Epithelial (Epidermoid) Tumors of the Cranium
Their Common Nature and Pathogenesis*

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Epithelial (epidermoid) tumors of the cranium comprise a confusing group. Misused words and misnamed lesions abound: the adjectives epidermoid and dermoid have been transformed into nouns, adamantinomas never contain enamel, craniopharyngiomas arise from structures having more oral than pharyngeal potentialities, cholesteatomas are named for a chemical substance rather than cell or tissue of origin, a tumor may be solid and still be called epidermoid cyst, and the dermoid tumors which are simply variants of epidermoids are mistaken for teratomas. Custom seems to have justified certain usages, but sometimes at the expense of clear understanding.

The epithelial tumors under consideration occur in diverse locations such as the ear, scalp, calvarium, jaw and base of the brain. The diagnostic problems and the surgical approach to these regions are so different that they are usually considered as separate entities. The otologist views "cholesteatoma" of the ear as a pseudo-tumor, the result of longstanding infection. The neurosurgeon views "cholesteatoma" at the base of the brain as etiologically distinct from the otic mass, and both are thought to be different from craniopharyngiomas. We intend in this paper to show the unitary character of these epithelial tumors of the cranium, based on histological appearance and embryological origin. We contend that they arise by a common process of epithelial misplacement early or late in life, that they range in growth capacity from masses enlarging by accretion of normally formed cellular material to malignant neoplasms growing by cellular proliferation and properly designated as carcinomas, and that modern embryological theory accounts for most of these phenomena and the wide range of biological behavior.

Histology of Epithelium

The epithelia discussed here are derived from the primary germ layer, the ectoderm, and form the epidermis and its appendages such as hair and sebaceous glands, and the ectodermal components of mucous membranes and teeth. These epithelial membranes are attached to connective tissue. Thus skin is composed of an outer epithelial portion, the epidermis, and an inner dense connective tissue derived from mesoderm.

Epidermis is squamous epithelium composed of five layers. The deepest layer is the stratum germinativum (basal cell layer), attached to the connective tissue of the dermis, and formed by columnar epithelial cells normally germinating new cells which are pushed into the layer above. The stratum malpighii (stratum spinosum, prickle cell layer) is several layers thick, having a spiny appearance formed by the intercellular bridges. The stratum granulosum is thinner, the cells are flattened and the cytoplasm contains keratohyalin granules. In this layer, the cells of the epidermis undergo physiological death or necrobiosis. The 4th layer, the stratum lucidum, is a thin homogenous band, seen best in the thick skin of palms and soles, and is not present in thin skin. The outermost layer, the stratum corneum, has horny scales of keratin, the result of cell death by desiccation. Mucosal epithelium

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is similar to epidermis, but lacks a stratum granulosum and is not keratinized, although granules of keratohyalin may be found; hair and glands are absent. The tooth bud or enamel organ is characterized by an outer and inner layer of epithelium enclosing a central stellate reticulum. The inner layer is composed of ameloblasts, capable of forming enamel.

The epidermoid tumors under consideration arise from ectoderm and then differentiate into epithelium resembling epidermis, mucosa, or tooth bud. Epidermis and its derivatives are found in the cholesteatoma of brain and ear, and in epidermoid tumors or cysts of calvarium and jaws. Mucosal epithelium occurs in some cranio-pharyngiomas, and structures resembling tooth buds are seen in "adamantinomas" in the pituitary or the jaw.

Material and Selected Case Reports

Sixty-three specimens from 61 patients were studied. The origin of the tumors is shown in Fig. 1. Forty-one were in the ear, 11 were suprasellar or in 3rd ventricle, 5 were diploic or in the fontanelle, 3 in the pontine angle and 3 at the base of the brain. Three epidermoid cysts of the jaw were also examined.

Case 1. The lacerated scalp of a 28-year-old man was sutured primarily. The patient returned 1 year later complaining of a slowly enlarging mass at the site of suturing. The tumor was excised and was found to be an epidermoid cyst containing keratin (Fig. 2).

Comment. This case illustrates the surgical induction of an epidermoid tumor. The epidermis was approximated in such a way as to allow desquamated stratum corneum to accumulate in a dermal-lined cyst. Epidermoid cysts may thus be induced late in life (see Discussion).

Case 2. A full-term male baby was born spontaneously to a 24-year-old mother. The child lived only a few hours. The cranial vault was absent. The cerebral hemispheres lay at the base of the skull in a mass about 4 cm. in thickness. Epidermis was seen microscopically in the leptomeninges of the occipital region, extending deep into the sulci, and containing abundant linear strands of keratin. The diagnosis was epidermoid tumor in an anencephalic newborn infant.

Comment. This epidermoid tumor is clearly an intrauterine malformation of development, comparable to reported cases of cranio-pharyngioma and adamantinoma present at birth.

Case 3. A 41-year-old woman had progressive loss of vision for 2 years. The left eye was blind and the nerve atrophic; papilledema was not
Necropsy revealed a huge tumor extending along the base of the skull from the frontal lobe to the left cerebello-pontine angle. Numerous adhesions were present between tumor and arachnoid (Fig. 3). The diagnosis was epidermoid tumor.

**Comment.** The capacity of epidermoid tumor to increase enormously in size by cellular proliferation is illustrated by this case. The epidermis was normal in appearance, hence this tumor is considered a benign neoplasm.

**Case 4.** A 53-year-old woman was seen in 1950 because of watering in the left eye, left cranial nerve deficits including the 8th, and ataxia.* Suboccipital craniotomy revealed a pearly tumor at the base of the brain, and partial removal was accomplished. Mature, cornified epidermis was seen microscopically (Fig. 4). She improved for 6 months, then became gradually weaker during the next 6 months. The patient was readmitted to the hospital in 1951, and a 2nd craniotomy was performed with removal of the tumor, but she died the next day. The 2nd surgical specimen contained proliferating squamous epithelium with many mitotic figures, and some cells with giant nuclei or vacuolated cytoplasm (Fig. 5). The

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* We are indebted to Dr. Kenneth Strully for permission to report this case.

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**Fig. 4.** Case 4. The first specimen contains a thin layer of epithelium with stratum granulosum and large amount of keratin. H.&E., X250.
basal cell layer was disorganized. Necropsy revealed invasion of the pons by the tumor (Fig. 6). The final diagnosis was squamous cell carcinoma, arising from epidermoid tumor.

Comment. A benign epidermoid tumor underwent a malignant change in histological appearance. The invasive character of the mass also was indicative of malignancy. Carcinoma of this type is rare (see Discussion).

Case 5. A 29-year-old woman was admitted to the North Carolina Baptist Hospital in 1951 with headaches and left 5th and 7th nerve paresis. In 1941 Dr. Walter Dandy had removed an epidermoid cyst from beneath the right optic nerve. An epithelium was found, intermediate in histological structure between epidermis and mucosal epithelium; it lacked a stratum granulosum, but was keratinized. Exploration of the left cerebello-pontine angle in 1951 disclosed a brown, thin-walled cyst replacing the 7th, 8th, 9th and 10th cranial nerves laterally and posteriorly. The tumor extended beneath the brain stem and up through the tentorium. After evacuation of the contents which resembled machine oil, the wall of the cyst was almost totally removed. The patient made a good recovery from this procedure and has shown no evidence of recurrence of the tumor up to the present time. Microscopically, the epidermoid tumor was similar in appearance to that removed in 1941.

Comment. Multiple intracranial epidermoid tumors are rare. It is unusual to find an epidermoid cyst beneath the right optic

Fig. 5. Case 4. Second biopsy reveals foamy cells and mitoses in widened epithelium. H.&E., X250.

Fig. 6. Case 4. The neoplasm on the left extends from the leptomeninges and enters the pons. Arrows point to the invasive edge of the tumor within the pons. H.&E., X3.

† Material reviewed by courtesy of Dr. Earl Walker.
nerve on one occasion and a similar lesion in the left cerebello-pontine angle several years later. These were assumed to be part of the same tumor spreading along the base of the skull. Although the sella was not involved, this tumor on both occasions closely resembled a craniopharyngioma.

Case 6. A 24-year-old woman was admitted with a chief complaint of drainage from the right ear for 15 years and progressive loss of hearing on the right. She had a perforated right drum, and pus in the external canal. Roentgenograms revealed chronic mastoiditis on the right and sclerosis of the surrounding bony structures. Exploration of the antrum disclosed pearly material. A radical mastoidectomy was done. Microscopic examination revealed typical epidermis containing numerous hair follicles and sebaceous glands (Fig. 7). The diagnosis was dermoid tumor. Postoperatively, the drainage gradually decreased, and when last seen 18 years later, she had no complaints referable to the ear.

Comment. Both clinically and by macroscopic observation, this mass was a typical “cholesteatoma” of the ear. It is extremely doubtful that a well developed epidermis with cutaneous appendages could be a reaction to infection. The possibility of epithelial ingrowth in this case was not eliminated. The diagnosis of dermoid tumor here meant simply an epidermoid tumor containing hair follicles and sebaceous glands. These dermal sequestration masses have often been confused with teratomas. The latter are neoplasms containing tissues of multiple origin; this dermoid tumor was not teratomatous.

Discussion

The feature common to the epidermoid tumors is the inclusion of ectodermal elements in sites not normally containing these structures. Misplacement usually happens in embryonic life, but may occur later by mechanical means. The developmental origin is widely although not universally accepted, but the later traumatic origin of epidermoid tumors has often been questioned. Case 1 demonstrates one method of mechanical induction in an adult. Choremis et al. described 6 children aged 7 to 12 years who had repeated lumbar punctures for treatment of tuberculous meningitis. Three to 6 years later, the children had signs of intraspinal masses. Epidermoid tumors as heavy as 3.2 gm. were removed; some were multiple. Evidence of congenital defects was lacking, hence the tumors were properly considered to be the result of misplacement of epidermis.

The fact that most epidermoid tumors appear clinically in children or adults more often than in infants has occasionally been used to deny the developmental origin of the tumors. The tumors, however, may occur at birth, as reported by Iyer\textsuperscript{11} and Gass,\textsuperscript{5} and as further illustrated by our Case 2. Furthermore, the adult human being has within his jaw, tooth germs capable of developing as late as the age of 25 years. There may also be dormancy within misplaced epithelia. Failure to find squamous cell nests in the pituitary or its stalk in infancy has been used to deny the concept of epithelial misplacement. Recent evidence by Goldberg and Eshbaugh\textsuperscript{6} indicated that these “nests” may be found in newborn infants. These
observations reduce the validity of objections to the "rest" theory.

Cellular division in the basal cell layer of the skin normally produces new cells without creating a mass because of external desquamation of the keratin. An epidermoid tumor continuing to grow in a closed space will enlarge as keratin and fluid accumulate. In addition, epidermoid tumors may enlarge by excessive cellular proliferation as in Case 3 in which the base of the skull was covered with tumor of the usual histological appearance. Such an enlargement is obviously not the result of normal cell division, but the typical epidermal appearance was well maintained. The concept of the epithelial "rest" is thus enlarged to include formation of benign neoplasms.

Epidermoid tumors rarely become malignant as in Case 4, with histological alteration and an invasive character. Davidson and Small reviewed 5 cases and presented one of their own. Our case is the 7th to be reported, but is unique in showing the benign character of the tumor removed at the 1st operation, and the malignant change a year later. These cases indicate that although the growth potential of misplaced epithelium is low, the range of variation is wide enough to include malignant growth.

The problems of the epidermoid tumors in various sites will now be considered, and a general theory of origin proposed.

1. **Epidermoid tumor of the ear.** "Cholesteatoma" is a poor name; modern nomenclature is based on the cell or tissue of origin rather than on chemical content or product. Traditionally, cholesteatoma of the ear is described by most authors as a pseudo-tumor secondary to prolonged infection. Some writers have suggested that these tumors are not the result of infection, but are growths comparable to epidermoid tumors arising elsewhere in the body. Cushing wrote in a footnote to a case report: "it is my impression that many of the cholesteatomata reported by otologists are true epidermoid tumors which originate from aberrant epidermal rests, laid down in the temporal bone during the early formation of the complicated special sense structure which it contains. Certainly all of the tumors which have a demonstrable epidermal membrane such as those encountered more often in the mastoid process and which may reach a considerable size, are in all likelihood actual Cruveilhian tumors. It is not improbable indeed that in many of the recorded cases the cholesteatoma itself was responsible for the otitis media, rather than the reverse. Excessive desquamation of epidermoid cells which have grown from the canal into the middle ear in a long-standing case of otitis media may occur and produce a pseudo-cholesteatoma, but another explanation of the process seems the more likely for the majority of the cases."

The frequent association of otitis media with cholesteatoma is the chief reason for assuming the first to be the cause, and the second the effect. However, there have been many cases of cholesteatoma without otitis media, of cholesteatoma in the mastoid bone without connection to the middle ear, and bilateral cholesteatomas with unilateral otitis. The significance of association with infection diminishes when it is realized that more than two-thirds of patients with chronic otitis media never suffer from cholesteatoma. Furthermore, chronic infections of other closed spaces such as the nasal sinuses are common, but cholesteatomas in these regions are extraordinarily rare. If otitis media is the cause, and cholesteatoma the effect, a decrease in otitis should result in a lessened incidence of cholesteatoma. With the advent of chemotherapy and antibiotics, an opportunity occurred to test this significant hypothesis. The incidence of chronic otitis media has declined strikingly, but the occurrence of cholesteatoma is virtually unchanged. The evidence then suggests that if the two disorders are related, it is more likely that cholesteatoma causes an aural discharge than the reverse.

McKenzie, who agreed with Cushing that cholesteatomas of the ear are true epidermoid tumors believed that only one major point was unanswered: the unusually high incidence of epidermoid tumors in the ear
when compared with other regions. A review of the origin of this sensory organ reminds us that it is indeed complicated, as indicated by Cushing. Fig. 8 demonstrates the origin of the inner ear as an ingrowth of epithelium (the otic placode) sinking toward the neural tube. The otocyst ultimately forms the inner ear. The middle ear begins as a condensation of mesenchyme, and then is covered by mucosal epithelium arising from the first pharyngeal pouch. Finally, the external ear results from an invagination of epithelium. The deepest part is an unsplit ectodermal plate, growing deeper until it meets the epithelium of the tympanum to form the tympanic membrane. This complicated confluence of epithelia and the multiple invaginations and investments readily explain the greater incidence of congenital epidermoid tumors in this region than elsewhere.

Advocates of the post-inflammatory theory are divided between those persons believing that epithelium invades from the external canal to the middle ear through a marginal perforation of the tympanic membrane (invasion theory), and those who believe that infection changes the simple columnar epithelial lining of most of the middle ear into stratified squamous epithelium (metaplasia theory). The invasion theory is supported by authors who have seen epidermis growing from the external canal toward the middle ear. This observation, however, may be interpreted with equal justification as demonstrating the reverse pathway. Cholesteatoma may occur without perforation, and indeed McKenzie has described a case of atresia of the external canal with a deep epidermoid tumor. Furthermore, if the ingrowth occurred through a perforation of the ear-drum, the immediately adjacent tympanic cavity should most often contain the mass, but actually the antral region and mastoid are the most common sites.

Morphological evidence of the non-infectious origin of these tumors is found in the presence of hair and glands in cholesteatomas of the ear (Fig. 7). Histological examination...
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shows a mature epithelium with all the layers of normal epidermis present although often in different proportions. A well-defined stratum granulosum is invariably found in cholesteatoma of the ear. It is highly unlikely that dermal appendages or a stratum granulosum could be a metaplastic reaction to infection, or regularly arise from mucosal epithelium.

2. Cranial epidermoid and dermoid tumors. These tumors may occur in the scalp, the calvarium, or intracranially most often at the base of the brain. They are usually epithelial sequestration cysts, the result of early misplacement of epithelium in embryonic life, or of trauma in later life.\(^9\) An example of the latter is given in Case 1. When misplacement occurs in the embryo, the effects are usually not apparent until many years have elapsed. The delay occurs because the sequestration cysts gradually enlarge by accumulation of keratin and cellular debris from the desquamating skin. Epidermoid tumors have rarely been reported in the first few years of life, but recently described cases occurring in newborn infants\(^5,\)\(^11\) offer additional evidence of their origin by misplacement during embryogenesis (see Case 2).

In addition to increasing in size by internal desquamation and accumulation of fluid, epidermoid tumors may acquire neoplastic properties and grow by proliferation of the epithelial cells. The growth capacity of epidermoid tumors usually is not great, but on occasion they may become enormous, as is shown in Case 3. These tumors may even become histologically malignant on rare occasion,\(^4,\)\(^8,\)\(^18\) as illustrated by Case 4.

3. Tumors derived from oral mucosal and dental epithelium. Craniofacial neoplasms are not keratinized and never contain a stratum granulosum. The absence of granular cells, easily understood when the origin in mucosal epithelium is considered, may be used in differentiating this tumor from other types of epidermoid tumors, although the distinction is not indicative of a fundamentally different method of induction or tissue of origin. The growth of craniofacial neoplasms is not neoplastic but by desquamation of epithelial debris into the center or by an excessive cellular proliferation of epithelium resulting in a benign neoplasm. There is the rare possibility that it may become carcinomatous. The tumor may grow in any direction from its origin near the sella turcica.

4. Theory of origin. Modern embryological concepts provide a reasonable explanation for the development of the epidermoid
tumors in their various forms. The usual explanation is that ectodermal cells are misplaced during development of the embryo and continue to grow if the blood supply is adequate. The differences in degree of organization between epidermoid and dermoid tumors are explained by the age of the embryonal cell rests misplaced during development, or by depth of position. More recently, it has been shown that ectodermal cells in their earliest stages are not inevitably destined to become either skin or neural tissue, but that their fate is decided by the influence of mesoblastic tissues containing organizer substance. In a sufficiently early stage, a piece of ectoderm destined to become skin, if grafted into a suitable surrounding, could be made to differentiate into neural tissue. The influence of the mesoderm in inducing the overlying ectoderm to differentiate in specific directions, such as eye, ear, hair, nails or teeth is well accepted. Invaginations of ectoderm are determined by the organizing influence of the underlying mesoderm. If, for example, epidermis is separated from dermis at an early stage, hair does not develop.

The following theory is suggested. If epithelium alone is misplaced during embryonic life, or traumatically later in life, epidermal cells will be found as rests in the adjacent connective tissue. The histological appearance will depend on the site of origin of the misplaced epithelium, resulting in epidermal or mucosal types of epithelium. On the other hand, if developing ectoderm is in contract with adjacent mesoderm, these misplaced tissues together will have the capacity to form the more complex dermoids. The appearance of the resulting mass depends on the time of displacement as well as the site of origin of the misplaced tissues. The difference between a simple rest and a dermoid tumor is therefore dependent on the presence of mesodermal tissue containing the specific organizer factor. Growth in either case is usually by accretion of normally formed material and by normal cellular division, although a capacity for greater growth is potentially present. The cause of the less common benign neoplastic growth and the even rarer malignancy is of course unknown.

Epidermoid or dermoid tumors of the cranium arise by this common mechanism, whether in ear, scalp, skull, jaw or the cranial contents. Regional variations in incidence are explained by those events in development allowing greater or less chance of epithelial misplacement. The complicated invaginations in the formation of the ear are the richest source of epithelial sequestration, and hence the ear most frequently contains these masses. The normal rise of oral epithelium toward the brain accounts for the second most frequent of these tumors, the craniopharyngioma. This concept explains why dermoids are uncommon in the cerebello-pontine angle. The closure of the angle occurs early, and the opportunity for epithelium to be included with mesoderm is thus limited. Further in accord with this theory is the fact that dental cysts are much more common than simple cysts in the hypophysis. The ectoderm of the tooth does not become apparent until the 7th week of fetal life, and within this time, simple misplacements of epithelium alone may occur. Organizer substances do not reach the tooth until the 7th week, and adamantinomas may then develop. Rathke’s pouch, by contrast, is apparent in the 4th week and adjacent mesoderm is clearly associated with it, hence tumors arising from its cells are most often complex tissues rather than simple cysts.

Summary

This report is based on a study of 63 specimens of epidermoid or dermoid tumors of the cranium and 3 epidermoid cysts of the jaw. Selected cases are used to demonstrate features of epidermoid tumors: surgical induction in an adult; their appearance in the newborn; their capacity to undergo benign or malignant neoplastic change; their rare multiplicity; and the striking histological similarity of the aural cholesteatoma to the dermoid tumor found elsewhere in the body.

Review of the literature on epidermoid tumor of the ear reveals a widespread belief that their origin is post-infectious. Data challenging this view are presented. The
major argument against the post-infectious theory is the unchanged incidence of “cholesteatoma,” despite a striking decline in the occurrence of otitis media. The high incidence of the aural lesion is readily explained by the complicated embryological development of the ear in which multiple epithelial invaginations occur more often than anywhere else in the body, thus allowing epithelium and adjacent mesoderm to be sequestered. The frequency with which these tumors occur in other regions is well correlated with the developmental possibilities of misplaced epithelium. It is also shown that epidermoid tumors may be induced mechanically late in life. Histologic and embryologic evidence indicate a common mode of origin for epithelial (epidermoid) tumors of the cranium, whether they occur in the jaw, scalp, calvarium or intracranially.

References