice changes and dysphagia had also occurred.

Examination. Drooping of eyelids. Unable to swallow saliva or expectorate. Was unable to lift the arms and her grips were weak. All signs and symptoms disappeared after injection of Prostigmine.

X-Ray examination. 20. 6. 47. Large lobulated tumour in the anterior mediastinum. Displaced somewhat by the depressed sternum. This patient was also X-Rayed before tomography was adopted as a routine procedure.

I L L U S T R A T I O N S

CASE 9. G.F.

1. 20. 6. 47. Large tumour just above the right hilum.
2. 20. 6. 47. Mass in region of right pulmonary artery.

The tumour was not so well defined in the true lateral position, owing to depression of the sternum.

This patient was X-Rayed before tomography had been adopted as a routine procedure.



FIG. 1

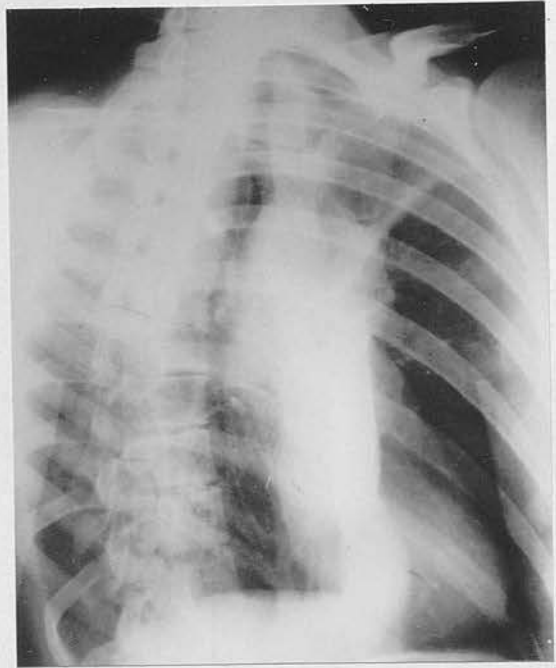


FIG. 2

She responded to radiotherapy and has had no recurrence of symptoms. Operation has not so far been carried out.

This tumour is also likely to have been present before the onset of symptoms.

CASE 10. V.B. (M) AGED 58.

History. 17. 3. 50. For three months has noticed difficulty in eating. Then he could not keep his head up. For the last three weeks has had difficulty in getting out of bed, and has had ptosis of the left eyelid. His doctor treated him with Prostigmine, to which he responded.

Examination. Ptosis of left upper eyelid. Has some weakness of the extensor muscles of the arms.

X-Ray examination. 11. 3. 50. A fairly large tumour was discovered in the left upper anterior mediastinum. There was obvious lobulation on the tomographic films.

The thymus and the tumour were removed in August 1950.

This is another example of a short clinical history and a fairly large tumour, which suggests that the tumour was present before the onset of myasthenia.

Pathological Report.

Macroscopic description. The specimen consists of a thymic tumour weighing 27 gms.

Histological Report. Sections of the thymic neoplasm show so much fibrosis and distortion of cells, due to the original X-Ray therapy, that it is difficult to decide the original nature of the neoplasm. The appearances are compatible with this having arisen from the thymic reticulum, and, while there is still viable tumour present, containing moderate numbers of mitoses, the neoplasm

ILLUSTRATIONS

CASE 10. V.B.

1. 13. 3. 50. Tumour visible in region of left hilum.
2. 11. 3. 50. Oval tumour visible in anterior mediastinum.
3. 11. 3. 50. Lateral tomograph which defines the posterior surface of the mass and shows that it is not aortic in origin.



CASE 10



FIG. 1

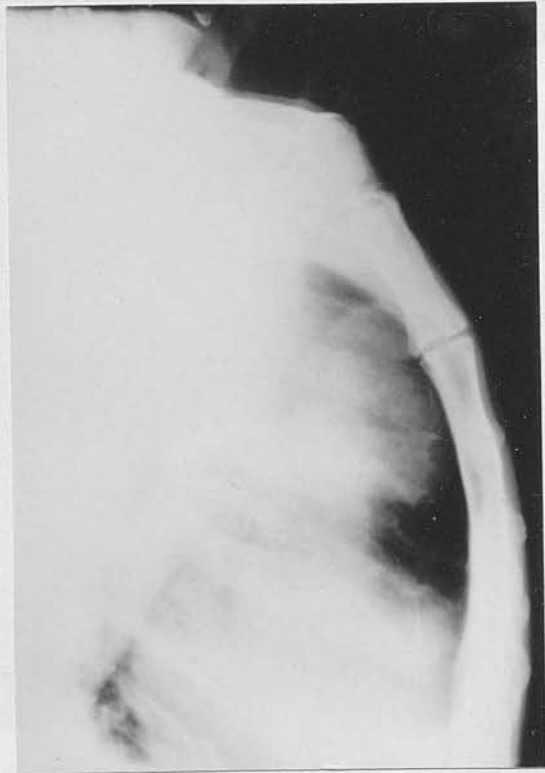


FIG. 2



FIG. 3

I L L U S T R A T I O N S

CASE 10. V.B.

(cont)

4. 12. 7. 50. Tumour and atrophic thymus after operative removal. The tumour weighed 27 gms. and contained some calcification which was not visible on X-Ray examination.



FIG. 4

is mostly surrounded by a well-marked fibrous capsule. A number of calcifications are present.

Section of the tongue of thymic tissue attached to the neoplasm shows that this contains a parathyroid gland showing some adipose involution.

CASE 11. F.L. (M) AGED 36

History. This patient had a routine X-Ray examination by mass radiography means, when an opacity was seen in the region of the mediastinum. This was at first thought to be an aneurysm of the ascending aorta, but tomographic examination clearly showed that the opacity was separate from the aorta and displayed features in shape and position in the anterior mediastinal position, namely a rather elongated and slightly lobulated outline, which suggested thymic origin. It was removed and was found to be a thymoma.

Pathological Report.


Received. Tumour mass, composed of an ovoid lobule and an elongated ovoid lobule covered on each side by a smooth glistening serosal surface, the posterior surface bearing indentation of aorta. The cut surface reveals a diffuse white fleshy tumour, mottled by haemorrhagic staining and fine connective tissue trabeculae which show xanthochromatic deposits. At one pole there are two or three haemorrhagic cysts with smooth walls.

Sections. The microscopic appearance is of a highly cellular tumour divided into irregular lobules by broad dense fibrous trabeculae. The cellular masses are composed of diffuse epithelial type cells forming whorls and definite surface linings round the margins of the masses. Scattered throughout are



ILLUSTRATIONS

CASE 11. F.L.

- 
1. 16. 11. 48. Edge of tumour projecting in right hilar region.
  2. 16. 11. 48. Tumour seen to lie in anterior mediastinum.
  3. 22. 7. 49. Tumour clearly defined in lateral tomograph.

CASE 11

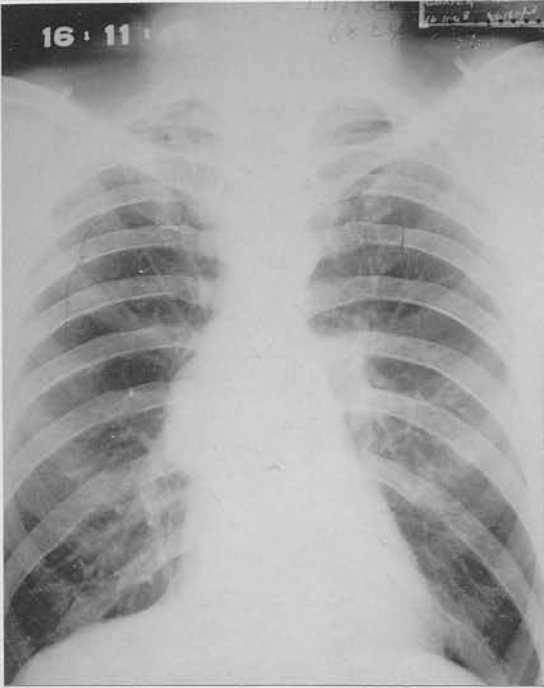


FIG. 1

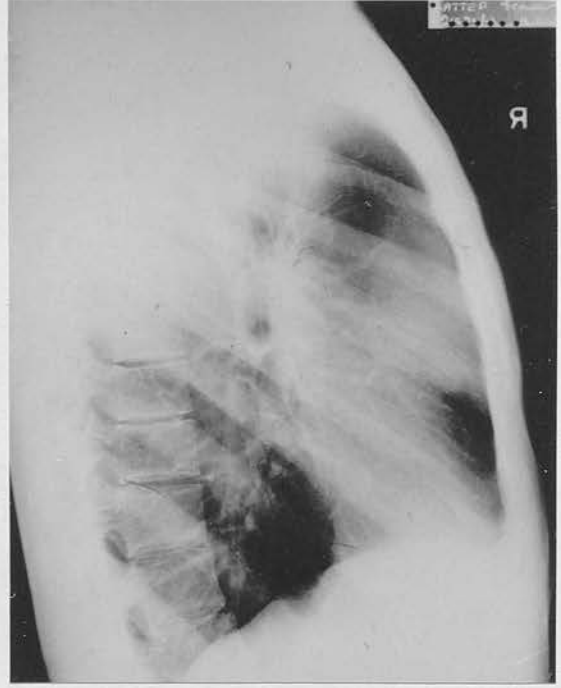


FIG. 2



FIG. 3



numerous cells of lymphatic type. Many cavernous vascular spaces are seen in the tumour substance and the contained blood is separated from the tumour elements only by a single layer of flattened elongated cells. In reticulum preparations no reticulum is seen between this "endothelial" lining and the adjacent tumour constituents. A small fragment of thymic tissue is present at the periphery separated from the tumour by a broad fibrous trabeculum. These appearances are consistent with those of a diffuse carcinoma of thymus of lympho-epitheliomatous type.

At operation, the tumour was found to extend from in front of the left innominate vein down in front of the pulmonary artery, the ascending aorta and the heart. It was attached to the pericardium and pleura, and both pleural cavities were inadvertently opened during the dissection.

The patient was last seen in February 1951, when his condition was satisfactory and there was no indication of myasthenia.

This is the only patient so far encountered in which a non-myasthenic tumour has been found. It may well be that, if it had not been removed, this patient would eventually have developed myasthenia, as, from the history and findings of Cases 8, 9 and 10, it seems likely that a tumour may in certain instances precede the appearances of symptoms and signs recognizable by the patient.

TYPE III. THE PLAQUE-LIKE TUMOUR.

This is the most difficult type to diagnose, as it may resemble dilatation of the aortic arch or pulmonary artery, or lie over one or other of the hilar areas and resemble a dilated right or left main pulmonary artery. Careful screen examination and tomography usually enable a definite decision to be made.

CASE 12. F.G. (F) AGED 52.

History. 3. 11. 50. The patient noticed diplopia and right ptosis in September 1949. In April 1950 she was unable to bite properly and one week later had to hold her chin up, and could not talk properly.

She was diagnosed as suffering from myasthenia gravis and was given a course of radiotherapy in Bristol; she was later referred to Mr. Keynes.

X-Ray examination. 1. 11. 50. Revealed a rather ill-defined plaque-shaped tumour lying low down over the root of the aorta, which was only reasonably well-defined by tomographic examination. It may be that definition was poor in this case owing to the reaction in the mediastinum as the result of the radiotherapy. I have noticed this effect in tumours after irradiation in cases where the tumour has been clearly demonstrated and delineated prior to radiotherapy.

Owing to the poor general physical condition of the patient, the thymus has not yet been removed. Some improvement in the myasthenia followed the course of X-Ray therapy.

CASE 13. F.W. (M) AGED 41.

History. 17. 11. 50. In March 1950 the patient complained

ILLUSTRATIONS

CASE 12. F.G.

1. 1. 11. 50. Flat projection seen in region of left hilum.
2. 1. 11. 50. No definite tumour seen in lateral film.
3. 1. 11. 50. Flat extension of the mass into the lower part of the anterior mediastinum.

This decreased after X-Ray therapy.

CASE 12



FIG. 1

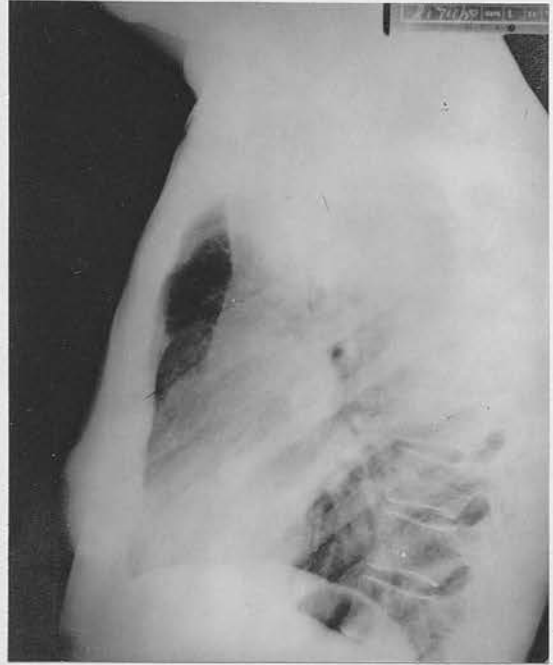


FIG. 2

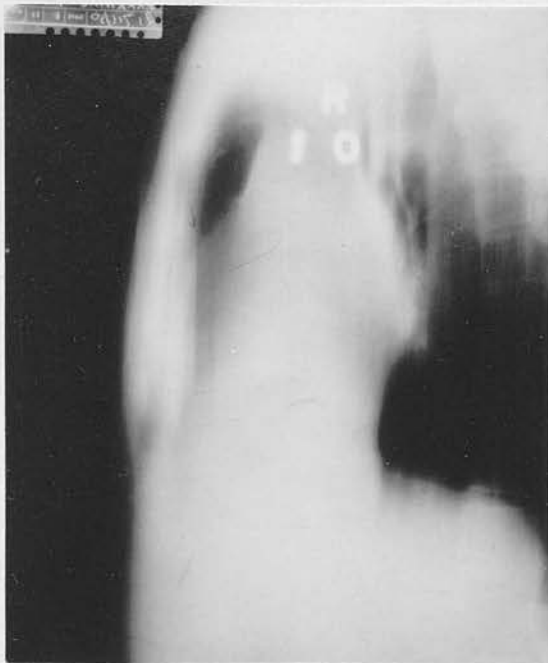


FIG. 3

I L L U S T R A T I O N S

CASE 13. F.W.

1. 13. 11. 50. Ill-defined opacity in region of right cardiac border, which was seen on screen examination to be independent of, although closely adherent to, the heart.
2. 7. 11. 50. Poorly defined mass in lateral view.
3. 9. 11. 50. The tumour is clearly defined in the antero-posterior tomograph.
4. 10. 12. 50. Decrease in size of tumour following X-Ray therapy.



FIG. 1



FIG. 2



FIG. 3



FIG. 4



of general tiredness, aching and stiffness in the thighs and shoulders. He was a fireman and was unable to climb ladders. Diplopia appeared and has since increased. In addition, there was increasing inability to swallow, speak or cough. He was treated at the local hospital and stabilised on 840 mgn. Prostigmine daily.

X-Ray examination. 20. 11. 50. showed a curious bulge at the right cardiac border, which on screen examination was seen to be localised and apparently was not cardiac in origin, as judged by the acute angle at which the lower edge met the cardiac contour.

Tomographic films in the usual lateral position did not produce good definition, and so an antero-posterior series was taken. The film taken at a depth of 2 cms. revealed good definition of the mass, which was obviously very close to the right antero-lateral surface, but not of cardiac origin. It was fairly small and plaque shaped.

The tumour was much smaller after a course of X-Ray therapy, but was still clearly visible. It was subsequently removed by Mr. Keynes.

#### Pathological Report.

Macroscopic description. The specimen consists of several portions of thymic tissue removed from an organ weighing 27 gms. No useful details can be made out from the macroscopic examination, but representative portions are put on for histological examination.

Histological Report. One section of thymic tissue received shows the features of an adipose involution normal for age.

I L L U S T R A T I O N S

CASE 14. M.E.

1. 12. 7. 51. Tumour not visible in P.A. film.
2. 12. 7. 51. Elongated calcified mass in the anterior mediastinum
3. 12. 7. 51. Tomographic examination showed that practically the whole of the thymic tumour was calcified.

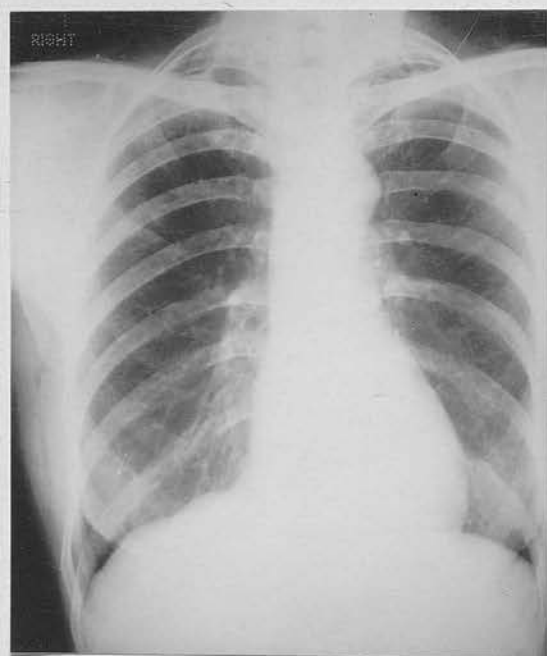


FIG. 1

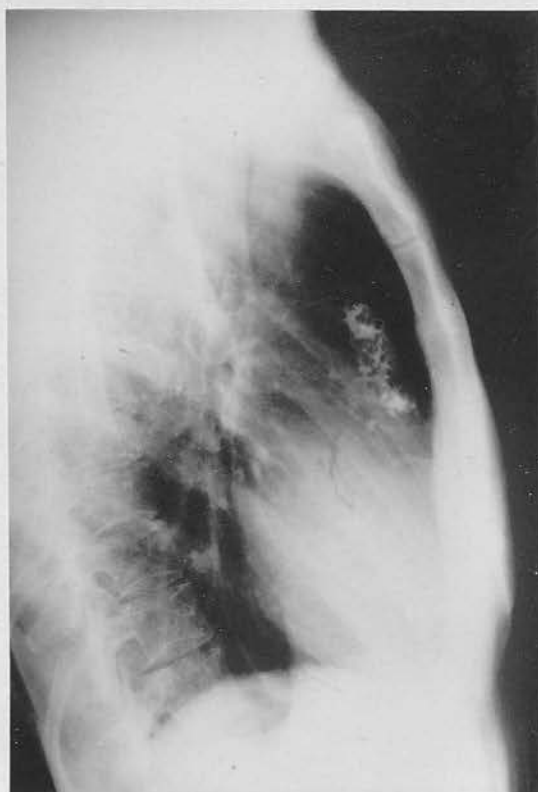


FIG. 2



FIG. 3

Sections of another portion of tissue, however, show the "thymoma" to be composed of hyperplastic cortical tissue. This contains closely packed lymphocytes and reticulum cells, and the cytological features of these do not suggest malignancy. Separating these areas of hyperplastic tissue are bands of fibrous tissue, and here and there some medullary tissue is recognised. One section, particularly, shows hyaline fibrosis (post irradiation). No germinal follicles are seen.

CASE 14. M.E. (F) AGED 57.

Admitted. 11. 6. 51.

History. Twelve years ago noticed weakness of jaw on eating. Has grown worse and swallowing difficult. Was diagnosed and treated with Prostigmine, which restored her to normal.

Six or seven months ago symptoms recurred and became steadily worse. Swallowing and neck weakness main complaints, but also had ptosis and weakness of arms. Speech possible only with Prostigmine.

X-Ray examination. 12. 7. 51. Calcified tumour in anterior mediastinum. Invisible in postero-anterior view, in which it was hidden by the sternum.

TYPE IV. METASTASISING TUMOURS.

As described by Seybold et alia and by Castleman and Norris, and from our own experience, a few tumours are found to metastasise locally in the thorax. These deposits are mainly in the mediastinum and in the pleura. Three patients showing this feature have so far been encountered, one following operation and

and the other two spontaneously.

Of genuine authenticated cases of thymic tumour in myasthenia gravis, none appears to have been recorded which metastasised outside the thorax.

In view of the firmness with which these tumours usually adhere to the pericardium and pleura, it is easy to see how seeding may occur post-operatively, as both are frequently opened during dissection of the tumour.

CASE 15. P.H. (M) AGED 40.

History. 10. 6. 48. In 1939 the patient noticed weakness of the jaw followed by weakness of head, neck and limbs. Diplopia ensued and myasthenia was diagnosed and he was treated with Prostigmine. He returned to work but gradually he became worse and in 1942 was operated upon by Mr. Keynes.

A bilobed enlarged thymus 6" long was removed and an encapsulated adenomatous mass 2 x 1 x 1" was found at the lower end.

The tumour was adherent to the pleura, which was opened during dissection, and "sebaceous-like material" oozed out during the removal. The patient, after a stormy post-operative period, was much improved. Gradually, however, his condition deteriorated although he had a remission in 1946 which lasted until two months before this examination.

During these two months, he has complained of dyspnoea, cough and pain in the chest; then he was admitted to Hill End Hospital, where he had originally been operated upon, with a large left hydrothorax and a mass 2" in diameter above the sternum and attached to the skin.

On 24. 5. 48. the mass was removed and was found to be

ILLUSTRATIONS

CASE 15. P.H.

1. 7. 6. 48. Postero-anterior film after partial removal of hydrothorax.
2. 10. 6. 48. Postero-anterior film after replacement of fluid by air. Multiple large pleural masses are seen.
3. 29. 6. 48. Marked decrease in size of masses following the X-Ray therapy.



CASE 15



FIG. 1

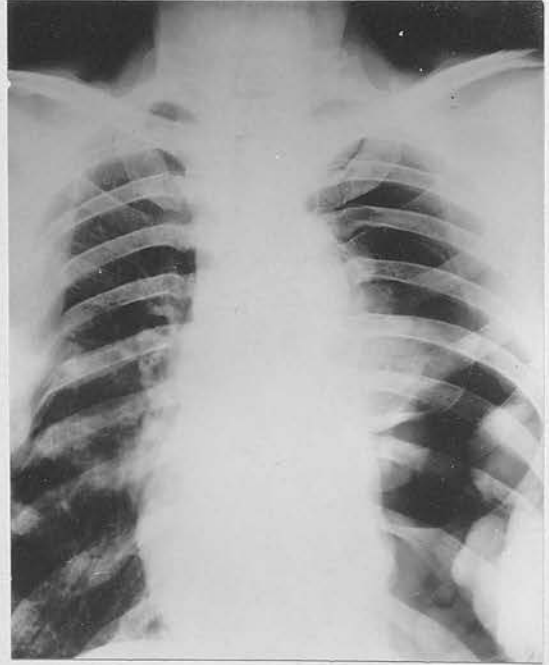


FIG. 2



FIG. 3

I L L U S T R A T I O N S

CASE 15. P.H.

(cont)

4. 10. 6. 48. Anterior mediastinal masses seen after removal of fluid.
5. 29. 6. 48. Decrease in size of masses following X-ray therapy.

CASE 15

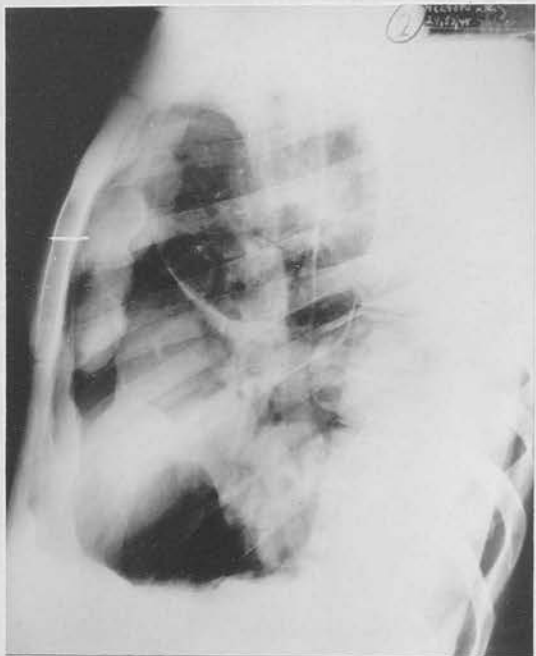


FIG. 4

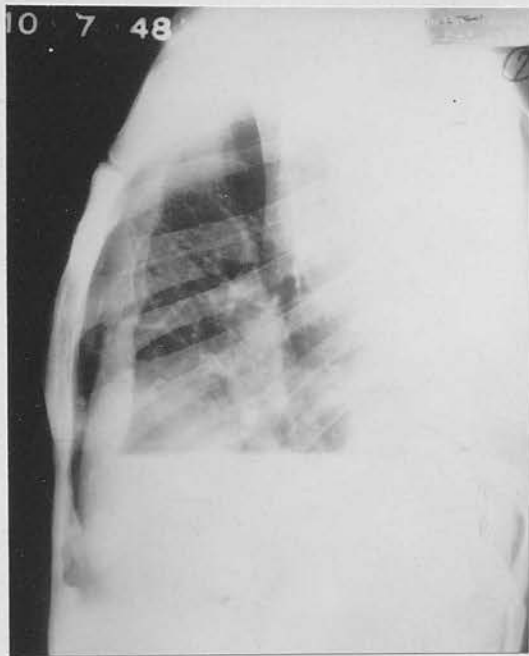


FIG. 5

invading the pre-tracheal fascia and muscles. It proved to be of almost pure epithelial type like the original tumour. He was transferred to St. Bartholomew's Hospital, where the hydrothorax was replaced by air.

X-Ray examination. 7. 6. 48. Showed extensive masses throughout the length of the anterior mediastinum, and several large masses on the pleural surface.

These responded to some degree following a course of deep X-Ray therapy, but after about a year back at work he died fairly suddenly in another hospital in November 1949.

CASE 16. D.L. (M) AGED 39.

History. 10. 10. 49. For nine months had experienced difficulty in swallowing and talking. For eight months has had difficulty in lifting his arms above his head.

Has had double vision intermittently for sixteen months.

X-Ray examination. 4. 10. 48. Revealed a mediastinal and several rounded and oval opacities in the left side of the chest. These seemed to be fairly superficial, but without pneumothorax it would not be easy to say if they were in the lung or the pleura.

The masses diminished with X-Ray therapy and have remained the same since.

CASE 17. E.S. (F) AGED 51.

History. November 1948. In December 1946 the patient noticed drooping of the eyelids and double vision which was worse when she was tired.

In May 1947 she was admitted to Maida Vale Hospital, where the eye symptoms and facial weakness were noticed. She responded to

ILLUSTRATIONS

CASE 16. D.L.

1. 29. 8. 49. Mass obscuring left upper mediastinal region. Several small masses on pleura at periphery of lung.
2. 29. 8. 49. Under-exposed lateral film showing large anterior mediastinal mass.
3. 28. 9. 49. Considerable shrinkage of mass during course of X-Ray therapy.
4. 8. 11. 49. Almost total disappearance of mass after conclusion of course of X-Ray treatment. Patient still alive but not operated upon.



FIG. 1



FIG. 2



FIG. 3



FIG. 4



I L L U S T R A T I O N S

CASE 16. D.L.

(cont)

5. 2. 12. 49. P.A. film showing disappearance of pleural deposits. Fuzzy mediastinal outline due to inflammatory changes following the X-Ray therapy. Pleural reaction at left base also. These changes usually clear in due course.
  
6. 2. 12. 49. Clear anterior mediastinum. Basal pleural reaction.

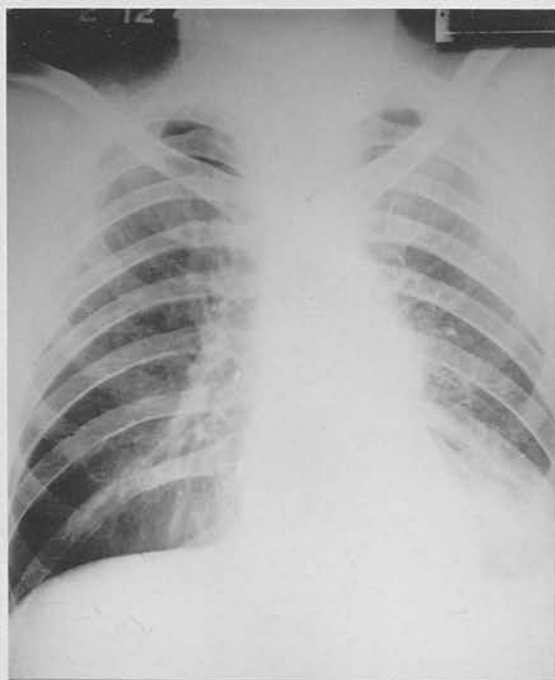


FIG. 5



FIG. 6

Prostigmine but in September 1948 weakness of the legs developed and swallowing became difficult. Her voice was husky and the left eye closed.

Examination. Patient very stout and pale. Ptosis of left upper eyelid. Nystagmus on looking to left.

X-Ray examination. 22. 10. 48. This showed a massive shadow to the left of the aorta and behind the sternum. By tomography it appeared to be independent of the aorta, but definition was not good owing to the stoutness of the patient.

She was given a course of X-Ray therapy and marked regression took place in the size of the tumour.

She returned in March 1950 with severe dyspnoea and engorged neck veins.

X-Ray examination. This time showed a much enlarged cardiac contour, and a dense shadow in the mid mediastinum. The films showed the appearance of pericardial effusion, probably from pericardial involvement by the tumour, or perhaps by the secondary mass displayed below the left main bronchus in the mediastinum.

A further course of irradiation resulted in great improvement. The mediastinal secondary mass regressed and the cardiac contour gradually returned to its original size. This tended to confirm the diagnosis of pericardial effusion resulting from invasion of the pericardium.

She was discharged in April 1950 in good general condition.

I L L U S T R A T I O N S

CASE 17. E.S.

1. 6. 5. 47. Large lobulated left upper mediastinal mass.
2. 6. 5. 47. Large ill-defined opacity in region of anterior mediastinum.
3. 6. 5. 47. Lateral tomograph showing large ill-defined shadow in anterior and middle mediastinal area.
4. 2. 12. 48. Disappearance of mass following X-Ray therapy.



FIG. 1

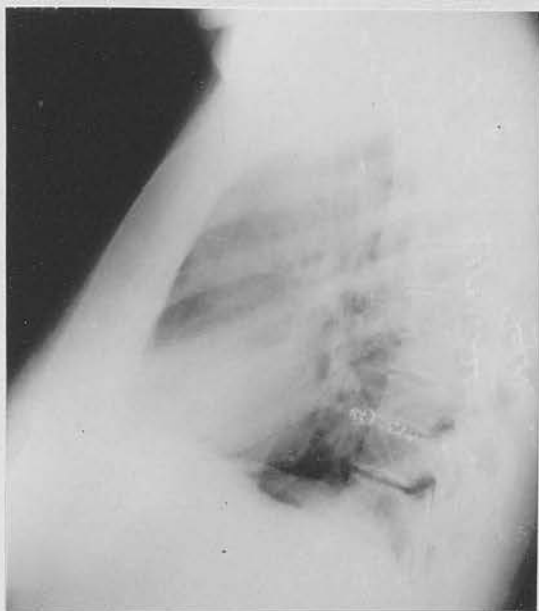


FIG. 2



FIG. 3



FIG. 4

I L L U S T R A T I O N S

CASE 17. E.S.

(cont)



5. 21. 3. 49. Enlarged cardiac outline resulting from pericardial involvement and due to pericardial effusion. This subsided after X-Ray therapy.
6. 10. 3. 50. Development of mass in lower posterior mediastinum. Seeding in mediastinum from original tumour, although there had been no operation.
7. 2. 5. 50. Diminution of mass following radiotherapy. Patient still well but not operated upon.

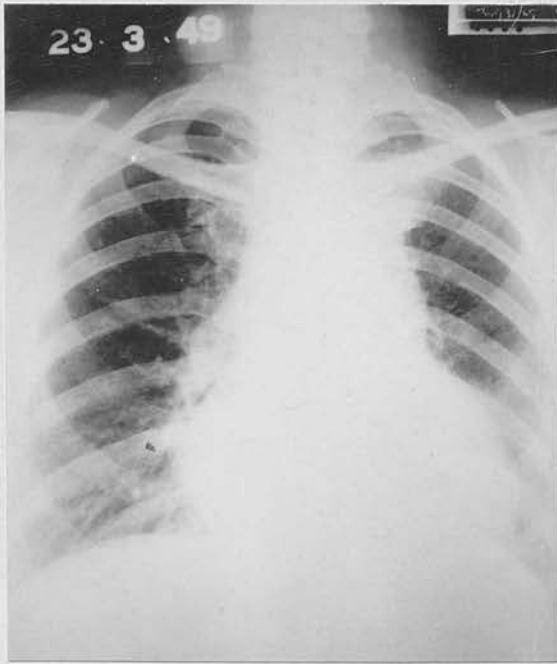


FIG. 5



FIG. 6

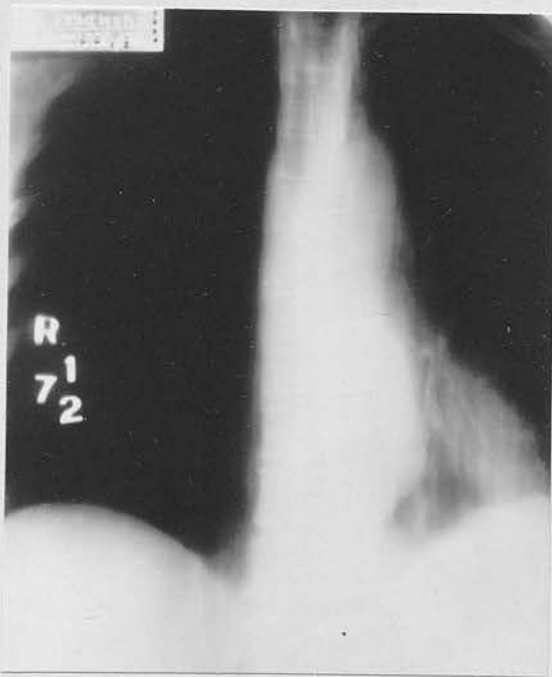


FIG. 7

## DIFFERENTIAL DIAGNOSIS.

As the purpose of this thesis is primarily to describe the features of tumours of the thymus rather than to discuss mediastinal tumours as a group, it has not been considered necessary to embark on exhaustive discussion and illustration of tumours which occur in the mediastinum. It is, however, apposite to discuss certain of the masses which appear in the anterior mediastinum.

Probably the commonest tumour to be seen in the anterior mediastinum is the dermoid group. They frequently exhibit calcification and are not lobulated, but can be confused with rounded thymic tumours. Thus the presence of myasthenia becomes important, and if not present it may not be possible to make a definite diagnosis without removal of the mass.

Anterior mediastinal glandular masses due to lymphoblastoma may resemble thymic tumours and require further examination in the way of blood investigation and other features such as superficial glands or marrow biopsy to enable diagnosis to be made.

A tumour has also been simulated by anterior mediastinal abscess associated with a tuberculous gland, but anterior chest wall swelling and the absence of myasthenia served to exclude a thymic tumour.

Other odd lesions, such as pericardial cysts, may resemble thymic tumours, but the former are usually rounded, whereas many lateral thymic tumours are lobulated or plaque-shaped. The main diagnostic feature, however, is undoubtedly the presence of

myasthenia gravis, when the mass is in the great majority of cases certainly of thymic origin.

Any tumour in the mediastinum, but not in the anterior section, is very unlikely to be thymic, except in the rare instance of an ectopic rest of thymic tissue. There must remain, however, a few odd tumours which may resemble thymic tumours but which in the absence of myasthenia gravis cannot be diagnosed with certainty except by surgical removal.

#### POST-OPERATIVE APPEARANCES.

The operation of thymectomy has to be seen before one realises the degree of adhesion which may be present between the tumour and the surrounding structures, especially the pericardium and the pleura. The radiographs taken before operation may give no accurate indication of the degree of fixation of the tumour, although the tomographic films which we carry out are of value in this respect.

As a result, certain complications may and often do occur during the operation. These are:-

(1) Mediastinal haemorrhage and effusion. This is an universal occurrence after thymectomy and varies considerably in extent. The mediastinal shadow is enlarged towards both sides. It is important to realise that the effusion may increase for a day or two after the operation before it begins to subside. It usually does so without undue distress to the patient or surgeon.

(2) The pleura is frequently accidentally incised during the mobilisation of the tumour and so a pneumothorax is an occasional sequela also, but it is seldom of any great extent and clears up

fairly quickly.

The pneumothorax may be a hydropneumothorax, but the amount of fluid seen is usually not very marked and is rapidly absorbed.

If the patient is X-Rayed within 24 - 48 hours of the operation, air is always seen in the anterior mediastinum in the lateral view. (Figs. C.D.E.)

#### EFFECT OF RADIOTHERAPY.

There has been much controversy regarding the effectiveness of radiotherapy in myasthenic patients with tumours.

In St. Bartholomew's Hospital, it has become routine to give a course of pre-operative radiation to tumour patients, and to postpone operation for several months until the full effect of radiotherapy has taken place.

Most American reports have been unfavourable as regards the response of the tumour, and Seybold states that of twelve patients irradiated ten showed no change in size after the treatment. In one only could definite decrease in size be seen. The clue to this is in the statement by them that in the doses employed no change took place in the microscopic picture, but the report of Reid and Marcus (1949) states that in every inoperable tumour a course of X-Ray therapy should be given.

Our experience is that at least 50% of tumours show decrease in size, and some of the smaller tumours have almost completely disappeared radiographically. (See Cases 1.4.5.13.15.17.)

The larger tumours are sometimes less affected as regards size, and this is due probably to the fibrous, cystic and calcific

ILLUSTRATIONS

FIGS. C, D, E.

Fig. C. Pre-operative chest film of patient suffering from myasthenia gravis.

Fig. D. Antero-posterior post-operative film of same patient, showing the broadened upper mediastinal shadow.

Fig. E. Lateral post-operative film showing air in the anterior mediastinum.

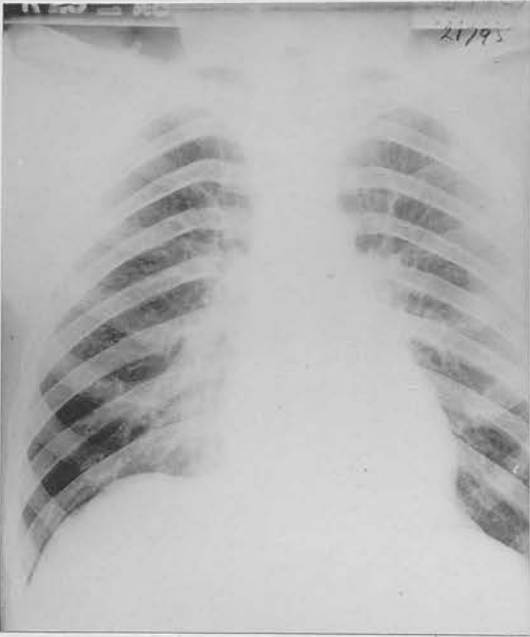


FIG. C



FIG. D

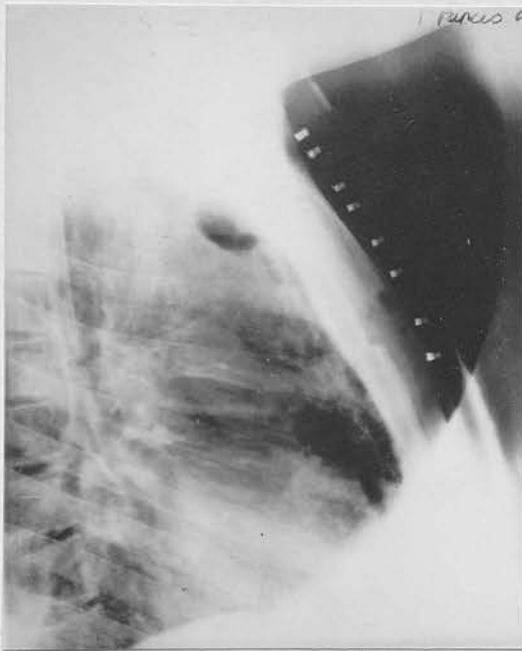


FIG. E



changes which tend to predominate in these larger tumours. Nevertheless, there are marked changes in the cell constituents after a course of irradiation, and most of them become degenerate and structureless, to such an extent that detailed microscopic study was impossible.

It is obvious that, in our series, the dosage applied to the tumour is much greater than it has been the custom to apply elsewhere, and especially in the U.S.A., whence most of the reports to date have emanated.

### D I S C U S S I O N

It is many years since the association of myasthenia gravis and thymic tumour was first observed.

Sporadic reports of further cases occurred, but it has only been since the introduction of thymectomy in myasthenia gravis that accurate figures of the association of the two conditions have been elicited. The main series have been at the Mayo Clinic and at St. Bartholomew's Hospital, where special interest has been shown in this disease.

From figures to date it is apparent that tumours are present in approximately 13% of myasthenics. It is also apparent that the age group of tumour patients is higher than that of non-tumour myasthenics in general.

It is of general interest to speculate on the possible development of non-myasthenic tumour patients into myasthenics, and it would appear that they do so. To serve as an example, Case 8 as reported had shown myasthenic symptoms for a short time, although it was obvious from the size and appearance of the tumour

that it had been present for many years.

Nor does the failure of thymectomy to cure myasthenia in many cases necessarily invalidate the sequence, as irreversible changes may have been produced in the response of myo-neural junctions which prevent cure being produced by thymectomy alone.

It is not, therefore, a valid deduction to make that because of failure to cure by removal of the gland, there is no connection between the tumour and myasthenia. Surely the high percentage of tumours in myasthenia is enough to indicate the presence of some connection between them.

In my own series, a very small tumour found at operation but not shown radiologically proved to be a chondroma with no thymic connection. All demonstrated "tumours", with one exception, have been thymic in origin.

Some thymic tumours are not associated with myasthenia when discovered, but also many tumours primarily reported as thymic have obviously been of other origin. Bronchial carcinomata, lymphadenoma, teratomata and metastatic tumours have all been labelled thymic in the past. Pathologists are now clearing up the variability of pathology of thymic tumours, and can with considerable certainty differentiate secondary from primary tumours of the gland and so eliminate many cases which in the past would have been classified as thymic. This has led to a much better and more accurate assessment of the pathology of these tumours and of their frequency in myasthenia gravis.

There is no infallible way of diagnosing the presence of a thymic tumour in a patient, but at St. Bartholomew's Hospital all myasthenics and suspected myasthenics have the mediastinum thoroughly

explored radiologically to see if a tumour is present. A tumour in this area can confidently be regarded as thymic and the prognosis is thereby more grave. Patients with tumours often have more severe symptoms, and require pre-operative irradiation as well as very careful medical supervision and control before, during and after the operation. It is therefore necessary to be meticulous in the search for a tumour. Seybold states that the presence of a tumour cannot be diagnosed clinically unless the patient has signs of mediastinal pressure, venous obstruction or pain in the chest, when a tumour with local spread may be presumed to be present. This, however, should be confirmed radiologically.

It is now certain that patients with tumours are much more difficult to control, especially when the operation is being carried out, as they are prone to the so-called myasthenic crisis which may produce sudden flooding of the lungs with secretion, or acute respiratory arrest.

The series of tumour patients which it has been my good fortune to examine has enabled a special study to be made of these cases.

The decision that tumour patients should be irradiated before surgical treatment is contemplated has placed on the radiologist the responsibility of ensuring accurate diagnosis. I have therefore evolved a technique which is not too complicated but which has proved very reliable in practice.

The procedure therefore is to:-

- (1) Screen the patient carefully.
- (2) Take lateral and postero-anterior chest films.
- (3) A localised soft tissue film of the anterior mediastinum in the lateral view.

(4) Tomographic films - usually in the lateral position, but in certain instances where the lateral tomographic films do not demonstrate the tumour adequately, I find that those taken in the postero-anterior position may do so.

I am convinced that this technique has greatly improved the accuracy of diagnosis, and so far have erred rather on the side of commission than of omission.

One of the lateral tomographic films of a patient who was suffering from myasthenia gravis showed a small rounded mass in the anterior mediastinum (Fig. D). This was diagnosed by me as a small thymic tumour. The patient eventually came to post mortem, as she had two malignant tumours in addition. There was no thymic tumour, but a hard fibrotic gland was found close to the thymus. The patient had had a course of irradiation which alters appearances markedly, but there seemed no indication of a remnant of thymic tumour.

Time alone will show if the method is sufficient to enable us to discover all tumours. Few methods are infallible and the technique is dependent on mechanical methods; the quality of films is much impaired in very stout individuals and in such patients as these mistakes may well be made.

Comparison with cases so far reported has, I feel confident, increased the accuracy of diagnosis, and has also been of great help in demonstrating the extent of the tumour, both for purposes of irradiation and of operation.

T A B L E I.

INITIALS	AGE	SEX	DURATION OF SYMPTOMS	TYPE OF TUMOUR	CALCIFICATION	SIZE	RESPONSE TO DEEP X-RAY THERAPY	OPERATIVE REMOVAL
1. D.L.	39	M	1y 4m	Lobulated	-	+	+	-
2. G.F.	37	F	3m	Plaque	-	++	+	-
3. V.B.	58	M	3m	Lobulated	-	++	+ -	+
4. H.W.	52	M	1y 1m	Spherical	-	+ -	++	+
5. E.B.	53	F	4y 6m	"	-	+ -	-	
6. G.P.	31	M	6m	Lobulated	-	+++	Not treated	+
7. A.K.	38	M	3m	"	-	+	+ -	+
8. N.T.	40	F	1y	"	-	++	+	-
9. M.B.	57	F	2y	"	-	++	?	+
10. G.S.	48	M	2y	"	+	++++	++	-
11. G.G.	69	M	2y	"	++	++++	-	-
12. F.L.	36	M		Plaque	-	+++	Not treated	-
13. F.G.	52	F	1y 2m	"	-	+ -	+	-
14. F.W.	41	M	8m	"	-	++	++	+
15. M.E.	57	F		"	++++	++	-	-
16. P.H.	40	M	3y	Spherical	-	++	-	+
17. E.S.	51	F	3y 8m	Lobulated	-	++++	++	-

ANALYSIS OF TABLE I ELICITS THE FOLLOWING FACTS:-

1. The age range for tumour patients is from 31 years to 69 years, with an average age of 46.
2. There is no appreciable sex preponderance.
3. Whilst a few patients have long histories, the indication is that most patients have fairly short histories with rather rapid deterioration in their condition, but there is no real correlation between length of history and size of tumours. The average length of symptoms was eighteen months.
4. The tumours tend in the main to be lobulated, as half of those so far encountered have shown this feature. It may therefore be adduced that a lobulated anterior mediastinal tumour is likely to be thymic in origin. The other half were equally divided between rounded and plaque-like tumours.
5. Calcification is not an uncommon feature, being present radiologically in three tumours, and even more frequently on microscopic examination.
6. The size varies greatly and may be very small, or extremely large; in the latter case lobulation is frequent.
7. Most of those treated by X-Ray therapy responded to the treatment, but certain patients who were too advanced failed to be influenced and rapidly progressed to a fatal termination, e.g. G.G. Case 8.
8. Contrary to the opinion of Seybold, a tumour may well be suspected clinically in the absence of chest pain, as it is found that patients over thirty years of age with a short history and rapid deterioration in their condition are likely to have a thymic tumour.

## CONCLUSIONS

1. There is a close relationship between the thymus gland and the occurrence of myasthenia gravis, which is strengthened by the fact that tumours occur in the thymus in approximately 13% of myasthenics.
2. There is no relationship between the size of tumour present and the duration of symptoms, but in general it can be said that the more rapid the progress of the disease, the more probable is the presence of a tumour.
3. The tumour is frequently associated with an atrophic thymus.
4. Wide variation is seen in the position, size and shape of the tumours, which may be round, plaque-shaped or lobulated. The plaque-like type is the most difficult to diagnose, as it is often superimposed on the great vessels or hilar structures, and can be very difficult to dissociate from them.
5. The tumour group of patients suffering from myasthenia is in general higher than that of the non-tumour group, the average age at the time of discovery of the tumour being forty-six years.
6. These tumours are not truly malignant as, so far, they are known to metastasise only locally within the thorax. No proved distant metastases have yet been discovered.
7. Considerable improvement usually follows a course of radiotherapy if sufficient doses are given.
8. Accuracy can only be achieved by fluoroscopy, films in the postero-anterior and lateral positions and tomographic exploration of the mediastinum.
9. In general, an anterior mediastinal tumour in a myasthenic

patient can be regarded as a thymic tumour.

10. It is highly probable that the tumour is present in at least some of the patients before the onset of myasthenic symptoms. Attention has been drawn to this in the individual case histories.

#### S U M M A R Y

1. It appears that many cases previously reported as being malignant tumours of the thymus are probably secondary tumours.

2. Tumours occur in the thymus gland in approximately 13% of patients suffering from myasthenia gravis.

3. Some of these tumours are probably present for some years before myasthenic symptoms occur.

4. So far as can be ascertained, these tumours are only locally malignant, deposits being confined to the mediastinum and pleura, and rarely within the lung.

5. Seventeen cases of thymic tumour in myasthenia gravis are reported, three of which have metastasised locally, i.e. 18%.

6. A special radiological technique has been developed to demonstrate fully the various types of these thymic tumours.



## B I B L I O G R A P H Y

1. Bell, E.R.J. 1917. Nerv. and Ment. Dis. (45.130)
2. Blalock, Alfred. 1941. Amer. Jour. Surg. (54.1149)
3. Blalock, Harvey, Ford and Lilienthal. 1941. J.A.M.A. (117.1529)
4. Castleman, B. and Norris, E.H. 1949. Medicine (28.27)
5. Derow, H.A. Schlezinger, M.J. Persky, L.  
1950. New England Jour. Med. (243.478)
6. Good, Allen. 1947. Amer. Jour. Roent. (57.3.305)
7. Hampton, A.O. 1947. Amer. Jour. Roent. (57.3.312)
8. Harper, R.A.Kemp. The Investigation of Thymic Tumours in Myasthenia  
Gravis. J. Fac. Radiol. In the press.
9. Heuer, G.J. and Andrus, W.D. 1940. Amer. Jour. Surg. (50.146)
10. Keynes, Geoffrey. 1949. Brit. Med. Jour. (ii.611)
11. " " 1950. Personal communication.
12. McBurney, R.P. Clagett, O.T. and McDonald, J.R.  
1951. Proc. Staff Meetings of Mayo Clinic (26.19)
13. McEachern, Donald. 1943. Medicine (22.1)
14. Meggendorfer, F. 1908. Ann. Alle. Krankerh Munchen (13.116)
15. Norris, E.H. 1936. Am. Jour. Cancer (27.421)
16. Reid, H. and Marcus, R. Brit. Jour. Surg. 1949 (36.271)
17. Seybold, W.M. McDonald, John R. Clagett, O.T. Good, Allen C.  
1950. Jour. Thor. Surg. (20.195)
18. Weigert, Carl. 1901. Neurol. Centralb. (20.597)
19. Willis, R.A. 1948. Pathology of Tumours.