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THE LYMPHO-EPITHELIOMATA*

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WE are indebted for the idea and first description of the lympho-epitheliomata to Regaud and Schminke who published independent papers in 1931. It seems that attention was first turned to this class of neoplasm because of an extreme degree of radiosensitivity. This characteristic was coupled with a distinctive histological structure and a certain degree of clinical typicality, which was thought to justify a separate group and name for the neoplasm described. Regaud originally noted a tumour consisting of two elements, a primitive type of epithelium and lymphocytes, and suggested that the association was constant and characteristic, thus justifying the name lympho-epithelioma. Both Regaud and Schminke, in seeking an explanation for this structure of the tumour made reference to the works of Jolly and Mollier in 1911 and 1914 regarding the entity of a normal lympho-epithelium in the pharyngeal lymph collections. Such areas are either directly or distantly associated with the alimentary canal, and the type of structure is well shown in the palatine tonsil (Figs. 1 and 2) where it was pointed out that as well as a close association of epithelium and underlying lymphocytes there was in parts an actual infiltration of the epithelium by the lymphocytes, the two cells bearing a very close relationship, this symbiosis being an essential feature and characteristic of the regions

* A Hunterian Lecture delivered before the Royal College of Surgeons of England on January 26th, 1938.

concerned. In the superficial parts of the tonsil there is a well-marked area of connective tissue between the epithelium and the subjacent lymphocytes, but in the depths of the crypts this interval disappears and the lymphocytes infiltrate the epithelium to a marked degree. They do, in fact, pass through it to be found in the crypts in plugs associated with desquamated epithelial cells and are said to reach the buccal cavity and form the so-called salivary corpuscles. A very similar structure holds good for the lymph follicles at the base of the tongue and the various pharyngeal lymph collections (Fig. 3), the same intense lymphocytic infiltration being found.

The Peyer's patches and solitary lymph follicles of the intestine have been also classified as lympho-epithelial structures and it is true, especially of the larger collections, that the lymphocytes do bear an exceedingly close relationship to the epithelial coat. Under such teaching the appendix must be included in the same class but altogether the idea as applied to the intestine is rather unsatisfactory. A difference must be appreciated between the single-layered columnar-celled epithelium found there and the squamous elsewhere.

A significant fact is that no one has as yet described a lympho-epithelioma of intestinal origin.

An appreciation of its mode of development will suggest that the thymus belongs also to the group of lympho-epitheliomatous organs but this will be left for the moment to follow the consideration of the tumours originally described.

The original description given by Regaud was expanded by Jovin in 1926. He discussed the histology under two headings : an epithelial element and the lymphocytes.' The former was described and illustrated (Fig. 4) as a bulky mass of cells with poorly delimited cytoplasm forming, at times, a syncytium. The nuclei were clear and pale but with a definite outline, sometimes lobulated or notched and usually contained one or two nucleoli. Mitotic figures were fairly frequent. Constantly intermingled with the epithelium were the lymphocyte-like cells breaking it up in parts into a network. The proportion of the two elements varied considerably ; in some parts the small cells were almost absent, making the study of the epithelium particularly easy ; in other parts, however, they predominated to such an extent as to obscure the epithelial structure and give the appearance almost of a lymphosarcoma. The connective tissue stroma of these neoplasms was described

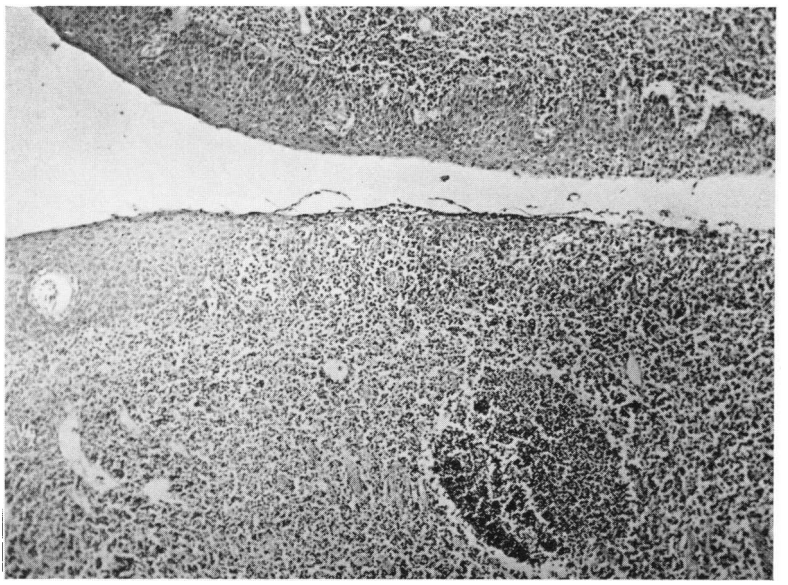

FIG. 1.

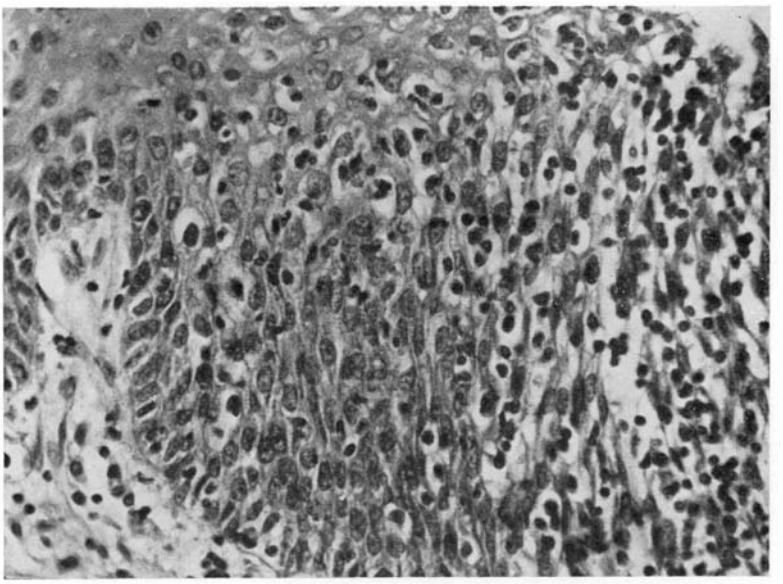

FIG. 2.

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as a very variable element especially rich in cells, all types of wandering cells being described. The line of demarcation between the epithelial sheets or strands and the stroma was ill-defined and although no actual intermingling was noticed, at some points at the edge of the epithelial sheets signs of penetration were found in the remnants of connective tissue lying in among the extending cells. Special staining did not show blood vessels or find connective tissue reticulum inside the sheets of cells.

The small lymphocyte-like cells were believed to be real lymphocytes. They were small with rich nuclei occupying nearly the whole cell and it was suggested that they had penetrated from the connective tissue stroma where they were constant and predominant. They could be found in various stages of migration and sometimes had been fixed in amœboid shapes. Why they should infiltrate and live in the epithelial element was not obvious but Jovin suggested that it was a special feature of the epithelium in that it exerted a type of chemiotaxis towards them. For evidence of this specificity he cited the cases in which the stroma contained many other wandering cells such as polymorphs and eosinophiles of far greater migratory capacity than the lymphocytes and yet they alone penetrated the epithelium. As an extra facilitating feature for this penetration the close relation of epithelium and stroma previously mentioned was referred to. The only exception to this lymphocytic infiltration is in the case of infection and ulceration when polymorphs do appear in the epithelial element. Although he had not any personal material Jovin put forward as evidence of the specificity of this infiltration the fact that in certain described cases, notably that of Derigs in 1923, the same structure was found in distant metastases even in organs not particularly rich in lymphocytes. As a final point it was stated that the characteristic structure occurred only in tumours found in certain locations with the one feature in common that one finds normally in these regions, a similar type of normal structure previously described and designated as lympho-epithelium. The tumours then appeared to Regaud and Jovin as epitheliomata having as a special characteristic an attraction for lymphocytes with resulting infiltration. The lymphocytes, although not fortuitous in their presence, were not believed to take part in the active neoplastic features of the tumour. The idea of a complex

epitheliosarcoma was discounted and the tumour was looked upon merely as perpetuating, to some extent, in its structure the structure of the normal area from which it arose and thus justifying in every way the name " Lympho-epithelioma ".

Schminke published a series of five cases in the same year as Regaud and his descriptions of the histology seem to correspond. It appears that he was first struck by the detached appearance of the lymphocytes and actually tried to wash them out of his sections but, whether or not from failing to do so, he ended by suggesting the possibility of the lymphocytes being active factors in the neoplasia. There has been a tendency among subsequent authors to look upon these two descriptions as different and to speak of a Regaud type and a Schminke type. Ewing in 1929, regarded Jovin's cases as true lympho-epitheliomata but thought that Schminke's cases were more closely allied to the transitional-celled carcinomata. Cappell, in 1935, tried to follow out the same idea but saw no worth-while reason for so doing. These tumours, as do others, show great variations in structure both as regards the degree of structural development of the epithelial cells and the amount of lymphocytes present. If it were accepted that the tumour was truly epitheliomatous and the special features were inherited characteristics from the parent organ, then it might be expected that variations would occur, as for instance does keratinization, and might even be of value in grading them with regard to probable malignancy.

Apart from confusions due to variations in the class, there is great difficulty in confusion with other similar tumours and there is no doubt that the histological diagnosis can be extremely difficult. Ewing pointed out the difficulty of diagnosis from the transitional-celled carcinomata, and previous authors, including New in 1922 and Quick and Cutler in 1927, had apparently not thought the lympho-epitheliomata worthy of a special class and included them in the epitheliomata as such or as transitional-celled carcinomata. Much of the confusion has arisen from a difference in point of view. The pathologist will attempt definite histological classification and derive great interest from ætiological considerations, but the clinician is concerned rather with behaviour as such in the living organism, and attaches paramount importance to grading as to malignancy with the treatment and prognosis hanging thereon. Berven, in a personal communication, although admitting the entity

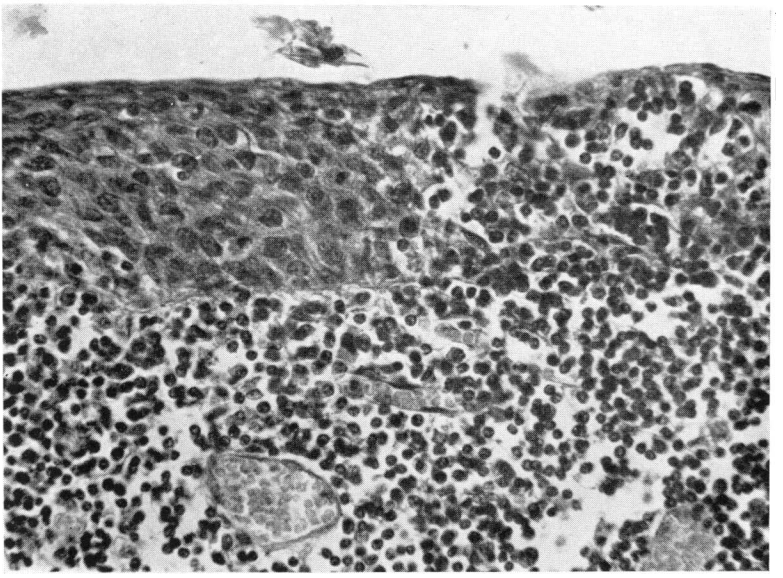

FIG. 3.

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in his published work, states that in Stockholm the tendency is to think of the lympho-epitheliomata as more closely allied to the sarcomata and being really a class of the reticular or endothelial-celled sarcomata. This view can be said to be popular at the moment with pathologists, and a group has emerged known as the retocelled sarcomata. A recent paper from the laboratory of the Royal College of Physicians in Edinburgh ends with the view that the lympho-epitheliomata should not be looked upon as an entity but classed either with the epidermoid carcinomata or the reticulum-celled sarcomata, which are in fact lymphosarcomata.

The possibilities, then, which we have to study are firstly the original idea in which the neoplasm is looked upon as purely epitheliomatous—in which the epithelium is little differentiated and yet which retains a characteristic of attracting lymphocytes as a special feature; secondly, the tumour may be considered as an epitheliosarcoma, the epithelial element being accepted as such but the lymphocytes being looked upon as neoplastic cells, and thirdly, a reticulum-celled sarcoma where the whole structure arises from the primitive mesenchymal cell, giving rise to the reticular or endothelial elements and the lymphocytes. The second view has been practically discounted and the first and third only considered. In both cases the presence of lymphocytes, whether normal or neoplastic, may be looked upon as evidence of differentiation and prognosis modified accordingly. It does seem that where the structure of the larger cells is regular and distinct, the lymphocyte content is high, but in either case enhanced differentiation would account for this. A real deciding point is going to be that of specificity of situation, for if these tumours are really reticular-celled sarcomata they should be found wherever there are lymph nodes as primary tumours. On the other hand, if in reality lympho-epitheliomata they should be found only in regions where lymph collections have a covering epithelium—the areas previously described as lympho-epithelium. Time alone will decide this point.

The original name, or even a modification to lympho-endothelioma, if the mesoblastic origin is demanded, does, however, seem to convey some degree of valuable information, always remembering that diagnosis is very difficult and class overlapping inevitable. An illustration is given (Fig. 5) which may be typical, and in diagnosing such a case it would seem

that the structure denotes a lesser degree of malignancy than would be expected in cases showing much less definity of the large cells and the absence of lymphocytes. In the absence of lymphocytes the diagnosis of transitional-celled carcinoma or sarcoma would have to be made.

In justifying the entity of lympho-epithelioma one must realize that the idea of lympho-epithelium must be accepted without question and it seems that even this may be doubted. If the infiltration of the normal epithelium is not a special feature of that epithelium but a migration of the lymphocytes due to some protective phenomenon, then the whole idea falls to the ground and the neoplasms must be looked upon as reticulum-celled sarcomata, that is if the lymphocytes are to be looked upon as an essential feature of the tumour. Confusion with other tumours is unavoidable and many rapidly growing undifferentiated squamous carcinomata showing some degree of lymphocytic infiltration, probably reactionary in nature, are indistinguishable on biopsy.

We may, then, accept the idea that one finds a class of tumours consisting of a large fairly poorly differentiated cellular structure and characteristically infiltrated with lymphocytes, a feature essential for the definition but variously explained. Or we may refuse to accept the lymphocytes as anything more than a natural reaction upon the part of the host, in which case the lympho-epitheliomata do not exist as such but are cases belonging to the squamous carcinomata or the sarcomata. It seems that the point cannot be settled until we know more about the normal genesis of lymphocytes and have much more information concerning the neoplasm occurring in lymph nodes generally. During the following clinical consideration the name "Lympho-epithelioma" is used but it must not be thought that the entity is accepted. The views are based upon cases which seem to be as near as possible to the original description but there are many more cases which have to be left out and, from the pathological point of view, it does appear that the original idea is not justified in practice.

Clinical Characteristics

From the foregoing pathological considerations the difficulties in diagnosis will have been appreciated, yet there has arisen in clinical circles an idea that the class manifests typical

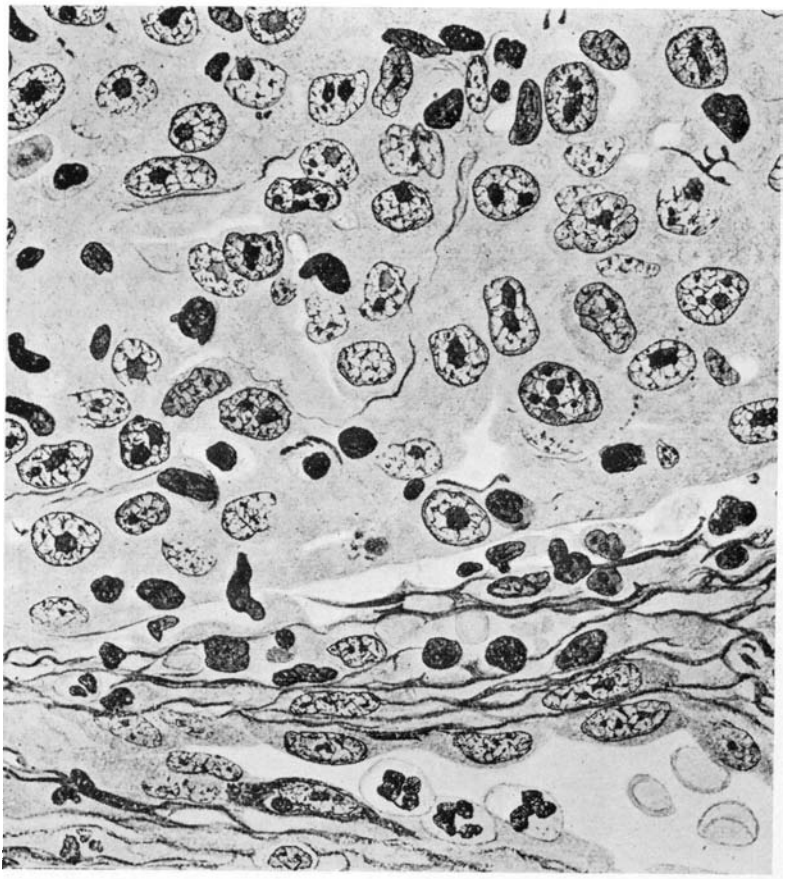

FIG. 4.

The illustration in Jovin's article in *Annal. de Maladies de l'Oreille*, etc., 1926, xlv, 729.

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clinical characteristics. At the very outset of a study of these clinical characteristics it must be stated that although the lympho-epitheliomata do possess certain outstanding features they are by no means confined to this class alone but are shown equally well by any highly malignant, rapidly growing and radiosensitive tumour such as transitional-celled carcinomata of little differentiation, or sarcomata and even by lymphadenoma. Diagnosis must rest upon histological examination and is of great importance regarding prognosis. It may be said that the features shown are : a tendency for early spread to adjacent lymph nodes whilst the primary is still small and obscure, the great radiosensitivity of the lesions produced and, after treatment, a habit of distant metastasis to vertebral column and abdominal organs.

The Primary Lesion

Apart from the thymus, which will be discussed later, the neoplasm arises as a rule in the tonsillar region or naso-pharynx, although cases have been described as occurring in the hypopharynx and the thyroid. The visible primary only will be dealt with at present, those occurring in the obscurity of the naso-pharynx being discussed later.

The lesion is described by Jovin as a soft medium-sized fungating neoplasm, which does not reach the size, unless following injudicious surgery, which is usual for the sarcomata and which tends to displace rather than infiltrate the surrounding structures. It is usually somewhat ulcerated and bleeds a little when touched, but is not painful. There is often a history of sore throat such as would be expected with a rapidly growing neoplasm and in consequence a diagnosis of inflammatory change is not uncommon. Subsequent authors seem to have copied or modified this description, but Ewing and Boyd describe a type which begins and spreads deeply in the structures concerned, only appearing on the surface and ulcerating later in the course of the disease. Berven, in describing his own cases, says they reach a size equal to or even larger than the sarcomata. They have a granular appearance and ulcerate late, and when they do so it is rather a deep cleavage, an appearance being produced which is more characteristic of the epitheliomata. In the case of the tonsillar growths the primary is usually evident but even so cannot be diagnosed clinically as lympho-epithelioma. Much, however,

regarding malignant grading should be learnt from the primary lesion and of course from any metastases which may be present. In my personal experience a case which appeared to be a very extensive squamous-celled epithelioma proved on biopsy to be a lympho-epithelioma and responded very well to X-ray therapy. On the other hand, cases have been encountered which are more suggestive of a rapidly growing sarcoma and have behaved as such. Where the primary lesion is present alone it is typical only of a rapidly growing neoplasm, but in the case of the lympho-epithelioma is usually associated with a condition which is often the first sign of the disease ; namely the metastases in the regional lymph nodes.

Lymph Node Metastasis

Lymph node metastasis has been a practically constant feature in all published cases. Here again it is not unique in the lympho-epitheliomata but occurs in tumours of similar malignancy. The adenopathy is usually bulky and situated in the upper deep cervical group of lymph nodes. It is described by Jovin as usually bilateral with one side predominating, but this is not a constant feature. The mass is firm but lacking in the hardness of squamous-celled carcinoma. Deep fixation and lack of definity in its outline are common, but involvement and ulceration of the overlying skin does not occur. This habit of early adenopathy and obscure primary growth has given rise to much confusion in diagnosis, such cases often being treated as tuberculosis or lymphadenoma, and sometimes after biopsy diagnosed as primary lymph node or branchiogenic neoplasms. Ewing, in a personal communication, writes that he believes the entity of primary cervical lymph node endothelioma must be accepted, but that he is tending more and more to class such cases as lympho-epitheliomata in which the primary has not been discovered. New, in 1929, writing of malignant tumours of this region, noted that of his seventy-nine cases fifty-one had cervical adenopathy, and that of these fifty-one, eighteen had had operations upon the neck in ignorance of the presence of the primary neoplasm.

The great point about the mass of neck glands is its amazing response to irradiation. In many cases it has almost disappeared before the completion of the full course of therapy, and it was this point which really first drew attention to this

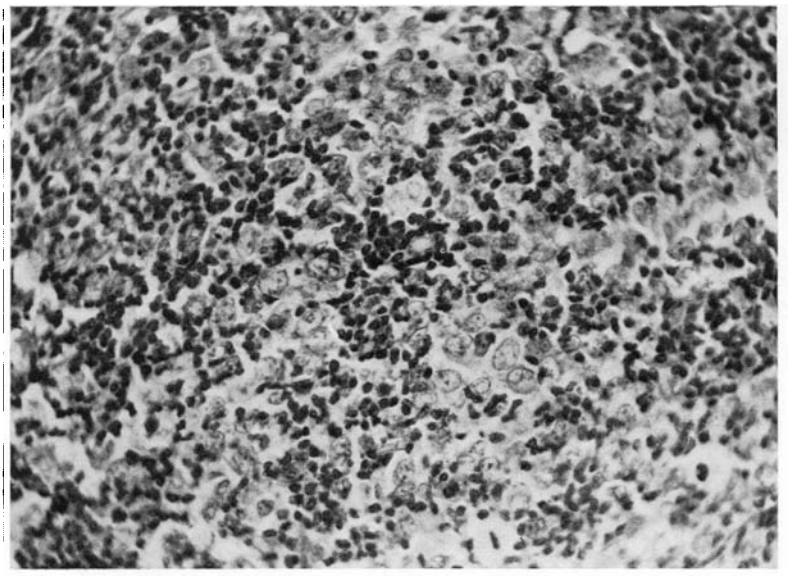

FIG. 5.

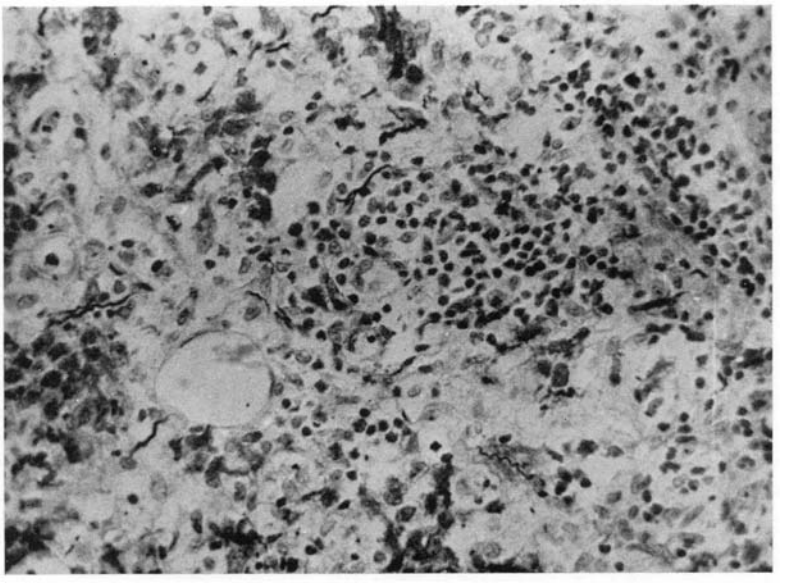

FIG. 6.

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class of tumours. It was at one time thought that this amazing radiosensitivity was typical and diagnostic of lympho-epitheliomata but experience has shown that, although typical, it is not diagnostic.

Distant Metastasis

A final point is the terminal feature of distant metastasis in many cases which have terminated fatally following treatment. Full autopsy information is rare, but such cases as are reported reveal a tendency to abdominal lymph node and liver involvement and a peculiar disposition to metastasis in the vertebral column. A very full case was described by Derigs in 1923 and the signs and symptoms of the latter feature have appeared at the end of many other cases described in the literature. Kienboch and Selka, in 1935, described the X-ray appearances of the osseous metastases and describe a case of multiple skeletal deposits. This question is not of great practical interest but is a feature to be borne in mind when thinking of prognosis.

Pathological examination of these distant metastases would be of great interest and value but unfortunately such opportunity has rarely arisen. One personal case had an apparent cutaneous deposit excised and examined, revealing the structure shown (Fig. 6) and although this might possibly be considered to be a lympho-epithelioma the primary lesion, Fig. 7, shows a picture of great malignancy probably sarcomatous and the case behaved as such. She was a female, aged 57, who died four months after the application of radium to a primary tonsillar neoplasm, followed in four months by X-ray therapy for cervical adenopathy, from massive recurrent deposits in the glands of the neck and metastasis in her cervical vertebrae.

Incidence

It will always be difficult to determine the relative frequency with which the lympho-epitheliomata occur owing to differences in opinion as to diagnosis. Schminke says that they are not so rare as might be thought and that he had no difficulty in collecting his five cases. Ewing, in a special effort to arrive at figures for the relative degree of incidence for tumours in the regions discussed, made a study of 300 cases and gives the following figures :

	Tonsil (200).	*Naso-pharynx* (100).
Squamous	72%	30%
Transitional	12%	37%
Adeno-cystic	0%	4%
Lymphosarcoma ..	9%	15%
Lymphoepithelioma ..	4%	11%
Adenoma malignum ..	0%	3%
Unclassified	3%	0%

Great difficulty was experienced in dividing up the lympho-epitheliomata, the transitional-celled carcinomata and the lymphosarcomata. Boyd thinks that the lympho-epitheliomata should be considered as a sub-group of the transitional-celled carcinomata, and that the total incidence in mouth and pharynx is about 10 per cent. of all malignant tumours. Berven, considering malignant neoplasms of the tonsil, classified his cases as :

Carcinoma	50%
Sarcoma	36%
Lympho-epithelioma	6%
Malignant mixed tumours ..	5%

Later writers have been concerned rather with discussions regarding the justification or otherwise of the entity than with figures of incidence based upon its acceptance. It seems that the type of tumour is rare and vague, statements that it is common if looked for are not really based upon fact.

Age and Sex Occurrence

The commonest age seems to be middle or late life, although Ewing states that a similar or identical tumour occurs in young people at about 15 years of age. Derigs' patient was only 15 and the present writer encountered a case aged 13 years when first seen (Fig. 8). Harvey, Dawson and Innes believe that cases in very young patients are really lymphosarcoma and quote cases in patients aged 8, 10 and 11 years. Previous to this paper no mention is made in the literature of any cases occurring in patients younger than this and it seems that the involuting or involuted lympho-epithelial organ is the most favourable one for this type of neoplastic development. The sarcomata usually appear earlier in life during the growth

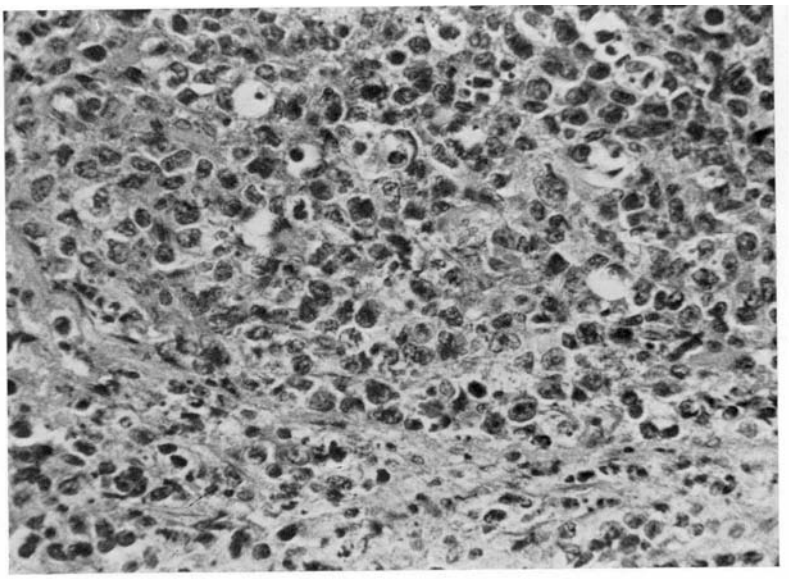

FIG. 7.

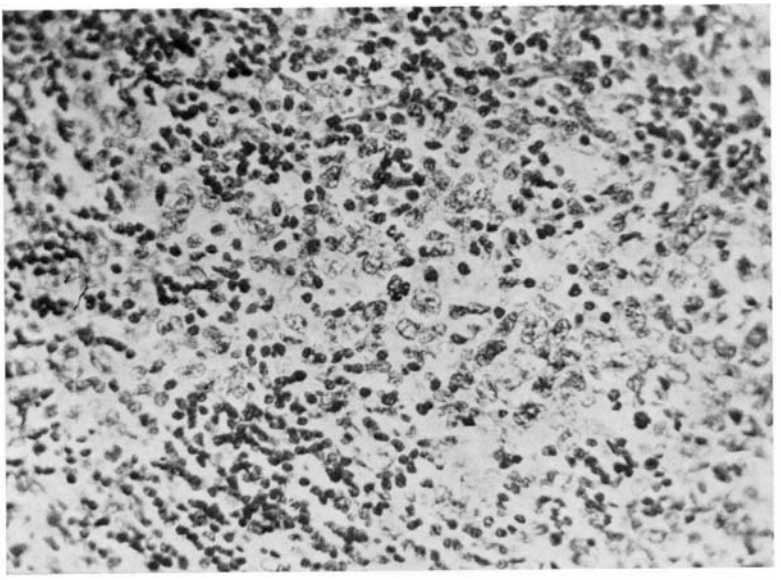

FIG. 8.

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period and although some sarcomata do occur in late life and thus a possibility of confusion arises, extreme youth in a patient should eliminate lympho-epitheliomata if the original conception of its nature be correct. In this point the tumour seems more particularly allied to the epitheliomata which have a tendency to occur in involuting organs. The tumour seems to be slightly commoner in males and as a general statement it seems that occurrence is unlikely during the period of development and greatest activity of the lympho-epithelial organs.

Naso-pharynx

The interest of the lympho-epitheliomata occurring in the naso-pharynx lies not in their pathological entity but in the fact of their anatomical position giving rise to an interesting symptom complex.

I do not wish to say much about it as the syndrome is, or should be, well known. The primary growth, occurring in the lateral naso-pharynx, often around the origin of the Eustachian tube, may declare itself by the production of unilateral deafness—trigeminal neuralgia or various nerve palsies. Later, spread up through the foramina at the base of the skull may produce further nerve involvement. To this must be added, especially in the present case, the presence of early cervical adenopathy. In fact it seems likely that the adenopathy would be the first sign of the neoplasm and the primary growth located then only if looked for. Later, if no treatment be given, the primary growth would progress and give rise to the syndrome associated with tumours in the naso-pharynx. It must not be supposed, however, that the case is hopeless when the syndrome is produced, as much of the damage is done by pressure—as is the case with many malignant tumours that grow so quickly that they have not time to infiltrate but just penetrate. It is becoming well known that when malignant disease invades bone, cure by irradiation becomes practically impossible unless massive necrosis is produced. In the case in question, however, the spread is in the foramina and the neoplasm does not seem to involve the bone structure itself. This interference with nervous function by pressure rather than by direct infiltration in a way explains the variation in the degree of palsies produced throughout the course of a case—transient improvement sometimes being noted.

The syndrome has been well portrayed since Trotter's original description in 1911 and in 1935 Ch'eng published seven cases of lympho-epithelioma of the naso-pharynx which had given rise to varying degrees of the typical syndrome. All cases were late ones and did not respond to treatment and it seems that in the case of the tumours of high malignancy, declaration by metastases will occur before that by local damage and that for treatment to hold out any hope of success a diagnosis should be arrived at before the characteristic syndrome is produced.

Diagnosis

From the foregoing it will have been noted that accurate diagnosis of lympho-epithelioma is impossible without biopsy, and even then is sometimes doubtful. Clinical diagnosis should reveal only a rapidly growing type of neoplasm and even this is not always certain. It is based principally upon the early appearance of bulky neck glands, probably the first sign, but accompanied—if looked for—by an obvious primary tumour in most cases. If an absolute diagnosis is needed or a full study of the cases desired, biopsy will be required. This raises the vexed question of possible danger to the patient by enhancing the possibility of metastasis, but owing to the extremely important information received, essential for a proper conduct of the case and full and fair opinion regarding prognosis to the patient, it must be justified. Berven states that all practitioners in Sweden have been circularized asking them to refrain from performing biopsy upon doubtful cases, but to send them undiagnosed to the Radiumhemmet when, should this be found necessary, it is immediately preceded by or followed by local irradiation. In this way it is hoped that no possible harm arises, but a warning is sounded that in the case of lympho-epithelioma, biopsy must be performed just before irradiation or immediately afterwards, otherwise the tumour may have disappeared owing to its extreme radiosensitivity. When performing the biopsy, as little local damage as possible should be done, many authorities advocating the diathermy needle. Other authorities have discounted this danger of biopsy and believe that no harm is done. It can only be stated again that it seems essential and that in view of the possibility of harm to the patient some precaution should be taken ; but the evidence that any harm is done seems unconvincing.

The Lympho-Epitheliomata

Previous difficulties in clinical diagnosis are obvious in all papers published upon the subject. Quite a usual feature in the case histories is a story of recent sore throat and many cases were treated as being of inflammatory origin until recognized as neoplasms. As a possible feature in differential diagnosis syphilis, in its tertiary manifestations is best forgotten.

The problem of diagnosis then resolves itself under two headings: the primary and essential one—that of diagnosing the presence of a neoplasm; and the secondary one of determining whether or not that neoplasm be a lympho-epithelioma. If the first is managed well and treated accordingly we have done our duty and may settle the second in leisurely contemplation later.

Thymus

It was mentioned earlier that in the classical descriptions of the normal lympho-epithelial organs the thymus has been considered to belong to that class. From a developmental point of view, it would appear that this is the case, its original outgrowth from the pharynx being essentially epithelial and the lymphocytic infiltration being a secondary feature to the surrounding mesoderm. This would result in an intimate association of epithelium and lymphocytes, as is found in the covering epithelium of the various lymphocytic collections previously described, and hence the formation of a lympho-epithelium. There has been a great deal of argument about this, usually centering round the point whether the stroma of the thymus is epithelial or mesodermal. If the latter view is supported, then all thymus tumours are in reality types of sarcomata. Whilst, no doubt, many are of this type it does appear that some epithelium survives and could give justification to the diagnosis of a lympho-epithelioma.

In 1923 Kneringer and Priesel described a tumour of the thymus and, accepting the view of its lympho-epitheliomatous nature, called their tumour a lympho-epithelioma. This was the first case so described and several others followed, finally the whole subject was well discussed by Wu in 1935 who described a personal case and collected what he decided were nineteen more from a total of 247 thymic tumours described in the literature. Of these nineteen, ten were originally published as lympho-epitheliomata and the others, although published under other names were classified as such by Wu. The paper is of great interest and reveals the information that

the tumours are nearly always benign, and so are frequently discovered accidentally at *post mortem*, and that they are often associated with symptoms of myasthenia gravis. This association of myasthenia gravis and thymic tumours or hypertrophy has been noted before, and it now just remains for someone to make the diagnosis during life and note the effect of excision or irradiation. The illustrations produced by Wu show a varying structure, some sheets suggestive of epithelium being present without lymphocytic infiltration, and one interesting cell is illustrated and described as a prickle cell. Other areas show what was interpreted as an attempt at concentric corpuscle formation whilst, as well, a palisading of cells was noted around perivascular spaces. This structure was considered as evidence in favour of the basic epithelial nature of the tumour and owing to the presence of infiltrating lymphocytes the tumour was diagnosed as a lympho-epithelioma. On histological grounds it does seem that the occurrence of lympho-epithelioma must be accepted and that, although in many ways different from those occurring elsewhere it does at least occur in an involuting organ ; the average age of the cases collected by Wu was fifty-one. Of all these cases, however, only six could be classified as malignant, and of these only three had metastases, a very different story to that of similar growths in the oro-pharynx.

Treatment

In all the highly malignant types of neoplasm with a special predilection for early metastases it has been found that surgical extirpation holds little or no hope of cure. The lympho-epitheliomata are no exception to this rule and, in addition, occur in places which owing to their inaccessibility are particularly unsuited to radical surgical extirpation. In the naso-pharynx, surgery is quite out of the question and, apart from Trotter's early attempts, has never been considered as a form of treatment. The tonsil, when the seat of lympho-epithelioma or some allied tumour, is frequently attacked surgically but usually under a mistaken diagnosis and enucleation only is performed. Even when the growth has appeared to be quite confined to the parent organ, rapid local recurrence has been the rule. Whether any harm is done by attempts at surgical removal before radiotherapy is applied, apart from the necessary delay must, in spite of definite statements in the literature, remain a little doubtful. As a definite attempt at cure,

knowing full well the nature of the disease present, it can only be strongly condemned ; but if done in error and followed by active radiotherapy before recurrence takes place, it does not seem that great damage will result. From a general point of view it is of great interest that Broders, in grading epitheliomata in malignancy according to their degree of differentiation, placed over 60 per cent. of tonsillar neoplasms in Grade 4 and said that he had not found any case cured by surgical extirpation alone.

The patients are sometimes presented as a problem of cervical adenopathy. As has been mentioned, every possible attempt should be made to find a primary growth but if, failing this or disregarding it, a mass of lympho-epitheliomatous lymph nodes are excised, almost immediate recurrence will occur, probably with increased malignancy. It can be stated definitely then that surgery holds no place in the treatment of lympho-epitheliomata, and under the heading of surgery one must include excision by diathermy. The one possible exception is when the primary growth is in the thymus, and nothing is as yet known as to what would happen or whether these tumours are as radiosensitive as they are elsewhere.

Thus one is dependent for treatment upon some form of radiotherapy and the available means are X-ray, interstitial radium, surface radium and tele-radium. Many of the earlier cases were treated with interstitial radium or surface application, but it was found that although the primary growth disappeared in most cases, rapid spread to adjacent lymph nodes was the rule. Nowadays it is deemed advisable to irradiate a large area owing to the difficulty of judging the limits of spread of the growth. The characteristic response is early and permanent regression of the primary and adjacent lymph nodes if present, and then possible distant metastases later. It may be thought generally that if a local recurrence occurs, the treatment has been deficient, but distant metastasis is a problem not easy or perhaps possible to solve.

Jovin states that some earlier cases were treated with interstitial radium but that in the light of modern knowledge it has been abandoned and now all cases are treated by X-ray. Berven likewise condemns interstitial radium therapy, and advocates a combination of internal surface radium and X-ray or tele-radium, concluding that in view of the extreme radiosensitivity present X-ray is simpler and quite adequate. The

general opinion is that the lympho-epitheliomata do not require the hard rays of radium or high voltage X-ray, quite ordinary X-ray therapy being sufficient.

Jovin thinks it advisable to give the dose in as short a time as possible, up to about two weeks, but mentions that it may be necessary to spread it over three weeks or so to avoid the great general reaction produced by the rapid disintegration of the neoplasm. This has been a common finding with all highly radiosensitive tumours. Berven, after trying most methods, now relies upon X-ray therapy, assisted if necessary, by local surface radium. Bauman-Shenker also uses X-ray therapy and finally destroys any remnants of the primary growth with radium. He mentions that the rapid appearance of a good mucosal reaction is favourable to a good prognosis, and advises giving the full dose in as short a time as possible.

This treatment is applicable to an uncomplicated primary growth or one with local lymph node metastases, in which case the whole is included in one or several fields of treatment. Attempts have been made to treat the distant metastases when these have occurred in cases in which the primary and local lymph node deposits have been cured, but without success. No mention has been found of attempts to treat distant lymph node or internal organ deposits, but Kienbock and Selka irradiated the caseous metastases of their case. The result was apparently only an increased rate of development. This bears out a common finding in cases of extraneous malignant disease spreading in bone. One personal case (Fig. 9) had X-ray therapy for what was diagnosed as supposed hæmangioma of the vertebrae. This type of neoplasm usually reacts well to irradiation, but in the case mentioned the growth was undiminished—a point which further bears out the view that the real trouble was metastasis of the lympho-epithelioma to the vertebrae. If, then, the disease is confined to its parent organ or not has spread beyond the adjacent lymph nodes, the treatment recommended is X-ray therapy given as soon as possible, and the dose kept within a short period of time.

Prognosis

It is said that the untreated lympho-epitheliomata run a fatal course in about two to three years, the end being reached with massive local spread of the tumour. Of the treated cases which have ended fatally, some have pursued the same course,

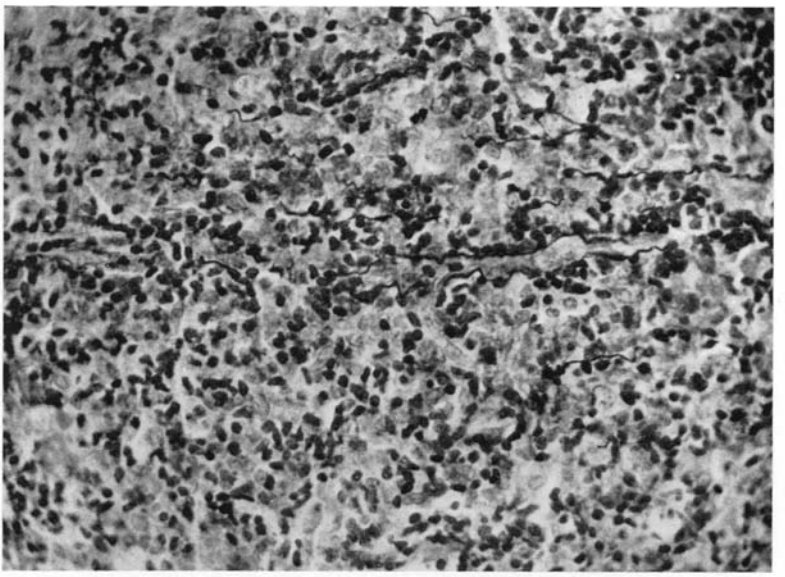

FIG. 9.

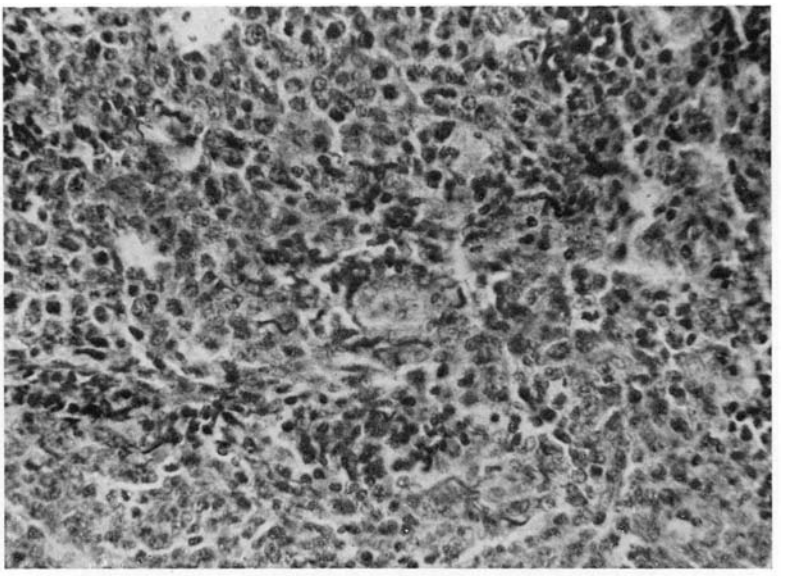

FIG. 10.

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local regression not having been retained, others have not suffered any local recurrence, but died as the result of distant metastasis. The natural life of a tumour is a factor not often enough considered when assessing the results of its treatment, but, as will be shown presently, the lympho-epitheliomata are well worth treating. As to whether such treatment after producing local cure modifies the course of the disease in favour of distant metastasis is a point to which no answer can be given. It is possible that if the untreated cases were followed up as carefully as the treated cases are, or should be, it would be found that many ended in the same way by distant metastasis. In so many cases one is dependent upon relatives' observations for a report.

The prognosis of the treated cases is variously stated in the literature, and some confusion seems to exist owing to premature optimism. Schminke said that the results were good owing to the great radiosensitivity of the tumour and this view has been freely quoted, but it is found that he was speaking only of immediate results and did not follow up his cases. The unfortunate characteristic of distant metastases occurring in internal organs and bones later in the course of the disease, in spite of no local recurrence has been mentioned, and thus one is dependent upon late and not immediate results for prognosis. If the local lesion, speaking of the primary growth and, if present, the cervical lymph nodes as one, responds satisfactorily to the initial irradiation and regresses, it is unlikely that it will recur. If local regression is not obtained, death will soon follow. Having obtained local cure, there remains the possibility of distant metastasis, and this is present up to about three years afterwards.

As has been mentioned, definite and accurate statements regarding prognosis are very difficult to obtain from the literature. Jovin reports seven cases of which only two are alive; one after one year and the other after four years. The others died at periods varying from three months to one year following treatment, three with metastases in the vertebral column.

Berven's most recent figures show:

4 cases treated 1923-27—alive and well at 5 years	75%
9 cases treated 1928-30—alive and well at 5 years	55%

These figures were exactly the same for the three year cure

rate, a point of some importance in assessing a cure, as it may be reliable to base rates on the three year figures.

Of twelve cases published by Cappell in 1934, the result was known in eleven, and of these three were alive at the end of three years and one at two years. All other authors are rather vague in their remarks. Maier says the prognosis is good and quotes Stockholm as getting 55 per cent. of three year cures, and Paris as 45 per cent., but that all reports are not so good. Bauman-Shenker reported twenty-three cases of which eighteen were alive, fourteen symptom-free, but few of which had then passed the three year limit. He notes that four of his patients received the full treatment in one dose, and survived an average of forty-one months, whilst the remaining nineteen in whom the dose was fractionated over some time, survived only an average of fifteen months. It was upon these results that he based his views regarding condensation of the X-ray therapy into as short a space of time as possible. Of Ch'eng's seven cases, none survived, but he explains this by the fact that the average duration of symptoms before treatment was one year. Quick and Cutler reported twenty cases of transitional-celled carcinomata, which as we have seen are very similar, and which series probably contained some lympho-epitheliomata : only seven remained alive, none over three years, and only one up to that period at the time of publication.

In a consideration of personal cases the great difficulty has been that of diagnosis and, guided by rigid criteria, the number of cases has been reduced to six. Some of these cases have been used as illustrations previously, but pictures of the others are given now (Figs. 10, 11 and 12). Of the six cases, two are alive at five years and one at two years, the remainder survived each a little over one year following orthodox treatment.

The final impression gained, then, is that of a malignant neoplasm running a fatal course, untreated in under two years. Treatment by X-ray therapy should produce very rapid local regression. Failing a quick response, the patient must be abandoned as hopeless. Having obtained a good immediate result, local recurrence is unlikely, and if the patient passes the three year limit, without developing distant metastases, it appears that all will be well. It must always be remembered that lymph-node deposits can be treated and regression obtained but that treatment of skeletal deposits is probably useless.

Conclusion

The general impression gained from a study of these tumours is that of confusion, and many tumours which would possibly be described as lympho-epitheliomata have behaved in a variety of different ways and altogether suggested that they are of different types. The small group which I have isolated as sufficiently similar to be classified together give the impression of a moderately well differentiated tumour, probably best thought of as sarcomatous, but whether or not they are typical of what has been described as lympho-epitheliomata is difficult to judge. It does seem at the moment that the diagnosis of lympho-epithelioma is probably best left alone in clinical circles and a description of the tumour given—dealing principally with the degree of development of the large cells and mentioning the extent of lymphocytic content of the tumour, thus determining the best treatment and a fairly accurate prognosis.

APPENDIX

Cases used as Examples

Fig. 5.—*T.C., male, age* 42. Right tonsil enlarged to mid-line, mobile neck glands. Tonsillectomy with biopsy followed by X-ray therapy in February 1933. Alive and well now—5 years.

Figs. 6, 7.—*E.M., female, age* 57. Ulcerated right tonsil tumour. October 1934—partial removal and radium. February 1935—neck glands and cutaneous deposit in cheek—X-ray therapy—regression. December 1935—died—massive recurrent neck glands and metastases in cervical vertebrae—1 year 5 months.

Fig. 8.—*F.O., male, age* 13. Enlarged right tonsil, bilateral neck glands, bigger on right side. Tonsillectomy and biopsy April 1933—X-ray therapy. Alive and well—nearly 5 years.

Fig. 9.—*J.B., male, age* 65. Ulcerated left tonsil tumour with local cervical adenopathy. November 1934—biopsy, X-ray therapy. December 1935—X-ray therapy for lumbar vertebral lesion. July 1936—died—abdominal and vertebral metastasis.

Fig. 10.—*S.A., male, age* 35. June 1931. Tonsillectomy left with radium collar. November 1931—tonsillectomy—right. March 1932—X-ray therapy to neck. Died March 1933—local recurrence and generalized metastasis—1 year 9 months.

Fig. 11.—*W.T., male, age* 34. Excision of neck glands in June 1934. X-ray therapy to recurrence and primary in August 1934. Died August 1935 from local extension of growth—1 year.

Fig. 12.—*I.B., female, age* 50. Tonsillectomy for left tonsillar tumour in December 1935—local recurrence in 3 weeks—January 1936—X-ray therapy. Alive and well now—2 years.

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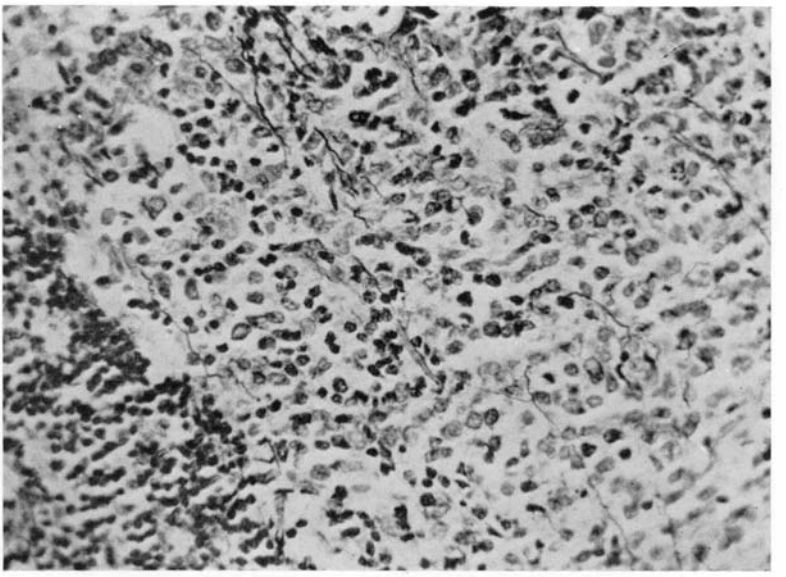

Fig. 11.

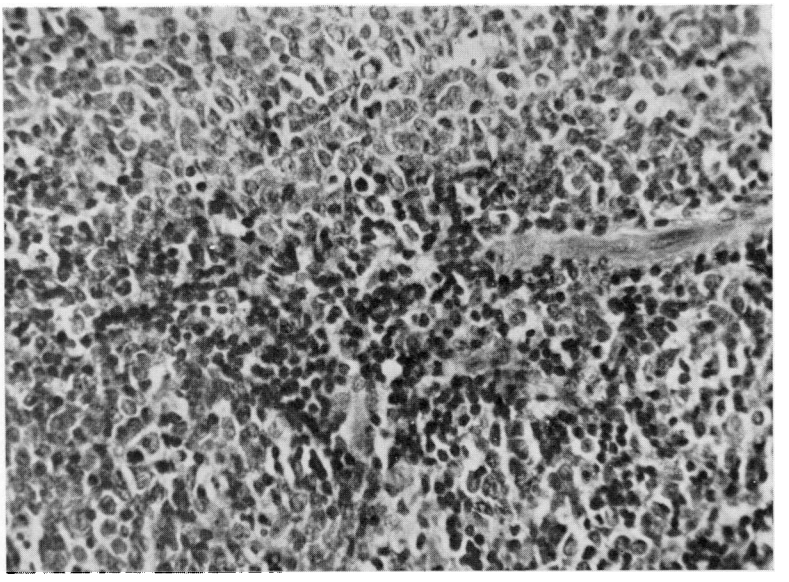

Fig. 12.

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The Lympho-Epitheliomata

Der allgemeine Eindruck, den man beim Studium der Lymphoepitheliome erhält, ist derjenige einer gewissen Unsicherheit. Viele Geschwülste, die man möglicherweise als Lymphoepitheliome beschreiben könnte, zeigten ganz verschiedene Verlaufsarten, so dass man auf verschiedene Typen zu schliessen versucht ist. In dieser Arbeit trennt der Verfasser eine kleinere Gruppe von Geschwülsten ab, die genügende Aehnlichkeit und Differenzierung aufweisen, um zusammengefasst werden zu können und bei denen am ehesten an Sarkom zu denken ist. Doch ist es schwer zu entscheiden, ob sie wirklich mit den als Lymphoepitheliome beschriebenen Geschwulstarten übereinstimmen.

. . . .

L'impression générale qui se dégage d'une étude sur le lympho-épithéliomatome est une impression de confusion, et beaucoup de tumeurs qui auraient pu être décrites comme les lympho-épithéliomatomes, se sont comportées de façons variées et ont paru appartenir à un type différent.

Dans cet article, l'auteur isole un petit groupe de cas suffisamment semblables pour être classés ensemble, et pour donner l'impression d'une tumeur assez bien différenciée, probablement se rattachant au groupe des sarcomes. Mais il est difficile de dire si ces cas sont ou ne sont pas typiques de ce qui a été décrit comme lympho-épithéliomatome.

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