BRANCHIOGENIC PAPILLIFEROUS ADENO-CARCINOMA.

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(Plates XXXVI. and XXXVII.)

The specimen here described is one I believe of rare occurrence and of great pathological interest. It has recently been added to the Museum, although it has for many years formed part of the unclassified material, and was labelled "Sarcoma of the Neck." It was removed in March 1897 at the Queen's Hospital, Birmingham, by Mr. Marsh.

The specimen is from a man, at 43. He suffered from stiffness of the left side of the neck for 2½ years. A lump appeared just below and behind the left angle of the jaw 2 years before. This steadily increased in size and gave rise to neuralgic pains. On admission to hospital, on March 18, 1897, the patient weighed 15 stone, and had a round elastic swelling on the left side of the neck reaching from the angle of the jaw to within 1 in. of the clavicle. It was situated beneath the sterno-mastoid muscle, and more than half of it projected into the posterior triangle of the neck. It was perfectly circumscribed, slightly irregular on the surface, and moved fairly freely over the deep structures of the neck. It appeared to be distinct from the parotid, submaxillary, and thyroid glands. There was no difficulty in swallowing or breathing, no nerve paralysis, and no hoarseness. Nothing abnormal was found in the mouth, fauces, or larynx. The tumour was removed on March 22, 1897.

The tumour lay beneath the sterno-mastoid muscle and the great vessels of the neck. Its distinctness from the parotid, submaxillary, and thyroid glands was confirmed. It shelled out freely, although there was considerable haemorrhage. After removal the oesophagus and sympathetic cord lay exposed in the head of the tumour. The tumour weighed 1½ lb. The patient was discharged on April 24. The tumour recurred in October 1897. He was readmitted to hospital, when a tumour was found below the scar of about the same size as the primary growth. A second operation was performed, but owing to its firm attachment and severe haemorrhage it could not be completely removed. The tumour removed on this occasion weighed 1 lb. 3 oz. The wound never healed. The tumour reappeared directly after the patient left hospital, and at the time of his death in February 1898 it was the size of a Jaffa orange. Just before death an oesophageal fistula formed, and the patient was emaciated to a skeleton. An autopsy was unfortunately not made to determine the existence of secondary growths.
Macrosopical appearances.—The specimen illustrated in photographs is that removed at the first operation. It is roughly oval in shape, being 3½ in. long, 3 in. broad, and 2½ in. thick. Its surface is for the most part smooth, but here and there are well-marked low papillary growths (Plate XXXVI. Fig. 1).

On section the tumour is essentially cystic, consisting of two main cavities about 1½ in. in diameter, with several smaller cysts adjoining (Plate XXXVI. Fig. 2). The content of the cyst, now in a coagulated state, is soft and friable; whether or not it showed colloid material in the fresh state I do not know.

Microscopical appearances.—Sections have been taken from many parts of the wall of the cysts. The larger cysts have very dense walls, consisting of fibrous tissue and non-stripped muscular tissue in varying proportions. As a general rule the outermost layers consist entirely of dense fibrous tissue arranged in parallel layers. The fibrous bundles in some places are separated by empty elliptical spaces, which are in all probability artificial, due to the hardening agents used in preservation. In some sections this outer fibrous part of the wall is cut transversely, and exhibits distinct layers running at right angles to each other. Subjacent to this dense fibrous layer is a thick belt of tissue, rich in non-stripped muscle running in all directions, generally in long parallel bundles, many of which appear to branch (Plate XXXVI. Fig. 3). The blood vessels are for the most part placed between the fibrous and muscular layer. The larger vessels have enormously thick walls, and run in a tortuous manner through the tissue. Sometimes the vessels are crowded in large groups very similar to what is seen in the uterine wall. From the larger vessels capillaries run into the tissue and frequently become dilated into sinuses. A certain amount of adipose tissue is visible between the fibrous and muscular coats. The outer surface of the tumour, which shows papillary growths, is covered, over extensive areas, by low columnar or cubical cells (Plate XXXVII. Fig. 4). At some points the sections show no epithelium on the surface. The low papillary processes seen on the surface of the growth consist of a delicate core of fibrous tissue covered by a single layer of columnar cells which do not retain stains well. The inner lining of the cyst wall is invariably covered by epithelium. This consists of a single layer of high columnar cells with an elongated nucleus, situated about the middle of the cell, in protoplasm which retains ordinary stains. Numerous papillary elevations and villous growths spring from the inner wall. These consist of a delicate connective-tissue core, very vascular, often engorged with blood and covered by a single layer of columnar cells. Many of these intracystic papillomata show complex dichotomous division (Plate XXXVII. Fig. 5). At certain points the epithelial lining of the cysts dips down into the muscular zone of the cyst wall to form flattened acini, which run for a considerable distance; sometimes the lumen is stellate (Plate XXXVII. Fig. 6). They are also seen in the fibrous coat of the cyst; the epithelium lining these flattened acini is a single layer of cubical or low columnar cells. The contents of the cysts consist of a soft granular substance, which readily breaks down on handling. The appearance is not in the least like colloid matter after long preservation. Microscopically, it consists largely of granular débris, staining a pink colour with van Gieson's stain. Scattered thickly amongst the substance of the granular débris are crowds of nuclei, most of which are polynuclear, a few being mononuclear. The nuclei stain readily with hematoxylin. Large fat globules are present among the granular débris.

Remarks.

As to the nature of this tumour there can be no doubt. It is a papilliferous adeno-carcinoma. Both the histological appearances and the clinical history confirm this view. Regarding the site of origin,
there is some room for speculation. There are certain facts elicited by a careful histological study of the tumour which throw light upon its probable embryological origin.

Mr. Marsh was quite certain that the tumour was primary, and not a lymphatic enlargement secondary to a primary growth in either the nose, mouth, fauces, or larynx. He was equally certain after the operation that it was distinct from either the thyroid, submaxillary, or parotid glands. Its position in the neck prior to operation, namely, chiefly in the posterior triangle, goes far to proclaim its independence of any of the great secretory glands in this region. Yet it is a malignant epithelial tumour of a columnar-celled type situated deep in the tissues of the cervical region, and must have arisen from pre-existing epithelium similar in nature.

When I showed this specimen at the University Medical Society it was suggested that the tumour might have arisen in a diverticulum of the oesophagus, and, as bearing out this hypothesis, the establishment of a pharyngeal or oesophageal fistula occurring just prior to death was mentioned. To me the fistula, which occurred in the last week or two of the patient’s life, merely proves that the growth ulcerated from without into the upper end of the gullet. There was never any evidence that the primary growth arose there. It began just below the angle of the jaw at the side of the pharynx. Its histological characters alone suffice to show that it was not a primary growth of the pharynx or oesophagus. Malignant growths of this region are, almost invariably, squamous-celled carcinomata, or, very occasionally, alveolar carcinomata. After deciding that the tumour was a primary growth, and that it did not arise in any of the great deep epithelial masses of the neck, we narrow the probable site of origin down to either an unobliterated branchial cleft development or to an aberrant thyroid body.

The so-called branchiogenic carcinoma first described by Volkman in 1882 is essentially a squamous-celled carcinoma, showing solid columns of cancer cells and cell nests. Of these there are now something like twenty-six specimens on record. They are supposed to originate in the ectoderm, less rarely in the entoderm, of a branchial cleft which has remained unobliterated in the deep tissues of the neck. These epithelial inclusions lie dormant for a time, and may give rise to branchial fistulae, branchial cysts or branchial carcinomata later in life. Almost all of these branchiogenic carcinomata occurred in men over 40 years of age. They are difficult to extirpate, a fact not easily understood, but fully proved, by the almost universal recurrence of the cases recorded. Much valuable information has been obtained by the publication of these twenty-six cases. Many of the descriptions of the histological appearances of these tumours is so imperfect, however, that it is difficult to be certain what the growth actually was. Nevertheless, it must be accepted as quite certain that
most of these rare forms of cervical cancers were, as Volkmann first described them, squamous-celled epitheliomata. Berger was the first to suggest in 1897 that aberrant or accessory thyroid bodies might be the site of origin of carcinomata.

In that year, at the French Surgical Congress, Berger read a short paper upon epithelioma of branchial origin and of accessory thyroid origin. He showed a specimen removed from a woman which he believed to have arisen in an accessory thyroid. It contained colloid matter and papillary growths, and was cystic. The epithelium was columnar or cubical, and was classified by Fernand Besançon, who reported on it as a typical adeno-carcinoma, a name first adopted by Wölfler. Berger affirms that the histological characters of this specimen, described at the Congress, reproduce exactly the appearances presented by epithelioma of the thyroid body as described by Cornil in 1865. Berger clearly recognises that the tumour differs essentially from the branchiogenic carcinoma of Volkmann in its histological characters. He further asserts that these deep malignant tumours of the neck can be distinguished by their histological characters alone. If they are pavement epitheliomata they are branchiogenic; if they consist of cubical or columnar-celled epithelium they arise in accessory thyroids. I do not think that the question is to be dismissed so simply as this. It is quite unjustifiable to assume that all adeno-carcinomata of the cylindrical-celled type arising in the neck distinct from all the great epithelial masses necessarily arise in accessory thyroids. In going through the literature I have been able to find only three specimens which seem to resemble Mr. Marsh's tumour. One was described by Silcock in 1887, another by Treves in 1887, and a third by Berger in 1897, as above mentioned. Berger classifies the two cases of Gussenbauer as belonging to this order, but to my mind Gussenbauer's cases resemble much more clearly the branchiogenic carcinoma of Volkmann. In discussing these two theories of accessory thyroid and branchiogenic origins it is worth while referring to the malignant epithelial tumours of the thyroid gland itself. We find that the majority of these are of the alveolar form of carcinoma with cubical or columnar cells. They are almost all hard solid tumours of a very malignant type. There have been recorded, however, a few cases of papilliferous cystic tumours of the adeno-carcinoma type which are less malignant. Such cases have been described by Barker, Berger, Wölfler, Sulzer, and others. They form a group of tumours intermediate in malignancy between the common alveolar form and the ordinary adenomatous bronchocele.

Some years ago I described and published a case of adenomatous bronchocele in a newly born child which was perfectly encapsuled within the thyroid gland, and which showed numerous intracystic papillary growths covered by high columnar epithelium. Its stroma was studded with masses of cartilage. I suggested that the growth
was due to the carrying down into the ordinary thyroid recesses of a part of the branchial cleft and cartilage, and that the tumour constituted a form of branchial cyst or adenoma within the lateral lobe of the thyroid gland.

The occurrence of these rare forms of papilliferous adenocarcinomata of the thyroid gland serve to confirm Berger's assertion that these outlying columnar-celled carcinomata, such as the case under discussion, may possibly arise in accessory thyroids. Berger himself was no doubt influenced in this view by the fact that he met with not only a so-called accessory thyroid papilliferous tumour, but also with a similar specimen in the body of the thyroid. It is, however, highly dangerous to assume that, because a tumour of certain histological appearances far out in the neck exactly resembles a similar tumour found in the thyroid gland, the former is necessarily arising in an accessory thyroid. I admit at once that accessory thyroids may be the seat of both adenomata and adenocarcinomata. I am quite prepared to admit that Berger's specimen published in 1897 may have arisen in accessory thyroid tissue. I dispute, however, Berger's dictum that all such columnar-celled adenocarcinomata must arise in aberrant thyroid tissue.

In any endeavour to solve the problem of the origin of such tumours as these it is necessary to make a survey of the branchial clefts and the branchial epithelial bodies which give rise to the formation of the thyroid gland and the accessory thyroids. With this object in view I have taken the opportunity of studying specimens of fourth-week embryos of mammals. The entodermal ends of the branchial clefts at this stage are covered by high columnar epithelium, very similar to the epithelial lining of the tumour under discussion. It is at this stage that the branchial epithelial bodies, which give rise to the thyroid, thymus, and parathyroid glands as well as the postbranchial bodies, arise. Later, of course, the hypoblastic lining of the pharynx becomes transformed into stratified squamous epithelium. The thyroid developments, however, after migrating from the pharynx, still retain their columnar or cubical epithelium throughout life. The median lobe and the greater part of the lateral lobes arise from the floor of the second cleft. The extreme lateral lobes arise from the fourth cleft. The accessory thyroids are segregated masses of the extreme lateral lobes, and are probably developments of the fourth cleft. The parathyroids, which are developments of the third and fourth clefts, the thymus, which is a development of the third cleft, and the post-branchial bodies, which arise from the position of the fifth cleft, do not directly concern us.

There can be no doubt that we have still something to learn about the embryology of this region. It is, of course, quite certain that the branchial clefts of mammals are never complete; the mesoblasts never completely absorbed between the ectodermal and the entodermal ends.
The nearest approach to this is met with in the first cleft, where the tympanic membranes alone intervene between the hypoblastic and epiblastic development. In all the other clefts the thickness of mesoblastic tissue is considerable. The entodermal end of the second cleft remains in the adult as the fossa in which the tonsil is situated. Developments of the second cleft, therefore, almost always make their appearance just below and behind the angle of the jaw, the exact situation where the present tumour was found. The entodermal ends of the third and fourth clefts are represented in the adult by the sinus pyriformis of the larynx.

Another point of great importance which has a distinct bearing upon the teratological development of the tumour is the fact that muscular tissue has never been found in the normal thyroid gland. Thyroid tumours likewise, so far as I know, contain no muscular tissue.

So much importance did I place upon the existence of non-striped muscle in Mr. Marsh's tumour that I submitted it to Professor Leith and to Professor Carlier, and they both at once confirmed my opinion that muscular tissue was present in the wall in definite layers. I feel, therefore, that the presence of muscle alone is sufficient to exclude the accessory thyroid theory of origin in connection with my specimen. The only satisfactory explanation, in the light of our knowledge of thyroid tissue and its development, of the origin of such a tumour is that it arose from the entodermal end of a branchial cleft and, in view of its appearing at the angle of the jaw, from the second branchial cleft. It is therefore a true branchiogenic adenocarcinoma of the columnar-celled type, and it serves to refute Berger's dictum that all such primary adenocarcinomata occurring deep in the neck are necessarily developed from accessory thyroids.

In conclusion I have to thank Mr. Marsh for placing the tumour in my hands for investigation and publication.

**DESCRIPTION OF PLATES XXXVI. AND XXXVII.**

**PLATE XXXVI.**

Fig. 1.—Showing the outer surface of the tumour studded with low papillary growths.

Fig. 2.—Showing the tumour laid open, with its two large cystic cavities.

Fig. 3.—Showing the laminas of fibro-muscular tissue of which the cyst wall is composed.

**PLATE XXXVII.**

Fig. 4.—Showing papillary growths upon the surface of the tumour lined with a single layer of columnar cells.

Fig. 5.—Showing the intracystic papillary growths lined by a single layer of columnar cells.

Fig. 6.—Showing empty stellate lumina within the fibro-muscular wall lined by a single layer of cubical cells.