NOTES ON THE CAROTID BODY

By H. RUSSELL, M.D.

From the Department of Pathology, Edinburgh University, and the Laboratory of the Royal College of Physicians, Edinburgh

By whatever backward route the literature of the carotid body is followed into last century—be it that of anatomy, physiology or pathology—all the lines are found to converge upon Luschka's paper which was published in 1862.[23] This was a histological study of the *ganglion intercaroticum* and it was limited by the technique of the day, which consisted in dissection and cutting thin slices of the tissue and soaking them in various fluids. Luschka arrived at the conclusion that the so-called *ganglion intercaroticum*, the minute rice-grain knot of tissue lying behind the bifurcation of the common carotid artery, was a glandular structure, and not a nerve ganglion as the earlier anatomists had held, because he found that it had a glandular pattern and contained very few ganglion cells. He recognised the characteristic clumps or balls of cells of the carotid body, and described the nerve connections with the ninth and tenth cranial nerves and the superior cervical sympathetic ganglion. In this paper he referred to two small bodies which had been found in lower animals and which had been considered to be possible homologues of the carotid body in man. One of these, the *glandula carotica* of frogs, which is a capillary cavernous dilatation of the carotid artery,[34] he rejected as not at all like the carotid body in man because of its essentially muscular structure; the other, the axillary heart of reptiles, described by Leydig,[22] he found more comparable with the carotid body, for it was described as a small spindle-shaped swelling of the artery consisting of a "molecular mass" of cells and nerve fibres very closely bound to the neighbouring sympathetic ganglion. The references to these two bodies are mentioned here because they appear to have influenced later work on the carotid body. Luschka also suggested that in man there might be some similarity between the carotid body and the coccygeal body. The latter had been recognised by that time as a vascular tangle (glomus or glomerulus) on the terminal twigs of the sacral artery of man and many animals (*glomeruli caudalis* of Arnold[3]). This suggestion also influenced later workers.

Arnold [2] replied to Luschka's paper, and disagreed with him, maintaining that both the carotid and coccygeal bodies were vascular glomeruli and not at all glandular. He thought that the carotid body tissue ought to be called *glomeruli arteriosi intercarotici*, just as the scattered pieces of the coccygeal body in animals were called *glomeruli arteriosi coccygei*. However, he did describe the arteries of the coccygeal body as having thick, double muscular coats while those of the carotid body appeared like any other capillaries. It is interesting to compare the sketches of these two workers. Luschka's illustrations depict the type of tissue pattern with which a pathologist to-day is quite familiar in ordinary paraffin sections of the carotid body, while Arnold's pictures show the vascular tree with little other detail. Heppner [14] held that Arnold's preparations were grossly distorted by the method of injection which he used, and himself supported Luschka's ideas, finding that the balls of cells in the carotid body reminded him of early thyroid tissue. He stressed its relatively enormous nerve supply, and could not accept that it was like the coccygeal body because the capillaries were not at all unusual. He pointed out that to interpret the gland-like balls of cells of the carotid body as a kind of endothelium would introduce a new idea into angiology, and noted that the refractile molecules within the cells of the balls were a peculiar characteristic.

It was during the last forty years of last century that comparative embryology was first worked out, and as time went on it was realised that some of the glandular structures of the neck arose from the epithelium of the branchial arches ; and that discovery, combined with Luschka's idea that the carotid body had a glandular pattern, led various workers to believe that it arose also from branchial epithelium. It is believed now that these embryologists probably failed to distinguish the embryonic carotid body tissue from embryonic parathyroid tissue, and credit is given to Katschenko [18] for showing (1887) that the carotid body is definitely not epithelial in origin but appears first as a thickening in the wall of the carotid artery of the embryo.

In 1900 Kohn [19] made a study of the carotid body of man and animals, particularly pigs, and concluded that its cells were too irregular to be called epithelial, and decided that it belonged to the paraganglia, that is to say, one of the agglomerations of chromaffine cells which are scattered about in the body in close relationship to the sympathetic nervous system, and of which the best known is the suprarenal gland. Later workers, however, have not confirmed Kohn's [20] opinion about the chromaffinity of the cells of the human carotid body, although chromaffine cells are numerous in other species, including pigs, with which Kohn worked mainly.

After the last war several papers appeared which gave more detailed attention to the innervation of the carotid body (Gerrard and Billingsley [11] and Smith[35]). Smith described the development of the body in the embryo of man and animals and showed that its very early development is bound up with that of the artery and nerve of the third branchial arch, namely, the artery which becomes the internal carotid and the glossopharyngeal nerve. She showed that its connections with the vagus nerve and the cervical sympathetic develop later, and that in man and the rat chromaffine cells are not constantly present, while they are quite common in the cow and pig, and that the appearance of chromaffine cells in the carotid body is in any case a late development in the embryo. She stated that the capillaries were not unusual and showed no glomus-like arrangement, and decided that the body was a complex neuro-vascular parenchymatous mass bound up with the development of peripheral neuroblasts. She held that chromaffine cells are of ganglionic origin, while the non-chromaffine elements are of capsular origin: this latter, I assume, means that they arise from a ganglion satellite or neurilemma type of cell. She considered it unlikely that the carotid body would be shown to have an endocrine function.

In 1927, Hering [15] decided that the carotid body was not concerned with the carotid sinus reflex, because he found that the depressor reflex arose from nerve twigs in the wall of the carotid sinus itself and seemed to be quite independent of the carotid body. This appeared to narrow down the issue from the standpoint of physiology, but on the other hand De Castro [8] has shown that the carotid sinus branch of the glossopharyngeal nerve supplies the terminal filaments which ramify in the cell balls of the carotid body, and that these like other sensory nerves are centripetal, having their ganglion in the petrosal ganglion of the glossopharyngeus. This does not support the idea that the carotid body is a secretory organ, and to-day opinion tends to accept De Castro's suggestion that the carotid body is a unique type of nerve-ending which may be a chemical receptor for stimuli associated with the carotid sinus depressor reflex.

It is not yet clear whether the carotid body is a unique structure or whether there are similar bodies close to the aortic arch associated with the aortic depressor reflex. Penitschka[31] and Palme[29] have described small knots of tissue lying between the aorta and the pulmonary artery and close to the left coronary artery which appear to have the structure of the carotid body. They continue to use the word "paraganglion" for these structures, although they have not always found them to contain chromaffine cells: they resolve the difficulty by suggesting that the paraganglia at the cranial end of the animal body are parasympathetic in origin and non-chromaffine, whereas those of the caudal end are sympathetic and chromaffine like the suprarenal gland.

In a recent summary of work on the carotid body, Boyd[7] is unable to classify it as a paraganglion, but considers that it, and perhaps homologous knots of tissue in the wall of the aorta, may be parts of a pressor receptor apparatus.

When clinical and pathological records of the carotid body are sought out, the work goes back to 1888, when Hutchison[17] described a sarcomatous tumour developing under the upper half of the sterno-mastoid muscle. He called it a "potato tumour." He did not associate it at that time with the carotid body but recognised that he had seen eight cases of this curious tumour, growing in the upper part of the anterior triangle of the neck, which did not appear to originate in a gland or have any tendency to metastasise in glands. The case described in his paper occurred in a woman whom he had had under his care for ten years, and in whom the tumour had been growing for a year. He noticed that the temporal artery on the affected side had ceased to beat.

The first pathological account of a carotid body tumour was given by Marchand[24] in 1891 in his treatise on the carotid body for the *Festschrift* to R. Virchow. The tumour occurred in a woman of thirty-two years who had noticed it for four years. Histologically it showed an alveolar pattern with many blood spaces which were lined with endothelium, and Marchand thought it resembled an "alveolar sarcoma" although the name was not satisfactory. He noted that the alveolar pattern was less distinct at the edges of the tumour where active penetration of the surrounding capsule was apparent. He also recorded that the tumour was so tangled with nerve fibres that it reminded him of a plexiform neuroma. He studied many carotid bodies and decided that carotid *knötchen* was a suitable name, because it was neither a gland, ganglion, nor vascular glomus. A year later, Paltauf[30] also wrote an exhaustive paper on the carotid body and described four cases of tumour which he called vascular endotheliomas or angiosarcomas. His paper contains references to the origin of the terms endo- and perithelioma which have, and do still cause much difficulty in pathology. He concluded that the carotid body tumour ought to be called an endo- or perithelioma, but made the reservation that tumours of vessels are very rare, and that when they are described they are not at all like the carotid body tumour. He used injection methods when examining tissues, and favoured the idea that the carotid and coccygeal bodies were both primarily vascular structures. In 1904 in this country Gilford[12] gave an account of three cases of Hutchison's "potato tumour" which he called endotheliomata, and he correlated them with the descriptions of Marchand and Paltauf of tumours of the carotid body. In 1905, Mönckeberg[28] reviewed the whole subject at length and added three new cases of tumour to the nine which were already known in German literature. He decided that he could not consider the tumour to be a pure hyperplasia because it did not contain the essential nerve elements of the carotid body. Since that date an increasing number of cases have been recognised and recorded in medical literature.[9, 32]

When the term "paraganglion" became established by Kohn's work soon after the beginning of this century, Alezais and Peyron[1] sought to bring under one name all the tumours arising from the paraganglia, calling them *paragangliomes*, and pointing out that they were a group of tumours of neural origin which were usually diagnosed as of connective tissue or vascular origin. They suggested the *a priori* possibility that these tumours would be found to be associated with a clinical syndrome of hypertension. Later, this was confirmed for tumours of the suprarenal medulla,[4, 6] but not for carotid body tumours, and it became increasingly difficult to force the carotid body into a place among the chromaffine paraganglia.

Masson's work[25] on glomus tumours also emphasised the difference between the carotid body tumour and those arising from tissue resembling the coccygeal body.

By the courtesy of the Superintendent of the Royal College of Physicians Laboratory in Edinburgh, I have been allowed to examine the specimens of tumours of the carotid body which have accumulated there since the last war, and also specimens of normal carotid body tissue, and glomus tumours. Of thirteen tumours which were originally thought to be of carotid body origin, nine are typical carotid body tumours and the others have been classed as follows :—one ganglioneuroma, two parathyroid adenomas and one neuroblastoma (a large mass in the neck of an infant).

Fig. 1 represents a normal carotid body, and it shows the characteristic balls of cells lying in a connective tissue stroma which is full of nerve twigs. These cell balls are what Luschka described when he wrote of the glandular pattern of the organ. The cells within the balls are of irregular size and shape, but there is no definite lumen. De Castro [8] gives a fine description of two types of cells within the balls in specimens which were fixed very soon after death. The first type has a vesicular nucleus and vacuolated protoplasm, the vacuoles lying at the anti-vascular side of the cell, and the second type is a cell with a dark condensed nucleus and eosinophil protoplasm, caused, he says, by the closely-packed state of the mitochondria within the protoplasm.

It appears that the nerve twigs are continuous with the balls, and cells of the eosinophilic type may be detected within the small nerve bundles. It is therefore sometimes difficult to decide whether one is looking at a small nerve bundle or a small cell-ball.

Fig. 2 is a higher-power study of glomus tissue from the coccygeal region, and it is easy to see why the two structures have been so often compared with one another. The coccygeal body is built of whorls or balls of cells *around* vessels ; and the glomus cells, which are perhaps a primitive type of muscle cell, have dense nuclei and tend to stain deeply with eosin and lie within, and form, the thick vessel walls. These cells correspond to the "perivascular plasma cells" described by Waldeyer in 1875.[37]

In the nine specimens of carotid body tumour upon which this short study is based, some details of the clinical history were available in most and there was not anything in the data which was unexpected. It may be said that the tumour is generally slowly growing and is a neoplasm of adult life, and it does not usually metastasise even locally. It is, however, a serious condition, because its complete removal may require ligature of the carotid artery, although sometimes great deftness may enable the surgeon to strip the artery free.[13] There is no evidence that this tumour is associated with a clinical syndrome comparable with the vascular crises and extreme sensitivity to shock described in true paragangliomas of the suprarenal medulla ; nor is it painful as are tumours of the glomus type. Histologically, the nine tumours were very much alike. The fibrous capsule is surprisingly dense, and the substance of the tumour is frequently very like the normal carotid body, being characteristically arranged in cell balls packed into a rather fine stroma. Where the tumour most closely resembles the normal carotid body tissue, the irregularity of the individual cells of the balls is apparent and some of them are vacuolated (Fig. 3). In other parts, particularly at the growing edges, less differentiation is present and small clumps of undifferentiated cells appear to be squeezing their way into every available tissue space of the capsule (Fig. 4). These syncytial-like groups of small, yet irregular, undifferentiated cells remind one of undifferentiated neural tumours, particularly the cerebellar isomorphic glioblastomas [16] (medulloblastomas), and the neuroblastomas of the sympathetic nervous system.[33] (The word "neuroblast" is used here to name the small undifferentiated cell type which is seen in the developing nervous system of the embryo prior to differentiation.)

Discussion

If the carotid body is a nerve-ending, and unique, it is interesting that it should produce a so characteristic hyperplastic condition and tumour growth, and one searches in the records of oncology for references to analogous new growths. If it is not a unique structure, but similar to other nerve-endings of the vaso-depressor apparatus in the thorax, one might expect to find an occasional reference to carotid body-like tumours in the region of the aortic arch, and so far as I am aware this cannot be found. However, it is not beyond the limits of possibility that such a tumour might be mistaken for a bronchial carcinoma. In my experience, some bronchial carcinomas resemble primitive neural tumours to a remarkable degree, and the infiltrating edges of some of the carotid body tumours upon which this study is based are very reminiscent of undifferentiated nerve tumours, especially those of the sympathetic nervous system which are usually described as neuroblastomas in this country (*sympathomes embryonnaires* of French authors), in which rather syncytial-like masses of small and unequal cells are found resembling the undifferentiated nerve strands of the embryo.

It has never been a generally accepted idea, so far as I am aware, that nerve-endings may be the site of tumour formation. Tumours of the peripheral nerves develop in many parts of

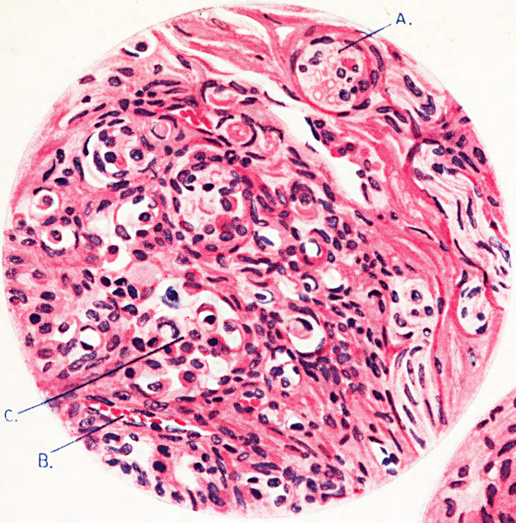

FIG. 1.—Normal carotid body (high power study) 9740.36. To show the characteristic balls of cells. (A) Nerve in which eosinophil cells of the type seen within the balls may be detected. (B) Small blood vessel. (C) Centre of a cell ball.

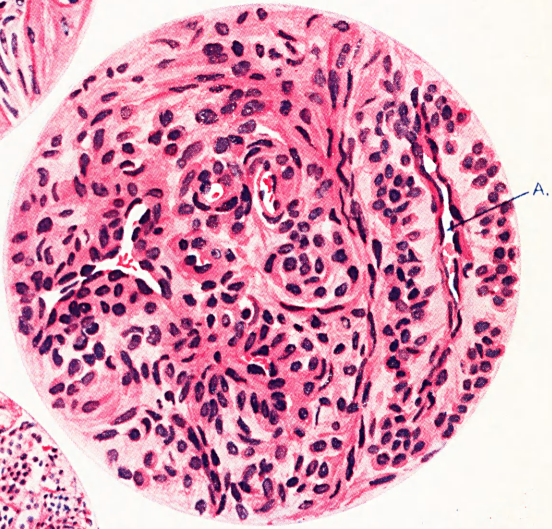

FIG. 2.—Glomus tissue from the coccygeal region (high power study) 544.36. (A) Vessel cut longitudinally shows the arrangement of the "glomus cells" within the vessel wall.

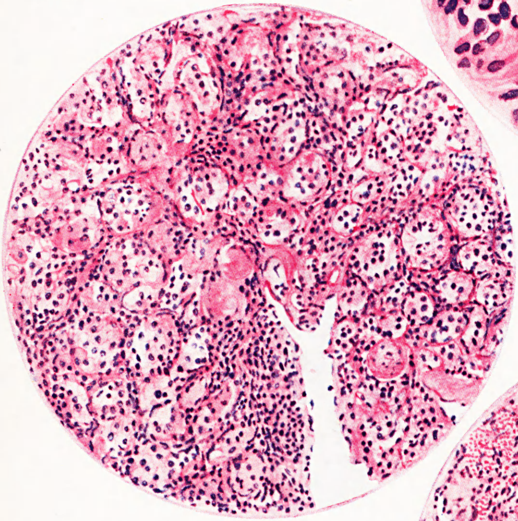

FIG. 3.—Carotid body tumour (low power). Male aged 29 years, in whom the tumour had been present for 8 years. The tissue is arranged in characteristic balls, and the cells within these are well differentiated.

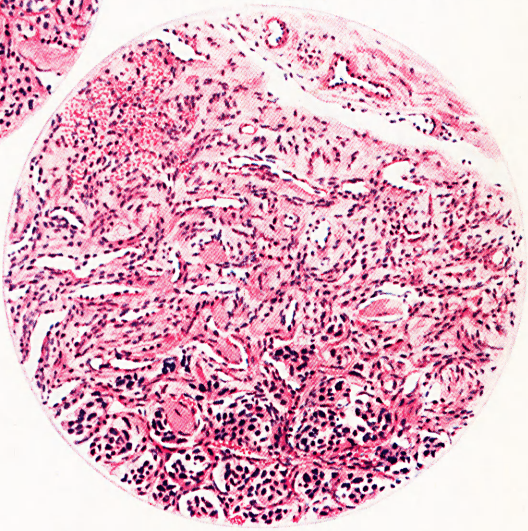

FIG. 4.—Carotid body tumour (low power). Male aged 37 years, in whom the tumour had been present for 2 years. To show the growing edge where syncytial-like clumps of small undifferentiated cells are filling up the tissue spaces of the dense fibrous capsule.

the body, and many years ago Soldan[36] decided that many tumours classified as soft fibromas were neurogenic in origin. He also thought that nævi were caused by the disturbance of local innervation, and recently this idea has been revived and amplified by Masson. It has also been suggested that some of the subcutaneous sarcomata may arise from nerve tissue, and from that it is not a great step to suggest that myosarcomas may arise in relation to muscle spindles.

During the past years great interest has been centred on Masson's[26] studies of the melanomas, in which he has revived Soldan's idea of the neural origin of melanomas, and has suggested that melanomas arise in relation to skin nerve-endings and are peripheral gliomas. He has also suggested that the melanin-bearing cell is a unicellular gland.[28] The idea that the pigmented cells of the suprarenal medulla are unicellar glands goes back to Balfour's[5] pioneer work on comparative embryology when he described the development of the interrenal body, and frequently since his day workers have touched on the comparison between ganglion cells, and chromaffine suprarenal cells[10] and the pigmented cells of the skin, which are all derived from the epithelial layer of the embryo. These specialised cells, at least in the first two instances, lie in close association with smaller, less differentiated satellite or neurilemma cells which become extremely active when the large dominating cell disappears or atrophies.[35] Nerve-endings are also associated with cells of the neurilemma type, and it may be that in the carotid body tissue there is also this balance between more highly and less highly developed nerve tissue, and that the carotid body tumour originates as a hyperplasia of differentiated tissue which disappears gradually and is overgrown by undifferentiated neural tissue.

It may be that a number of tumours which have been classed as sarcomas of one type or another will eventually be placed among those which arise from neural tissue, and that the carotid body tumour will be one of them. At present, however, it is not possible to be enthusiastic about the reclassification of tumours as it is not yet apparent that reclassification can contribute to the explanation of neoplastic growth.

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