7

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Local Invasion and Spread of Cancer

Volume Editor: K.W. Brunson

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SERIES EDITOR: HANS E. KAISER
Department of Pathology, University of Maryland, Baltimore, Md, U.S.A.

Local Invasion and Spread of Cancer

Edited by

KENNETH W. BRUNSON

Department of Immunology and Infectious Diseases
Pfizer Central Research, Groton, Conn., U.S.A.

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2

COMPARISON OF THE PROGRESSION OF SELECTED, TOPOGRAPHICALLY PARTICULAR, TUMORS IN THE HEAD AND NECK REGION

Laryngeal pseudosarcoma, primary cholesteatoma, paraganglioma and schwannoma of the VIIIth cranial nerve

G. BROICH

The head and neck region can be host to a great variety of tumors. In fact with the exception of those arising from the reproductive system, every type of neoplastic growth has its representative in this area. Carcinomas can arise from skin and mucosal surfaces, contained in the cephalic region. The sarcoma family is represented by tumors from all mesenchymal cell types (17), including connective tissue and its derivatives, endothelial tissue, lymphoid and both striated and smooth muscular tissue. Tumors from glial and nervous cells are present as well. Adipose tissue is less abundant and lipomas are less frequent in the oropharyngeal region than in the extremities and the retroperitoneum (42, 43, 62, 107, 113, 115, 124, 204), but Fu and Perzin (63) described a nasopharyngeal liposarcoma and recently a myxoid liposarcoma has been seen by Gaia and Coll. (143) confirming the presence of tumors of all tissue types in the cephalic region. The cephalic region harbors also several peculiar types of tissue. The teeth are formed by both an epithelial element, the ameloblasts, and mesenchymal elements, such as the odontoblasts, cementoblasts and fibroblasts. The former are only transient cells in the odontogenesis of the human, different from the rodents, where the continuously growing incisor teeth are maintained by a vital ameloblastic population. Neoplastic growth from both the ameloblast and the odontoblast has been described, sometimes as mixed odontogenic tumors (217). Ameloblastic growth is thought to derive from islets of less differentiated cells in the periodontal spaces, that are embryonic remnants of the epithelial sheet of the enamel organ, while the odontoblastic component may derive from fibroblasts exposed to cells of the early amelogenic epithelium of the dental lamina. Neoplasms can also arise from cell remnants of another transient organ present in the rhinopharynx, the chorda, and are called chordomas.

The main interest for a separate look on some forms of abnormal growth in the area rises not so much from special histologic features, but from the sometimes peculiar behavior expressed by these tumors. This can be due to special growing patterns or based on the conditions imposed by the unique anatomical relationship between the tumor and a multitude of close lying organ systems in the cephalic extremity. The presence of spaces limited by rigid, bony, structures together with anatomic entities of vital importance, as are the parts of the nervous system harbored in the cephalic extremity, introduces us to a special concept of tumoral behavior. The neoplastic growth, whose degree of malignancy is generally measured in terms of local histologic invasiveness and ability to metastasize, shows here a new feature of potentially life threatening behavior, that can be called topographical and functional malignancy. The neoplasm, growing in a fixed space, will extend first to occupy that area, displacing the other anatomical structures present in the space and limited by it. Encountering the borders of said area, the tumor will continue its growth by eroding and displacing them. The erosion of the generally bony borders happens not in an invasive, and so frankly malignant, process, but through compression induced resorption of bone. It is so a secondary phenomenon, well different from the invasion of bone by truly malignant cells. The result, perhaps, is in both cases the destruction of bone and the impairment of the structural integrity of the surrounding anatomical structures. Therefore the term topographical malignancy, since the neoplasm would behave in an unthreatening way if growing in other areas of the body, where expansion can be easily accomplished without immediate negative effects on the surrounding anatomical structures. Perhaps not only histologically benign tumors can express topographical malignancy. A malignant tumor may arise in areas where its growth becomes a danger for the life of the host not only by its invasiveness or metastasizing ability, but also by local factors. So a laryngeal carcinoma, certainly a malignant tumor, can cause death by obstruction of the airways much earlier than by general dissemination, if untreated. Local recurrences in the neck after surgery may produce exitus due to the erosion of the major local vessels, mainly the carotic artery and jugular vein, with a fatal catastrophic blood loss. The head and neck region with its abundance of vital structures and rigid anatomical spaces offers prime examples for topographical malignancy.

The concept of malignancy as distinct from histological features can be found in other living tissues as well. A reverse behavior is known in plants, where malignant growing cells may not threaten the survival of the plant as a unit, due to the lack of a proper dissemination medium (given in animals by the vascular circulation). Moreover, in a reverse condition that could be called topographical benignity, the local destruction of tissues in a plant, if peripheral to the roots, may not interfere with the general survival of the plant.

Four tumors which in this way can acquire a special interest under both clinical and pathological viewpoints will be brought here as brief examples for this concept. The selection is aimed to comprise a specimen of each major tissue system. It is not supposed to give a comprehensive look on the head and neck oncology, but to introduce the concept of the malignant progression of tumors due to their topography as distinct from their histology. Three histologically benign lesions will be described in conjunction with a malignant one.

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LARYNGEAL PSEUDOSARCOMA

The Laryngeal Pseudosarcoma, described for the first time by Szmurlo (215) and Kahler (112) and delimited as a histopathologic entity of the larynx by Lane (125) and Goellner (79), consists of the association of a laryngeal epidermoid carcinoma, generally of small dimensions, contained in a polypoid mass of great dimensions of proliferating tissue which at the microscopic examination shows cytoplasmatic and nuclear cellular abnormalities peculiar of a sarcoma. The gross appearance is generally that of a polypoid or pedunculated mass without areas of necrosis or ulcerations.

At the microscopic examination there is a great prevalence of sarcomatoid stroma with cellular anomalies and frequent mitosis. At certain times the intercellular edema allows the proliferating cells to assume a stellate and myxomatoid appearance and giant cells with clear nuclear anomalies are abundant. More frequently the cells maintain a fusiform shape embedded in a great amount of collagen and precollagen fibers and assume a disposition in parallel streaks. In rare areas of reduced cellular anomalies the tissue may resemble a granulomatous reaction, but more generally the overall appearance is more like a fibrosarcoma or leiomyosarcoma (79, 114). At certain times the anomalies are so expressed to resemble a liposarcoma or a xantofibrosarcoma (for the classification and review of these soft tissue tumors see (3)).

With exhaustive enough microscopic examination of the tumor, in a restricted area there can always be found a zone of clearly epithelial origin and with an aspect of a generally well-differentiated epidermoid carcinoma. This zone arises from the mucous covering of the polypoid tumor and remains or delimitated to the superficial area, or shows a droplet like ingrowth into the stroma.

Clinically the pseudosarcoma shows a rapid enlargement of the polypoint mass which brings the laryngeal lesions to be rapidly obstructive. It may request an emergency tracheotomy to maintain the airways patent. The further clinical behavior of the tumor is perhaps much less dramatic than could be expected by a sarcoma of that dimensions. It behaves generally much more according to the carcinomatous part embedded in it (7, 184). The incidence of the disease is referred to as rare, but it seems much less exceptional than generally stated. In 1965, Appelman and Oberman (5) could find 54 descriptions present in the literature and add 11 of their own. Additional cases have been reported (68, 69, 186). The overall presence of this type of lesion may well be greater than previously suspected (18).

The fact that the tumor behaves more according to the small carcinoma embedded in it than to the large sarcomatoid mass accompanying it, is of great importance for the treatment, since also large lesions which would have been considered only for palliative radiotherapy, can largely benefit from surgical treatment with a good survival prognosis.

The histogenesis of the tumor has long been debated. The problem lies clearly with the interpretation of the sarcomatoid component. In 1865, Virchow created the term 'carcinosarcoma' for such associated tumors with the definition of the epithelial part as true epidermoid carcinoma. Laryngeal carcinosarcomas have been described by Szmurlo (215), Kahler (112), Uhlman (222), Ricci (174) and Lang and Krainz (126). In a first general survey Saphir and Vass (183) consider the stroma as purely reactive. Carcinosarcomas can arise also in other oropharyngeal areas, in the esophagus about 50 cases have been described (21, 100, 176, 193, 205). Other areas of pseudosarcomatous growth in the cephalic region are among others the maxillary sinus (220) and the tongue (190). Several authors after 1938 have described carcinomas associated with a fusocellular atypic component (19, 29, 39, 45, 53, 90, 148, 149, 152), but it is with Lane (125) that this form is defined for the first time as a special entity, called pseudosarcoma, excluding other types of apparently mixed growth as for example the nodular fascitis (140). The tumor needs to be held distinct from other forms of atypic growth arising from mesodermal tissue, since, also if rarely, each tissue type present in the larynx may give origin to a neoplastic growth, from fibrous xanthomas (177) to synovial sarcomas (17, 187).

Several major opinions have been expressed regarding the histogenesis of the tumor. Some authors consider the stroma as a true sarcomatoid malignant tissue. Legier (135) and Minchler (141) report three cases with a highly malignant discourse, the presence of sarcomatoid lymphonodal metastasis, and without carcinomatous cells. They sustain the malignancy of the nonepithelial component. This view is held up also by Invernizzi (108), Kupper and Blessing (120) and Szimivasan and Tavalkar (214). A second group, with Lane, considers the tissue as an excessive stromal reaction to the carcinoma. The stroma is considered as exclusively reactive, an opinion expressed also by Baker (10) and Kratz and Ritterhoff (118). Goellner in 1973 (79) expresses the same theory presenting 25 cases of his own. It is supposed to be a special characteristic of these epithelial malignant cells to induce a mesenchymal reaction, for this is found also in the lymphonodal metastases (140, 197). A third group, with Aubry and Leroux-Robert (9) and Kleinsasser and Glanz (114) consider the stroma as of atypic epitheliomatous origin. They explain the whole tumor as of epithelial origin with the pseudosarcomatous component constituted by peculiarly differentiated epithelial cells. This theory has found many followers especially in Europe with Pietrantoni (165), Pizzetti and Leonardelli (166), de Vido (38), Fini-Storchi (46), Rucco and Zerneri (180), Himalstein and Humphrey (96). Rucco and Zerneri (180) and Minnigerode (142) suppose an inducing effect of the radiotherapy of the carcinoma on the pseudosarcomatous component. This theory has been further developed by Randall et al. (171) and especially Kleinsasser and Glanz (114) who describe the fusiform cells as carcinomatous epithelial cells which have lost unspecified surface characteristics becoming able to grow individually.

Finally it may be mentioned a further opinion by Haubrich (89), in which the tumor is seen as a primary benign mesenchymal reaction with the secondary insurgence of a carcinoma.

Also if the origin of the spindle cell component is still unsettled, recent new findings add new biochemical data to its assessment. A protein, called keratin, has been found to be specifically associated with almost all cells of epithelial origin (54, 55, 207, 208, 210). These proteins belong to the intermediate filament family as do vimentin in the mesenchyme, desmin in the muscle, neurofilaments in the nerves and glial filaments in the astrocytes. The keratin has up to now been found in all epithelial cells tested, but is absent in

cells of nonepithelial origin (8, 54–57, 207, 208, 210) and can so be considered a marker for cells of epithelial origin, both normal and pathologic. The keratoproteins have been shown to be formed by distinct keratin molecules and more than 17 proteins have been isolated (145, 212). Specific keratin types have been found according to epithelial cell type (40, 58, 221), cellular growth environment (64, 66, 208, 209), stage of cell differentiation (41, 65, 216), stage of development (233) and disease (146, 151, 227). The keratins have been catalogued and their expression in the different epithelial types has been followed (145, 211). Attempts to sequentiate the keratins have been done (59, 198–200) and cDNA sequences have been obtained (86, 87), showing that each keratin type is formed by the expression of a specific gene and not through modification of a primordial common protein. These findings have prompted the research of keratin in cells of uncertain origin, since its presence can be taken as an excellent evidence for their epithelial origin. Specific antibodies to the keratins have been developed (60) with a special effort for standardization by the group directed by Sun (41, 212, 227). The use of antikeratin antibodies on carcinosarcomas or other tumors with an uncertain cell component has given mixed results for different tissues (191). Its application on pseudosarcomatous tumors arising from the larynx has not shown any keratin-like reactivity in the sarcomatoid component (234). It has to be said perhaps, that only Woods tested specifically the pseudosarcoma, excluded in the more recent work of Shi *et al.* (190). Each used different monoclonal antikeratin antibodies, in no series Sun's AE1, AE2 and AE3 antibodies were used. Furthermore, the nonreactivity cannot exclude the presence of keratoproteins definitively. Nonetheless these results generate certainly more evidence for a mesenchymal, and so reactive, origin of the sarcomatoid stroma.

It can be concluded that the pseudosarcoma is certainly determined in its behavior by the carcinomatous component imbedded in it. Besides rare cases in which a true association of sarcoma and carcinoma may be present (141, 205, 214) the pseudosarcomatous part behaves as benign growth. The therapy has so to be focussed on the dimensions, site and extension of the original carcinoma, which generally permits a radical surgical cure, a surgery which may have been renounced of if the whole polypoid mass would have been considered as a sarcoma (18). The tumor will progress as a laryngeal carcinoma, regardless of its sarcomatoid component.

PRIMARY CHOLESTEATOMA

A cholesteatoma is a whitish mass, arising in the middle ear and petrous bone. It consists of lamellar or 'onion-skin-like' disposed layers of keratinizing epidermal cells around an amorphous center, constituted by the desquamated keratinocytes, forming an epidermal cyst. The continuous growth of the keratinocytes with desquamation in a closed cavity is the base of the clinical destructiveness of the tumor, which works its way through the petrous bone without invading it. Cholesteatomas are generally present as a complication of chronic middle ear inflammation. In this case the ingrowth of epidermis through a tympanic perforation is thought to give origin to the lesion. The tissue forms first a pocket in the middle ear cavity and autonomizes finally itself closing its internal cavity by losing the connection with the external ear canal. Sometimes identical tumors can be found in the petrous bone without any history of middle ear disease and with an intact eardrum. These tumors have generally been considered very rare if not exceptional, but a review of the literature shows easily a large amount of isolated case reports and the impression is that the overall incidence may be greater than originally assumed. They may arise at the cerebellopontine angle, at the jugular foramen, in the petrous pyramid or in the middle ear and mastoid (102). Described as 'tumeur perlée de l'oreille' by Cruveilhier in 1849 (30), Cushing in 1922 (32) expressed the hypothesis that the primary cholesteatomas showed a different pathogenesis than the usual growth found in chronic middle ear disease and were perhaps epidermoid cysts arising from epidermal cell inclusions formed during ontogenesis. This theory is sustained also by Cawthorne *et al.* (23) and Cawthorne (24, 25). The tendency to ascribe cholesteatoma-like lesions to embryonic cell remnant proliferation went so far as to try to describe some middle ear diseases with inflammations and eardrum lesions, principally middle ear cholesteatomas, as secondary to epidermal growth from embryonic cell nests. This point of view is today only of historical significance in middle ear lesions with a perforated eardrum. The majority of authors tend to ascribe only the origin of primary cholesteatomas to the proliferation of cells arising from ectodermal remnants included in the temporal bone during embryogenesis (136). For the diagnosis of primary cholesteatoma an intact eardrum should be present. Obviously the possibility of an unrelated coexistence of a primary cholesteatoma and a chronic middle ear inflammation exists, in which case the diagnosis should be given only if there is clear anatomical distinction and lack of continuity between the lesions. It is rather difficult in these cases to come to a clear diagnosis of origin. Tumors arising in or near to the middle ear cavity are considered to originate from remnants of the first branchial arch, where the cholesteatomas of the petrous bone apex arise from Sessel's pouch (26, 223). This theory has encountered some opposition lately, especially regarding the tumors of the middle ear and those of attical location. Ruedi (181) and Friedman (61) in extended histological studies could not find any epidermal cell remnants in normal temporal bones. Wullstein (235) describes as a frequent finding the presence of small perlaceous tumors right behind an intact attical membrane. The theory of Ruedi, which ascribes these attical cholesteatomas behind intact tympanic membranes to an ingrowth of the basal layer of the epidermis of the membrane of Shrapnell, gains to renewed interest (26, 236), leaving the disontogenetic theory to true apical primary cholesteatomas. Classifications have followed these interpretative difficulties (37) and a definitive viewpoint has still to be agreed upon.

The clinical onset is generally subtle with headaches and Eustachian tube compression as frequent signs, as well as a deficit of the trigeminal nerve, especially in its third branch (67, 156). The nerves of the extrinsic ocular muscles (III, IV, VI) and the acoustico-facial bundle are involved at a second time due to the mostly apical position of the tumor in the petrous bone, i.e. anteriorly to the internal ear canal. Finally the foramen jugulare nerves and the hypoglossus may be-

come involved. The differential diagnosis includes other expansive growth of the petrous bone apex, such as neuromas and meningiomas. The diagnosis relies mainly on radiographic exploration and especially the computerized tomography, which shows a lipidic hypodensity with geographic map like borders (20). A 'truncated' aspect of the apex and asymmetries are of special importance in the radiologic findings.

Due to its continuous expansion in a closed cavity and compression damage to the cranial nerves and the central nervous system these epidermal cysts may acquire a fatal decourse if untreated. The surgery is difficult because of the deep position of the tumor and only few ways of approach are possible (194). One way, reserved for small lesions on the upper side of the bone, is the extradural middle fossa approach (47, 48), the second is a translabyrinthine and transcochlear surgery (101, 106, 169, 170). For a short discussion of these approaches see the Schwannoma of the VIIIth nerve in this chapter. Complete removal is advocated by most surgeons, but it has to be kept in mind that this is not always possible, due to brainstem adherences and deep location. In this case it is of main importance to maintain the cyst's cavity open to the outside through the mastoidectomy opening for draining of the desquamating cells (permanent fistolization) and further medical cure (67). Since the expansion of the cholesteatoma is accomplished through the accumulation of centrally desquamating cells, the presence of a permanent fistula will relieve the internal pressure and arrest the expansive growth of the neoformation.

Comparing finally the local aggressiveness of the lesion with that of the basal cell carcinoma, several important differences have to be noted. The cells of the cholesteatoma remain always typical and with a mitotic count within the normal range. An organization in cell layers, closely resembling normal skin, can be observed. There are visible a basal proliferative layer, a spinous layer and a squamous layer, proceeding from the outside to the inside. There is no visible differentiation toward skin annexes like hairs or sebaceous glands. The local aggressiveness relies only on the expansive pressure created by continuous central desquamation. In the basal cell carcinoma cellular atypias are perhaps present and the dermal/epidermal junction is abnormal and at histologic sections isolated cell nests can be seen, distant from the primary tumor. Perhaps the cell differentiation in the cholesteatoma shows little deviation from the normal. The basal cell carcinoma is surprisingly similar in this, since the evaluation of at least one molecular marker of epithelial cell differentiation, the expression of keratoproteins, has shown no abnormalities or differences from normal skin (119). Keratoproteins as cell differentiation markers have been briefly referenced in the section of the laryngeal pseudosarcoma in this chapter.

The progression of the primary cholesteatoma is that of a topographical, functional malignancy, there is no known tendency of the cells to become histologically malignant. Carcinoma cells may exceptionally be coexistent, but there is no significant relationship of incidence. Three histologically distinct lesions can arise from epidermal tissue, which progress from the topographical malignancy with cellular benignity of the cholesteatoma, to the locally invasiveness of the basal cell carcinoma and finally to the frankly malignant cells of the squamous cell carcinoma.

PARAGANGLIOMA

Paragangliomas or glomus tumors arise from the paraganglia, small cell groups of close association to blood vessels and high vascularization (2), that originate from the neural crest according to the thesis of Masson (160). In the paraganglionic system the adrenal medulla is comprised as well as the carotic body (Luschka's gland, paraganglion of Kohn) and the vagal glomus. Extraadrenal paraganglia are nonchromaffin but are today supposed to possess neuroamine producing capacity (44, 132) and, according to certain authors, may produce neurotransmitting polypeptides. The carotic body and the aortic paraganglionic tissue have a well-established chemoreceptive role in the homeostasis of the blood O2, CO2 and pH (71, 74, 75). Specific O2 partial pressure values in different areas in the glomus tissue have been described by Acker (1). A sensory innervation of the carotic body has been demonstrated in 1928 by De Castro (33) and is established through the nerve of Hering (IX). The aortic paraganglia are innervated by fibers from the vagus (157), which form a distinct nerve only in the rabbit. Sympathetic fibers reach the intraglomic vessels. Microscopically the tissue is characterized by an extremely high vascularization (the carotic glomus has a unit blood flow of 2000 ml/100 g/min versus a renal flow of 420 ml/100 g/min!). Two main cell types are found in the glomus, around which some terminologic confusion has arisen and which we will continue to call type I and II cells (17). Type I cells contain a catecholamin, probably dopamin, and show reciprocal synapsis' with intraglomal nerve endings. These cells have been included by Pearse (159, 161) in his Amine Precursor Uptake and Decarboxylase system (APUD) due to cytochemical and ultrastructural characteristics.

Besides the first recognition of the paraganglia by Haller (cited by Rosenwasser (179)) two centuries ago and the studies of the carotic body by Kohn (116), as well as the description of the aortic glomera, paraganglionic tissue has been described in relation to the nodose ganglion of the vagus (229) and in various sites in the temporal bone (rediscovered by Guild (82, 83)), which are now known as a group, as glomus jugulare. Laryngeal paraganglia have been described in the larynx (131) and recently also in the recurrent laryngeal nerve (22). Normal paraganglionic tissue is also present in the trachea, thyroid capsule, orbita, mandible and in various extracephalic regions, not all of which have been clearly proven in humans. The first carotic body tumor has been described by Marchand (139) and the first aortic tumor by Monro (147). Perhaps the detection of tumors from paraganglionic tissue has sometimes preceded the histologic determination of normal tissue in that site, as happened with the laryngeal glomus, where tumors had been described as early as 1955 (4). Today more than 30 laryngeal paragangliomas have been described (99, 122, 225). So tumors in regions where up to now normal tissue has not been demonstrated, as in the nasopharynx (105), may herald the presence of paraganglia in that sites too (14).

Hyperplasia of carotic bodies has been described as a normal adaptation reaction in high altitude dwellers, in which a higher incidence of chemodectomata is also reported (6, 91, 121).

Tumors arising from glomus tissue, called also chemodectomata, are generally well delimitated and firm. Focal

hemorrhage and trabecular fibrosis may be present. The 'Zellballen' (cell clusters) of the type I cells are generally somewhat larger than in the normal glomera and are separated by an extensive capillary network. The type I cells have a pale eosinophilic cytoplasm and its granules stain brown and black with Grimelius stain (80, 195, 224). A capsule is generally present also if it can be very thin or even absent in certain areas (123). There is evidence of an increase in connective stromal tissue and hemosiderin deposition with the formation of fibrosiderotic Gamna-Gandy nodules. Small nerve bundles are sometimes visible, also if large nerves are seen exclusively in vagal tumors. The vessels have a thickened wall due to sclerosis, myxoid degeneration and hyperplasia of the smooth muscle tissue.

Malignant degeneration is relatively rare in extramedullary locations, in the head and neck region the most frequent site seems to be the laryngeal glomus (70). The transformation is heralded by the presence of necrosis in the 'Zellballen', invasion of the vascular spaces and presence of mitotic figures. Pluricentricity is present in 10–20% of the cases (133), also if the percentages vary widely in the literature. In certain cases a familial incidence has been observed and these cases account for the greatest part of the pluricentricity seen. The genetic transmission follows an autosomal dominant pattern (206, 232). The most widely accepted classification of these tumors has been established by Grimley et al. (81) and Glenner and Grimley (78), dividing intramedullary and extramedullary tumors.

The clinical symptoms are linked to the site of the tumor. Most forms show no endocrine activity (167), also if neoplasms secerning catecholamines have been described (137). The carotic body tumor appears as a growing tumefaction in the upper carotic region with well-defined margins, horizontal mobility, vertical fixity and transmitted or intrinsic pulsatility. Pain and dysphagia may be present in later stages, symptoms of carotic sinus hypperreflexia are rather rare if present at all. Carotic artery compression finally can give symptoms of reduced blood flow in its internal branch with cephalalgia and vertigo. The tumor can extend up to the skull base and in the parapharyngeal spaces. For surgical purposes three classes have been defined: 1. localized tumor not attached to the vessel wall, 2. tumor attached to the vessel and partially surrounding it, 3. tumor completely surrounding the vessel. Since in the last type the preservation of the carotid is impossible, some authors (134) have advocated surgical treatment only in the first two classes, due to the otherwise high mortality. Better techniques in vascular surgery have perhaps lately widened the surgical indications in these cases (34, 109). The surgeon has always to be prepared to perform vascular reconstruction in paraganglioma removals (189).

Glomus jugulare and tympanicum tumors, known since their description by Rosenwasser (178), arise from the IX and X cranial nerves. The jugularis tumor, laying lower in the tympanic cavity, can produce large bone defects with only few clinical symptoms. When it enters the tympanic cavity tinnitus and hearing loss become evident, a paresis of the VII cranial nerve is rare at this stage. Tympanic glomera tumors arise from the paraganglia along the nerve of Jacobson and give a much earlier symptomatology with pulsatile tinnitus, hearing impairment and visibility of the tumor through the tympanic membrane (94). To establish the diagnosis a radiologic assessment is always necessary and different techniques are used (138, 164, 218, 219) also if arteriography and CT scan remain the most useful ones. A retrograde jugular venography is generally necessary to assess sigmoid sinus invasion and complete the identification of the feeding blood vessels. The tumors have to be differentiated from vascular anomalies present in the middle ear (95). Nonsurgical ways of treatment have been attempted but have been disappointing. Radiotherapy can have only palliative effect (77) and embolization is useful only as a preoperatory attempt to reduce intraoperatory blood loss. The surgery of these tumors is difficult and different techniques have been described (76, 84, 196), but the determination of the surgical treatment is largely the merit of Fisch, who laid the basis of the modern surgical treatment of paragangliomas. Surgery remains the only way of treatment that carries a favorable longterm prognosis (213). Since a clear classification is the first major step for a successful clinical assessment and treatment, Oldring and Fisch (154) and Fisch (52) divided the glomus jugulare and tympanicus tumors in four categories with subdivisions in types C and D, the classification is here reported due to its importance (from Fisch (52)):

A – tumor limited to the middle ear cleft
B – tumor limited to the tympanomastoid area without destruction of bone in the infralabyrinthine compartment
C – tumors extending and destroying bone of the infratemporal and apical compartment of the temporal bone
  C1: tumors destroying the jugular foramen and jugular bulb and with limited involvement of the vertical portion of the carotic canal
  C2: tumors destroying the infralabyrinthine compartment of the temporal bone and invading the vertical portion of the carotic canal
  C3: tumors involving the infralabryinthine and apical compartments with invasion of the horizontal portion of the carotic canal
D – tumors with intracranial extension
  D1: tumors with intracranial extension of less than 2 cm in diameter
  D2: tumors with intracranial extension greater than 2 cm in diameter
  D3: tumors with inoperable intracranial extension

Types A and B are generally removable through a conventional tympanoplasty, while types C1–3 and D1 require the infratemporal fossa approach described by Fisch (51, 110). D2 tumors require a combined otoneurosurgical two-stage approach and D3 tumors need a similar technique for the removal of the extracranial portion of the tumor when indicated. The prognosis of the involved cranial nerves depends on the extension of the tumor. A lack of proper presurgical assessment leads invariably to long-term recurrences of the tumor, which bring to death the patient, like the untreated primary growth, through intracranial invasion and irrefrenable hemorrhage. The high vascularity of the tumor poses in fact certain special problems. A very precise assessment of the feeding vessels of the neoplasm is necessary, large vessels may be in direct contact with the vascular spaces of the tumor. The natural decourse of the tumor ends in fact mostly with a rupture of these vascular spaces and

catastrophic blood loss as the terminal event. In this case expansion itself contributes less to the functional malignancy of the tumor than does a special feature of the growth itself, its vascularity.

SCHWANNOMA

The Schwannoma of the VIIIth nerve has been described for the first time by Sandifort in his 'Observationes anatomicopathologicaes' in 1777 (182), reporting a small nodule arisen from the right acoustic nerve. In 1810 Levesque-Lasource recognizes the correlation between the autoptic finding of such growth and the clinical signs of vertigo, deafness, tinnitus, headache and deviation of the tongue. Ballance (11, 12) is supposed to have for the first time successfully excised an acoustic neuroma and with Olivecrona (155) starts the time of serious attempts to preserve the facial nerve in this surgery. Early comprehensive discussions of the tumor can be found in Henschen (31, 92, 93) and Cushing (1917).

Schwannomas can arise from cranial or proximal spinal nerves. They form round or oval, well defined and encapsulated masses with a smooth surface and are generally solitary and monolateral outside v. Recklinghausen's neurofibromatosis. In the latter disease a certain incidence of histologically malignant tumors have been described, but otherwise the neoplasm is mostly benign. The tumor arises from the Schwann cell of the nerve, generally at the transition from the oligodendroglia to the Schwann cell. This latter cell is known to be able to produce collagen and other stromal fibers and especially to give origin to the myelinic sheet of the peripheral nerves. The cell has also phagocyte abilities and originates from the neural crest epithelium. The tumor has an excentric location in the nerve, dislocating and compressing the fibers more than penetrating in between them. Nerve fibers are typically absent in the Schwannoma, a difference with the neurofibroma, where the tumor appears intimately mixed with the nervous fibers. The neoplastic cells are disposed in bundles and the nuclei may show a pseudopalisading pattern around the blood vessels. Fibroreticular tissue as well as hemorrhages and myxoid or xanthomatous degeneration may be present. Areas of high and low cellularity, called Antoni A and B tissue, are also found in Schwannomas, but not in neurofibromas (150, 173, 175).

Also if the solitary Schwannoma of the skull base can arise from virtually every cranial nerve, the more frequent sites are the superior vestibular nerve, the facial nerve and the nerve group of the foramen jugulare. The tumor retains in the majority of cases its benign histologic characteristics and slow growth, but its position in the cranial cavity makes it a life-threatening disease. The acoustic neuroma originates inside the internal auditory canal and in its growth it will then finally extend outside the porus acusticus internus and towards the pontocerebellar angle. The neoplasm will so compress the trigeminus and facial nerves, besides the nervus acusticus, and finally press against the bulbus and pons. This will block the normal liquoral deflux and cause an obstructive hydrocephalus. Besides growing towards the encephalon the neuroma may extend itself inside the temporal bone due to pressure induced bone resorption. In this way it may finally invade the inner ear labyrinth (85, 188, 230). Few cases of isolated primarily intralabyrinthine neuromas, without connection with the internal auditory canal, have been described (36, 231).

The Schwannoma constitutes 8–9% of the intracranial tumors and the incidence, after data from the Swedish Cancer Research Institute, is 0.7 clinically evident cases in 100,000 persons. The real incidence may even be higher, Moberg (144) found one Schwannoma every 100 autopsies done for reasons other than brain tumors.

To understand better the clinical and surgical implications of this neoplasm, a brief discussion of the surgical anatomy of the region of the internal ear canal may be appropriate. Excellent and comprehensive studies by Lang (127–130) have been published; they comprise the topography of the complete canal system of the os temporale, including the facial canal, semicircular canals, vestibule, internal acoustic meatus, sigmoid sinus, superior bulb of the jugular vein, carotic canal, eustachian tube, perilymphatic and endolymphatic ducts and sac, glossopharyngeal nerve and mastoid cell; these studies may be consulted for more information. The internal ear canal presents itself as an invagination of the posterosuperior face of the petrous bone. The porus acusticus internus is situated at about 30 mm from the temporal squama at the union between the medial third with the two lateral thirds of the petrous bone. The canal penetrates in the bone obliquely in a medio-lateral and postero-anterior fashion, forming an angle of about 45° with the major axis of the temporal bone. A posteriorly open angle of 91.7°–92.7° is formed with the mediosagittal line (129). Four internal faces of unequal length of the canal can be described, with the posterior longer than the anterior wall. The median length of the canal is 8.1 mm (129). The diameter of the canal is between 4 and 5 cm with a median value of 3.8 mm. The porus acusticus internus is cut obliquely by the surface of the petrous bone and has so an oval form, with the major diameter in the horizontal plane. The internal end of the canal is formed by an osseous lamina which is divided horizontally by the falciform crest in two parts. The superior fossa is divided again by a small crest, called "Bill's Bar" in otologic surgery. The cranial opening of the fallopian canal (VIIth nerve) is located in the anterior subfossa and in the posterior subfossa the superior vestibular nerve enters the bony labyrinth structures. The inferior fossa is formed anteriorly by the tractus spiralis foraminosus, exit of the cochlear nerve and base of the modiolus, and posteriorly by two foramina for the inferior vestibular nerve and, called foramen singularis Morgagni, for the nerve of the posterior semicircular canal.

The canal contains the VIIth and VIIIth cranial nerves, organized according to the described bony entrance sites. The fibers in the facial nerve are, from front to back: motor fibers, nasolacrimal parasympathetic fibers (from the nucleus Yagitae), gustatory fibers and fibers from the superior salivary nucleus of Kohnstamm. The so-called acoustico-facial anastomotic fibers are present between the facial nerve and the superior vestibular nerve and transport parasympathetic cochlear fibers or, according to other opinions, the efferent regulatory fibers of Rasmussen. Outside the canal the nervous bundle travels in the lateral pontocerebellar cysterna for about 29 mm while performing a rotation that positions the vestibular nerves on top of the cochlear nerve.

The vessels that enter the internal ear canal have been described for the first time by Siebenmann (1982) and subsequently by Konaschko (117). Two major distribution patterns have been seen by these authors. In the first type (of Siebenmann) the internal auditory artery forms one trunk, which then divides into the anterior vestibular artery and the common cochlear artery. This latter vessel then divides into the arteria cochlearis proper and the arteria cochleovestibularis. In the second version (of Konaschko) two distinct arteries enter the canal, called anterior vestibulo-cochlear artery and posterior vestibulo-cochlear artery. The first will then divide into the anterior vestibular artery and the arteria cochlearis proper. Clinically a certain variability of the vascular pattern can be observed, but the labyrinthic arteries enter the canal always through the antero-inferior area, penetrating the area between the facial and the cochlear nerve (228). The antero-inferior cerebellar artery can form a loop inside the canal by itself, with consequent surgical dangers. Lymphatics have not been clearly demonstrated in the canal, but recently a case of facial hemispasm due to a lymph node inside the internal ear canal has been described (153).

The anterior canal wall is in direct relationship with the carotic artery canal, from which it sometimes is divided by a few air cells, and with the basal part of the cochlea. The inferior wall faces the bulbus of the jugular vein. The posterior wall corresponds initially to the postero-superior face of the rocca and more laterally to the vestibular cavity. Its lateral end is in direct continuity of an imaginary plane passing parallel to the anterior wall of the ampulla of the lateral semicircular canal. The superior wall is separated from the middle cranial fossa by a thin bony lamina. Some air cells may be present also in this site, but they are exceptional. On the supero-anterior face of the petrous bone, in the middle fossa, from medial to lateral, the foramen spinosum of the middle meningeal artery, the Fallopian hiatus of the greater superficial petrous nerve, several small foramina for the lesser superficial petrous nerve and the deep petrous nerve and finally the eminentia arcuata can be seen. It should be stressed that the eminentia arcuata cannot be taken as a point of reference for the topographic site of the superior semicircular canal (13).

The treatment of the acoustic neuroma can basically be accomplished through three surgical approaches ((16, 97, 98, 103, 104, 162, 170) among others). The first is given by the suboccipital approach, done for the first time by Ballance and developed further by Dandy and Olivecrona. It consists of the opening of the posterior cranial fossa through the squama occipitalis posteriorly to the sigmoid sinus. The necessary dislocation of the cerebellar hemisphere was originally often followed by brain stem compression. Olivecrona was able to reduce the mortality of this surgery significantly through an hemicerebellectomy with conservation of the tectal and dentate nuclei, allowing so for a better postoperative functional recovery. The access is oriented towards the postero-superior face of the pyramid, reaching the porus acusticus internus through the pontocerebellar angle. It is rather large and permits the excision of tumors of greater dimensions, but generally it does not carry a good prognosis as far as the functionality of the facial nerve is concerned. A combination of neurologic and otologic techniques to approach the posterior wall of the internal ear canal and to open it has been proposed. So the complete tumor, which originates deep inside the canal, can be removed and the prognosis for the facial nerve will be decisively better, also if the incidence of postoperative functional indemnity remains rather low. The use of microsurgical techniques for the approach of the intracanalicular part of the neuroma is today definitively warranted.

The second way of access is given by the translabyrinthine approach. This technique has been used for the first time by Panse in 1904 (158) and, after a certain time of virtual oblivion, been reproposed mainly by House (104) and Garcia-Ibanez (72). Initially an as wide as possible mastoidectomy is done with wide exposure of the triangle of Trautman between the facial nerve and the sigmoid sinus. Posteriorly the opening should extend to the dura medially of the sinus and superiorly arrive at the dura of the fossa media and the tegmen tympani. Anteriorly the cavity will be delimitated by the geniculate ganglion, as well as the second and the third part of the facial nerve. Through the atticus the hammer and incus become visible and are extirpated. Medially the cavity is closed by the bony labyrinth block. Drilling on this bone block now, the lateral semicircular canal is encountered first. The posterior canal, which forms with the lateral canal a 90° angle, is found at a slightly deeper level. Sometimes a few air cells divide the canal from the dura of the posterior fossa, at other times the canal is in direct contact with the cortical layer of the petrous bone. At a significantly deeper level in the area superior to these canals the superior semicircular canal can be found, both following the posterior canal to the crus commune and the lateral canal to the ampulla. The bony vestibulum is now exposed with attention on preserving the anterior wall of the ampulla of the lateral semicircular canal, which lies in one plane with the lateral extremity of the internal auditory canal. The anterior wall of the lateral semicircular canal forms the anterosuperior limit of the dissection. The internal auditory canal is now opened and the nervous bundle exposed, encountering the two vestibular nerves at a primary level. This facilitates the enucleation of the neuroma. The superior and the facial nerves are divided by a small bony ridge, useful for the surgical separation of the nerves, especially if widely dislocated and compressed by the expanding tumor. The dissection of the facial nerve along the capsule of the tumor and the excision of the neuroma with special care for the possibly present major vessels follow. Finally the closure of the mastoidectomy and labyrinthectomy cavities concludes the operation. If the operating space should result insufficient due to an expansion of the tumor greater than originally assumed, it can be easily extended posteriorly by sectioning the sigmoid sinus and including a part of the occipital squama in the craniotomy.

The third access is given by the transtemporal operation. This more recent type of surgery has been developed and refined mainly by Fisch in Zurich (49, 50). A trapezoidal craniotomy of 4 × 3 cm with the minor basis at the level of the zigomatic radix of the temporal bone is done. The dura is detached from the anterosuperior face of the rocca petrosa up to the foramen spinosum medially and the superior petrous sinus posteriorly. The eminentia arcuata is so exposed and on a line between it and the foramen spinosum, at about 15 mm from the latter, the greater superficial petrosal nerve can be seen. To identify the location of the

lateral, deep, extremity of the internal auditory canal several procedures have been proposed. The most interesting are: 1. House (103) – identify the greater petrosal nerve and follow it to the genicolate ganglion first, by drilling the covering bone. The facial nerve can then be followed into the internal auditory canal. The extensive exposure of the facial nerve can result in damage of the nerve itself or of its vascularization. 2. Portmann *et al.* (168) – a line parallel to the superior ridge of the petrous bone passing through the superior extremity of the eminentia arcuata, should encounter the lateral extremity of the internal auditory canal at about 10 mm medially. The anatomical variances of the eminentia arcuata and the non direct visibility of the reference points constitute a major drawback of this method. 3. Fisch (48) – the angle between the superior semicircular canal and the internal auditory canal is supposed to be at a fixed angle of 60°. After drilling the bone until exposing the 'blue line' of the semicircular canal, the internal auditory canal should lay at 10 mm medial from it. An accidental opening of the semicircular canal with resulting deafness is the major danger. The drill may also contribute to an acoustic trauma to the ear. As said, the eminentia arcuata cannot be taken as a reference point for the semicircular canal due to a certain degree of anatomical variation. 4. Sterkers *et al.* (201–203) and Chouard (27) – the binaural axis is thought to cross the internal auditory canal, which should be found at 28–30 mm distance medially from the squama of the temporal bone. A major difficulty arises from having the reference points lying outside the surgical field. 5. Garcia-Ibanez (72) – the eminentia arcuata and the greater superficial petrosal nerve are taken as reference points. Two lines are drawn, the first along the course of the petrosal nerve and corresponding to the ampulla of the superior semicircular canal, the second along the eminentia arcuata. The two lines form an angle whose bisecting line should encounter the internal auditory canal the nervous bundle is visualized. Sectioning the dura longitudinally with a Wullstein scalpell the superior vestibular nerve posteriorly and the facial nerve anteriorly, united by the acoustico-facial anastomosis', will be in the primary plane. The neuroma is separated from the facial nerve and excised. The cochlear nerve lies deep in the field and can be preserved in a certain amount of cases, due to the dimensions of the tumor.

The anatomical topography of the vestibular nerves in the inner ear canal can explain most of the early signs of the neuroma of the acousticus. This tumor has a peak incidence at 45 years with a greater prevalence in the female. The clinical onset is mostly subtle, if compression of the labyrinthine arteries does not result in an inner ear infarct. In 1917 Cushing (31) described the sequence of symptoms as follows: 1. auditory and vestibular dysfunctions, 2. headache, 3. cerebellar signs, 4. cranial nerve deficits, 5. intracranial hypertension, 6. dysarthria and dysphagia, 7. respiratory dysfunction. It can be seen that besides point 1, all other signs are expressions of major tumors which expand widely into the pontocerebellar angle. Basically tumors larger than 20 mm can given origin to headaches that have no specific time pattern in their insorgence, equilibrium disorders of cerebellar origin with dysmetry, adiadochocinesis, asynergy and atony and finally compression signs from basically all cranial nerves in a very multiform pattern. The olfactory and optic nerves can be damaged through the endocranial hypertension, the other nerves may be compressed directly. Finally pyramidal signs may be present due to bulbar compression. This compression is then also the final cause of death with respiratory arrest. The tumor never invades the bulbus histologically. The dysfunctions of the nerves VII and VIII are the only useful signs for an early diagnosis. A generally slowly progressive hypoacusia centered on the higher frequencies is often the first and only sign. Tinnitus is frequently present, the damage is monolateral. Newer audiologic techniques are most helpful in detecting also very small tumors, under the 1.5 cm limit of the computerized tomography. A test battery including tonal audiometry, speech audiometry, tympanic reflex studies (28, 111) and especially electric potential audiometry (15) is generally able to detect small-sized intracanalicular tumors. The slow growth of the tumor allows the vestibular system to reach a good clinical compensation and the vestibular tests are of less use than originally thought, showing an aspecific hyporeflexia, which may confirm but not establish a diagnosis. The motor fibers of the facial nerve are more resistant to compression than the afferent fibers and so electrogeusimetry may monitor facial nerve damage before a paresis becomes visible. Radiological tests used are principally the computerized tomography (185), which generally can show tumors that sprout from the inner ear canal, but is of less use for the detection of intracanalicular tumors due to its separation limit at around 1.5 cm, pneumoencephalography and contrast cisternography. The use of air enhancement in computer tomography has been proven valuable for the assessment of intracanalicular tumors (172). The angiographic study of the pontocerebellar angle is important, especially to detect the presence of an intracanalicular loop of the antero-inferior cerebellar artery and the tumors' vascularization.

The main significance of this tumor is the striking importance of an early detection, which may not only allow its radical removal but also to preserve the function of the facial nerve in the inner ear canal. Every unilateral neurosensorial hearing loss has to be evaluated in this sense. An early detection leads to a good functional prognosis for the facial nerve, while big tumors show a rapidly worsening outlook and when the tumor extends towards the brain stem it may request a suboccipital approach with extensive manipulation of the cerebellum and consequent functional damage. Small tumors can benefit from transtemporal or translabyrinthine surgery which allow in a high percentage of cases the preservation of the facial nerve. The selection of the surgical approach is in fact mainly based on the size of the tumor. Neuromas may be classified in small (< 8 mm), medium (8–35 mm) and large (> 35 mm). For small neuromas the transtemporal approach may be used. It is the least traumatic, does not destroy the labyrinth and opens the dura only in a small area in the internal ear canal. Only minimal bony removal is necessary. Major dangers are a non-exact localization of the end of the internal ear canal with damage to the nearby cochlea and to the facial nerve after opening the geniculatum. The chief disadvantage is the small exposure. The major advantage is the possibility to preserve hearing, which may be as high as 25% (49). For tumors of median size the translabyrinthic approach is favored. This technique produces a complete destruction of the posterior labyrinth and consequent deafness. The dural opening is

wider than in the transtemporal approach and large part of the pontocerebellar angle can be explored. The facial nerve can be preserved in 80–90% of the cases. The access is limited by the sigmoid sinus posteriorly and the plane of the fallopian canal anteriorly. It can be widened by sectioning the sigmoid sinus towards the occipital side. An anterior extension of the surgical field is more cumbersome and would include the execution of a so-called transcochlear approach (35, 73, 106, 169). In this the facial nerve is freed in its whole length and rerouted posteriorly. The cochlea is then drilled out and the bone is removed up to the carotic artery and the apex of the petrous bone. This allows a large vision of the middle and posterior fossa's skull base. This technique is generally used for clivus or petrous apex tumors and not for neuromas which grow principally in the posterior fossa. Large tumors still warrant the suboccipital approach which permits an ample approach to the pontocerebellar angle, but carries a bad functional prognosis for the facial nerve and a significantly higher postoperative morbility and mortality.

Concluding, the acoustic Schwannoma is a prime example for a histologically benign tumor with clear topographical malignancy. The lesion, due to its expansive growth, produces a sequence of functional failures of the cranial nerves first and the cerebellum later. Functional malignancy is expressed here through multiple impairments in the nervous system. Finally, if untreated, the neoplasm, while still histologically benign, will bring the patient to death due to brain stem compression with obstructive hydrocephalus and respiratory arrest. Early diagnosis is essential to eradicate the tumor before it reaches large dimensions. The diagnosis and cure of the tumor warrants a close collaboration between several medical specialties, especially neurosurgery and otorhinolaryngology.

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