Remarks ON EXTENSIVE CARCINOMA OF THE OESOPHAGUS,

WITH UNUSUAL NERVOUS COMPLICATIONS.

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THE following case is of special interest because it appears to constitute an exception to Semon's law. It has been carefully worked out, and will, it is believed, be found to fulfil the conditions which Sir Felix Semon has insisted upon as being necessary:

Clinical History.

Francis L., aged 50, was admitted into the General Hospital on March 13th, 1902, complaining of difficulty of swallowing solids and to a less extent of swallowing liquids, and of constant vomiting with partial loss of voice. He had also pains in the left side of the body and across the right temple at night. He had been ill two years; he attributed his illness to having got wet through, after which he had running from the eyes and nose and swelling of both ankles. However, he seems to have recovered from this, and it was only at Christmas that his appetite failed. The pains had been coming on for three or four weeks and the loss of voice for a fortnight. His previous health had been quite good; he had never been laid up before.

The patient was a poorly-nourished man weighing 9 st. 10 lb. There was a hard, rounded swelling on the right side of the neck, which was not tender or painful, but was said to be getting larger. The left side of the chest was flattened before and behind; its movement was impaired, and the percussion note was less resonant over the upper two-thirds anteriorly. The breath sounds were not well heard at the base, but in front were harsh below the clavicles, especially on the left side: the vocal fremitus and vocal resonance were increased over the last area. The heart's apex was in the fifth interspace, integral to the nipple line, its sounds were pure but faintly heard; pulse 76, regular but small. The tongue was coated with a moist brown fur; the pharynx looked only slightly relaxed, and a large oesophageal bougie passed easily into the stomach. The vocal cords were adducted imperfectly. On March 16th there is a note that he had vomited most of his dinner on the previous day. The larynx was again examined; the cords were seen in a position of abduction; on breathing and phonation slight adduction only took place. A similar condition was noted on the 18th, and a drawing of the position of the cords was made (Fig. 1). On the 21st the deglutition sounds were

Fig. 1.—Position of vocal cords as seen on March 18th, 1902.

Observed on swallowing, and appeared to be normal. In the course of a month the patient lost a good deal of flesh and continued to vomit, while the area of dullness extended across from the left to the right apex. On April 2nd it was noted that the vocal cords did not approximate at all; on phonation the aperture remained quite wide. On April 21st his weight was only 8 st. 4 lb., and he had become exceedingly weak and complained now of extreme breathlessness. On April 29th the vocal cords were again examined and a drawing was made; they were motionless, but were fixed in a position of rather greater adduction than when last seen. The difficulty of swallowing food had not increased. The urine was examined repeatedly and, with the exception of one occasion when a trace of albumen was found, it deposited urates but was otherwise normal.

He died on April 30th from heart failure. At the necropsy the body was found to be much emaciated; the pericardium was densely adherent, and enlarged glands surrounded the aorta, involving both vagi and the left recurrent laryngeal nerve. The left pleura was densely adherent and the left lung showed much oedema, with pneumonic consolidation around the secondary deposits at the base. The right pleura was healthy, but in the right lung there were also several nodules of growth the size of a hazel nut. The larynx was healthy, the cords lying in the cadaveric position. The upper part of the oesophagus for 6 in. was involved in a sloughing, malignant growth, which

projected into the lumen and bound it to the trachea, which at one point was perforated. On the right side of the neck was a mass of malignant glands. There were some old peritoneal adhesions around the splenic flexure of the colon, but in other respects the stomach and intestines were normal. The liver was slightly fatty and the kidneys seemed fibrosed; the spleen was normal.

Naked-eye Appearances of the Dissected Specimen (Photographs 2 and 3.).

The growth occupies all that part of the oesophagus between the first ring of the trachea and a point about 2 in. below the bifurcation of the trachea, a longitudinal distance of 6 in. The calibre of the oesophagus between these two points is increased to three times its normal extent; no stricture exists at any point. The upper limit of the growth has a definite margin, exuberant in character and overlapping the healthy mucous membrane. The lower margin of the growth is less definite, being ulcerated and apparently infiltrating and spreading down into healthy tissues. Between these two points there is a soft friable growth everywhere infiltrating the entire wall of the gullet, and generally producing considerable thickening, but in certain parts—especially towards its lower limits—the

Fig. 2.—Oesophagus laid open and viewed from behind. Epiglottis is seen at the top of the specimen.

ulcerative process has been so rapid that the wall is as thin as wafer paper. On the right side, situated between the oesophagus and the trachea, is a mass of enlarged deep cervical lymphatic glands; several nerves are involved in this mass. A similar mass of deep cervical lymphatic glands exists on the left side, but is smaller in size. The bronchial lymphatic glands are also affected. The thyroid gland is normal. The trachea is densely adherent to the oesophagus during the whole extent of its course; towards its lower end there is considerable lateral compression of its walls by the two glandular masses, and, as these are not

on the same level, an S-shaped lateral curvature of the trachea has resulted, the mass of glands on the right occupying the concavity of the upper deviation, and the left mass the concavity of the lower deviation. In the mucous membrane lining the posterior surface of the upper part of the trachea there is a very minute point of growth. The bronchi are firmly bound to the oesophagus by infiltrating growth and in the upper inch of the left bronchus is a button-like mass of growth which has spread through from the oesophagus. The superficial area of this mass is about that of a sixpence. The great vessels, both arteries and veins, are not invaded or compressed by the growth. The pneumogastric nerves on both sides are free until they pass behind their respective bronchi; at this point they are surrounded by the growth and lose

Fig. 3.—Anterior view, showing some of the nerves involved in the growth. A, Right vagus; B, right recurrent laryngeal; C, enlarged glands; D, right cervical sympathetic branches; E, aortic arch turned down; F, thyroid gland; G, left vagus; H, trachea opened; I, left recurrent laryngeal; K, growth into left bronchus; L, cardiac plexus; M, pulmonary artery turned down.

their identity in the neoplasm. The right recurrent laryngeal nerve leaves the vagus opposite the sixth tracheal ring and turning upwards and inwards around the innominate artery enters the glandular mass; on careful examination it is seen to be eroded by the growth a short distance below the point at which it disappears in the mass, it emerges at the upper part of the growth and passes below the lower border of the inferior constrictor muscle to its ultimate destination. The left recurrent laryngeal nerve leaves the vagus opposite the eleventh ring of the trachea, hooks round the aorta where it gives off a branch to the superficial cardiac plexus, and almost immediately becomes involved in the left glandular mass; at this point it becomes thickened to two or three times its normal size, is nodular in outline

and very friable in consistence from infiltration by the growth. It is partly buried in the mass; after leaving it it resumes its usual calibre and smooth outline and passes below the inferior constrictor muscle of the pharynx. The main trunks of the sympathetic nerves seem to have escaped; the cervical sympathetic branches to the cardiac plexuses are, however, involved; on the right side they pass through the right glandular mass, and emerging at its lower margin pass in front of the right bronchus to the superficial cardiac plexus. On the left side the lower ganglionic supply alone is seen considerably thickened in character. It passes over the front of the left bronchus to its destination in the cardiac plexuses. The phrenic nerves had escaped without injury.

A dissection was made of the laryngeal muscles; the right posterior crico-arytenoid muscle was rather smaller than the left, and beyond a slight pallor of their fibres these were apparently normal. The crico-thyroid muscles were equally distinct on both sides and were apparently normal. The lateral crico-arytenoids and the thyro-arytenoids were about equal in size on both sides, and to all appearance healthy. The arytenoid muscles, beyond a slight pallor in colour, were apparently normal.

MICROSCOPICAL APPEARANCES.

Oesophageal Wall.—Sections have been examined from the centre of the ulceration and from several points in the growing margin. The ulcerating mass consists almost entirely of cells, arranged for the most part in masses of large size, though smaller masses are interspersed amongst the larger ones (Fig. 4). The cells are closely packed together and are not separated by any stroma. The cells are rounded or oval in shape, their protoplasm stains readily with Van Giessen's

Fig. 4.—Section of oesophageal growth showing the alveolar arrangement of the spheroidal cells.

stain or eosine, and contain well-marked vesicular nuclei which stain deeply with haematin. There is little or no increase of fibrous tissue in the ulcerating masses such as one sees in a scirrhus carcinoma. The heaped-up masses of cells are supported by a delicate framework of connective tissue. Towards the centre of the ulcerating surface, where there is rapid disintegration of the soft fungoid-like growth, the masses of cells are everywhere invaded by round polynuclear cells, and certain parts of the section where the cells have entirely lost their outlines show a process of complete necrosis. On examination of the extreme margin of the growth one can easily see the healthy stratified squamous epithelium overlying the masses of cells previously described. There is no evidence in these growing margins of any downgrowth of surface epithelium through its own basement membrane (Fig. 5). There are no cell nests in any of the sections examined. The entire thickness of the oesophageal wall is invaded by this cellular growth, except in the region of its growing margins.

Lymphatic Glands.—The cervical are almost entirely replaced by new growth similar to the alveolar masses described in the oesophagus (Fig. 6). The bronchial glands are laden with black pigment and scattered amongst the lymphoid tissue are numbers of large cells with well-marked vesicular nuclei and which are without doubt extensions from the primary oesophageal growth.

Lung.—Sections through the nodules show masses of epithelial cells identical with those found in the primary oesophageal growth. (Fig. 7.) The pulmonary alveoli surrounding these metastatic deposits are filled up with fibrin or with catarrhal cells.

Nerves.—Sections made across the recurrent laryngeal nerves and the trunks of the pneumogastric nerves, where they are

caught in the growth, show them to be infiltrated and in places largely replaced by masses of epithelial cells. (Fig. 8.) Sections across the recurrent laryngeal nerves after leaving the masses of enlarged glands stained with the ordinary histological stain, such as haematin and eosine, show that many of the nerve tubules are devoid of axis cylinders. These empty nerve tubules are scattered irregularly throughout the transverse section of the nerve. There is a slight increase of the fibrous tissue of the nerve.

Fig. 5.—Section of upper margin of growth, showing healthy stratified squamous epithelium on the surface, with large alveolar masses of cells below.

Muscles of the Larynx.—Sections were made of the muscles cutting the muscular fibres in a transverse and also in a longitudinal direction—that is, two sections were made of each muscle.

The Posterior Crico-arytenoids.—Right: There are many bundles of this muscle in a state of advanced degeneration. Many of its fibres have entirely disappeared or are considerably shrunken in size, and are irregular in shape. (Fig. 12). The degree of degenera-

Fig. 6.—Section of a cervical lymphatic gland, everywhere infiltrated with spheroidal cancer cells.

tion in this abductor muscle is less advanced than in the adductors on the same side, and more advanced than in the corresponding abductor of the opposite side. Left: There is degeneration in this muscle of a moderate degree, many fibres are quite healthy but interspersed amongst them are fibres that are shrunken, irregular in outline, or have

disappeared (Fig. 13). The degree of degeneration is less severe than that found in the adductor muscles of the same side.

Lateral Crico-arytenoids and Thyro-arytenoids.—Right side: Shows an advanced degeneration of the muscular tissue, a large number of the muscular bundles have entirely disappeared and are replaced by a loose fibrous framework. Even in bundles that are in a state of advanced degeneration, however, isolated healthy fibres are visible (Fig. 9). The thyro-arytenoid is slightly more degenerated

Fig. 7.—Section of pulmonary metastasis showing alveoli of cancer cells.

than the lateral crico-arytenoid. These right adductor muscles are much more degenerate than the abductor muscles on the same side, and slightly more degenerate than the adductor muscles on the opposite side. Left: The thyro-arytenoid and lateral crico-arytenoid are in a state of moderate degeneration. (Fig. 10.) The thyro-arytenoid is more degenerated than the lateral crico-arytenoid.

The arytenoids are in a state of fairly advanced degeneration. (Fig. 11).

Fig. 8.—Section across the vagus nerve, where it is involved in the primary oesophageal growth, showing its infiltration by cancer cells.

Crico-thyroids.—These muscular bundles are apparently quite healthy, they stain more brilliantly, are more regular in size and shape, and in every way conform to the appearance of healthy muscular tissue.

The nature of the oesophageal growth is, in all probability, a spheroidal-celled carcinoma beginning in the oesophageal glands. This is borne out by the alveolar character of the growth which is reproduced in lymphatic glands and pulmonary metastases. One takes this view of its nature rather than that of squamous epithelioma, because in none of the

Fig. 12.—Right posterior crico-arytenoid, showing its small muscular bundles, shrinking and disappearance of fibres.

margins examined was there any evidence of downgrowth or proliferation of the surface epithelium, even where the sub-epithelial tissue is richly invaded by the solid alveolar masses of cells. Cell nests are entirely absent from both primary and secondary growths. We know also by experience that

Fig. 13.—Left posterior crico-arytenoid. Showing its small muscular bundles; shrinking of bundles.

secondary growths are very rare in squamous-celled epithelioma. Alveolar sarcoma is quite excluded by the absence of any stroma amongst the alveolar masses. The type of carcinoma to which this most nearly conforms is the encephaloid carcinoma which in places has undergone inflammatory and even necrotic changes.

The clinical manifestations of this remarkable growth call for special mention.

There was absolutely no diminution in the lumen of the oesophagus, and the difficulty in swallowing must have resulted from an interruption of the peristaltic contraction which normally occurs in the oesophagus during the act of deglutition. Fluids would gravitate into the stomach much better than solids. Inasmuch as the muscular wall of the

Fig. 9.—Right thyro-arytenoid. Showing large healthy muscular bundles here and there, with shrinking and disappearance of the majority.

gullet was replaced by growth for quite several inches in extent, involuntary muscular contraction of that portion must have been impossible.

The flattening of the left side of the chest, its imperfect

Fig. 10.—Left thyro-arytenoid. showing many large, healthy bundles; the majority however, are shrunken, and many have disappeared.

expansion during inspiration and the impaired percussion note over that side were due to the button-like projection of growth into the left bronchus which produced a degree of collapse of the left lung.

The pains in the right temple could be accounted for by the pressure of enlarged cervical glands upon the trunk of the small occipital or of the great auricular nerves, both of which come from the second and third cervical nerves, and furnish

twigs to the skin of this region of the head. The pains in the left side of the body might, in a similar way, be due to pressure by the growth upon the anterior primary divisions of the lower cervical and upper dorsal nerves.

Fig. 11.—Arytenoideus. Longitudinal section, showing small muscular bundles, with shrinking and degeneration of its fibres.

The sudden attacks of vomiting, which were of almost daily occurrence, were probably due to the involvement of the trunks of the pneumogastric nerves in the posterior mediastinum, causing irritation of the sensitive afferent fibres. Irritation of this nerve in operations upon the neck of man is known to produce dilatation of the cardiac orifice, and reflex contraction of the diaphragm, abdominal muscles and stomach. This explanation is much the most likely in this case. It is, of course, conceivable that the vomiting was due to direct stimulation of the efferent motor fibres which pass to the stomach. The stomach was found at the necropsy to be healthy.

The cardiac weakness with attacks of sudden dyspnoea was a well-marked feature during the last few weeks of this patient's life, and can be accounted for by the implication of practically all the cardiac sympathetic branches in the cervical glandular masses. This set of nerves in the human subject not only bears the efferent cardio-motor nerves, but probably also the efferent depressor nerve of the heart, and, although in this case disablement of the former would most readily explain the cardiac weakness, irritation and stimulation of the depressor fibres is quite conceivable. The inhibitory nerves of the heart coming by way of the vagus trunk are given off at a point higher than the exact spot where the pneumogastric is involved in the growth, and thus would in all probability escape injury, and continue to transmit inhibitory impulses. We know too little, however, concerning the innervation of the human heart to speak dogmatically upon what effect such a condition of cardiac nerve involvement would mean, even if every nerve could be fully dissected out and identified.

The implication of the recurrent laryngeal nerves is a matter of special interest. The specimen had been left rather too long in formalin before coming to the museum, otherwise special methods of determining the exact nerve degeneration would have been made. The recurrent laryngeal nerves, however, were examined not only where involved in growth, but also after leaving the glandular mass, and in this latter situation they showed a very definite destruction of axis cylinders.

A careful examination of the laryngeal muscles was made by dissection and by the microscope. The patient had suffered from laryngeal symptoms such as loss of voice for a little more than two months. There was therefore ample time if the laryngeal nerves were involved to produce considerable alteration in the sarcois substance of the muscles supplied, if not in their bulk, at least in their histological structure.

Such a change was clearly seen on microscopical examination. The muscles showed a diminution and shrinking of their muscular bundles, loss of transverse striation and of longitudinal fibrillation. The sarcois matter had a hyaline appearance and did not react well to stains. Over large areas the muscle bundles had disappeared entirely, and were represented by the fibrous tissue framework of the muscle. Naked-eye examination of small muscles such as those acting on the vocal cords must of necessity be very unsatisfactory in determining the exact amount of degeneration, especially in a nerve involvement of only two months' duration.

In this case, though little abnormality could be seen by the naked eye, a very different state of affairs was revealed by microscopical investigation. The muscles which showed the most advanced degree of degeneration were those concerned in adduction of the vocal cords, the thyro-arytenoids more particularly, to a less extent the arytenoids and the lateral crico-arytenoids. The abductors were affected to a less degree. The muscles of the right side, both adductors and abductors, had suffered more than those on the left side, a fact which is readily explained by the greater degree of involvement of the right recurrent laryngeal nerve as compared with the left. The microscopical sections of the crico-thyroid muscles formed a striking contrast to the other laryngeal muscles, showing fairly conclusively that the external laryngeal nerve had escaped damage by the neoplasm.

The clinical evidence goes to show that the adductor paralysis was an early and constant feature of the laryngeal condition during the whole of the patient's life in hospital. The abductor muscles, on the other hand, appeared to act well until a few days before death, when a slight narrowing of the previously wide open glottis was noticed. This narrowing of the glottis was probably due to the advancing paralysis of the abductor muscles causing the vocal cords to assume a more nearly the cadaveric position. It could scarcely be maintained that the widely-open glottis in the earlier stage was due to spasm of the posterior crico-arytenoid induced by irritation of an early nerve involvement, in face of the fact that the adductor muscles were much more degenerate than the abductor muscles. The most reasonable explanation is that the nerve fibres going to the adductors of the vocal cords were disabled earlier and in much larger proportion than the nerve fibres going to the abductor muscles. This explanation of course takes for granted that the nerve fibres of the trunk of the recurrent laryngeal nerve are differentiated into special fibres for special muscles, though not necessarily arranged in any special position within the epineurium of the nerve.

Sir Morell Mackenzie and Sir Felix Semon have repeatedly drawn attention to the special proneness of the abductor fibres to injury as compared with the adductor fibres in chronic organic nervous diseases of either peripheral or central origin. Sir Felix Semon especially has collected a large number of cases to support this view, and he has been led to make the following statement, which has become generally known as "Semon's law": "The occurrence of an isolated paralysis of the abductor filaments of the recurrent laryngeal nerve in cases in which the roots or trunks of the spinal accessory, pneumogastric, and recurrent nerves are injured or diseased is not an isolated pathological curiosity. There is a distinct proclivity of the abductor fibres to become affected in such cases, either at an earlier period than the adductor fibres or even exclusively."

The case which has just been recorded, whatever be the correct explanation of the laryngeal paralysis, is clearly a distinct exception to this law. Both physiologically and pathologically, the adductor disablement was earlier and more intense in degree than the abductor. In conclusion, we would thank Professor Leith for kindly placing at our disposal the technique of the pathological department of the University for this investigation.

DONATION AND BEQUESTS TO HOSPITALS.—The Editor of *Little Folks* has sent £500 to the North-Eastern Hospital for Children as a further instalment towards the endowment of a ward by the youthful readers of that paper. Under the will of the late Mr. William Lee, of Higher Crumpsall, Manchester, £200 each has been bequeathed to the Salford Royal Hospital, St. Mary's Hospital, Manchester, and the Children's Hospital at Pendlebury. The late Miss Elizabeth Porter, of Halifax, has left the sum of £2,000 to the Royal Halifax Infirmary.