The Development and Fate of Epithelial Residues after Completion of the Human Odontogenesis with Special Reference to the Origins of Epithelial Odontogenic Neoplasms, Hamartomas and Cysts

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Summary: There is increasing but still not convincing evidence that residues of odontogenic epithelium play a major role in the pathogenesis of human, epithelial odontogenic neoplasms, hamartomas and cysts. In order to appreciate the development of these lesions, a knowledge of early stages of the human odontogenesis, is a basic requirement. The development of the dental laminae, the Hertwig's epithelial root sheath is reviewed, as is their final disintegration leading to the formation of Serres' pearls and rests of Malassez. The *gubernaculum dentis*, which connects the gingival lamina propria with the perifollicular tissue of the developing tooth, harbours dental laminae remnants which may develop into epithelial odontogenic lesions. Based on morphological studies, the likely origins of 10 odontogenic lesions from residues from dental laminae, oral epithelium, reduced enamel epithelium and Hertwig's epithelial root sheath are tabulated, and commented upon. The use of molecular methodologies in this field is just emerging, and the results will, in the years to come, undoubtedly change our viewpoints, and are awaited with great anticipation.

Key words: human odontogenesis, dental lamina, Serres' pearls, rests of Malassez, epithelial odontogenic neoplasms, hamartomas and cysts

INTRODUCTION

In order to understand and appreciate the origin of epithelial odontogenic neoplasms, hamartomas, and certain cysts, a knowledge of early stages of the normal human odontogenesis is a basic requirement. There is increasing but still not convincing evidence that residues of odontogenic epithelium play a role as sources of cells in the pathogenesis of several of the above-mentioned lesions (Reichart and Philipsen, 2004).

The purpose of this article is to give an overview of the early morphological evidence of human odontogenesis with special reference to the development of the dental laminae, the Hertwig's epithelial root sheath, and the outer enamel epithelium. These epithelial structures will finally disintegrate and give rise to residues of odontogenic origin. The mechanisms that are involved at a molecular level are only in very recent years emerging. Molecular and genetic methodologies may be useful for future investigations of the biology of odontogenic tumours.

EARLY EMBRYOGENESIS

Soon after the neural tube forms by invagination of the overlying ectoderm, migratory pluripotent neuroe-

pithelial cells, the neural crest cells (NCCs), migrate from the dorsal midline region of the neural tube (Garant, 2003). The NCCs lose their epithelioid characteristics and assume a mesenchymal phenotype capable of directed migration. Cranial NCCs invade the developing branchial arches and, in a series of reciprocal inductive interactions with early oral epithelium, produce tooth primordia.

Most investigations of molecular mechanisms of cell and tissue interactions during early tooth development have been performed using dental tissues from embryonic mice and rats or through studies of organ cultures. Thus, almost all current knowledge about the regulatory mechanisms involved in tooth development has thus far come from studies of animal models (Garant, 2003).

THE DENTAL LAMINA

The first morphological evidence of odontogenesis appears during the 6th week of gestation, in embryos of 8-9 mm crown-rump length (CRL) (Ooé, 1959). At this stage the primitive stomodeum is lined by ectoderm consisting of a basal layer of cuboidal to low columnar cells and surface layers of flattened squamous cells. The rich glycogen content of their cytoplasm gives the cells an empty or clear appearance. Cells in the basal cell layer of the oral epithelium, separated from the underlying NCC-derived ectomesenchyme by a basement membrane, begin to proliferate, and as a result an epithelial thickening arises in the mandibular, maxillary and medial nasal processes, commonly known as the dental lamina (the term used in the present overview), but should at this stage of development correctly be termed the dental plate or placode in analogy to 'neural plate', 'nasal plate' etc.

In embryos of 11-14 mm CRL, the epithelial thickening begins to proliferate into the ectomesenchyme forming an epithelial sheet, which creates a horseshoe-shaped structure in both developing jaws. Although the initiating events that trigger this downgrowth are still incompletely understood it is, however, known that neural crest ectomesenchyme is a necessary component (Graveson et al, 1997). The sheet divides soon into two processes of which the inner, lingual or palatal band, the dental lamina, develops into the primordium of the ectodermal portion of the deciduous teeth. In 15-20 mm (CRL) human embryos, the dental lamina shows signs of additional differential growth, reflecting the determination of incisor, canine, and molar domains. Continued site-specific enlargement of the dental lamina, along with condensation of the ectomesen-

chyme, gives rise to the individual deciduous tooth buds.

THE VESTIBULAR LAMINA

Whereas the inner process or band develops into the dental lamina (DL) (Fig. 1), the outer (buccal or labial) band occasionally referred to as the lip-furrow band develops somewhat later into the vestibular lamina (VL) (Fig. 1). The vestibular lamina grows slowly into the ectomesenchyme and at a certain stage, the core cells disintegrate to produce cavitation. The resulting slit-like cavity becomes the vestibule of the mouth (Fig. 1). Three-dimensional reconstructions of serial sections of human embryos (Radlanski and Jäger, 1991) have shown that the margin of the vestibular lamina consists of an abundance of individual epithelial excrescences, some of which give rise to the formation of the minor,
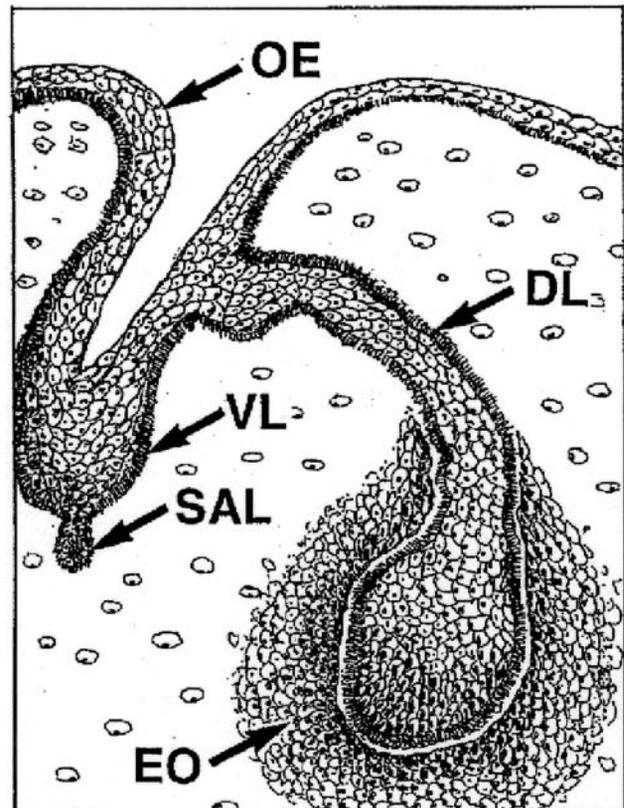

Fig. 1 An epithelial bud (enamel organ, EO) has formed at the end of the dental lamina (DL). Notice, cavitation of vestibular lamina (VL) as the first step towards formation of a vestibule. At the bottom of VL an initial epithelial proliferation leading to the formation of accessory salivary glands (SAL) (Figs. 1-3 modified after Mjör and Fejerskov (1979)).

accessory salivary glands (labial and buccal glands, SAL) (Fig. 1).

THE ENAMEL ORGAN

At certain intervals along the length of the dental lamina, small rounded epithelial swellings or buds are formed. Each swelling represents the enamel organ of the deciduous teeth (EO) (Fig. 1). The initiation of the entire deciduous dentition occurs during the second month *in utero*. As the enamel organs differentiate through the characteristic bud, cap and bell stages, localized condensations of ectomesenchymal cells become engulfed, forming the dental papilla (DP) (Fig. 2). Peripherally, the condensing ectomesenchymal cells extend around the enamel organ forming the dental follicle (DF) (Fig. 2). Together, all of these developing dental tissues are known as the tooth germ.
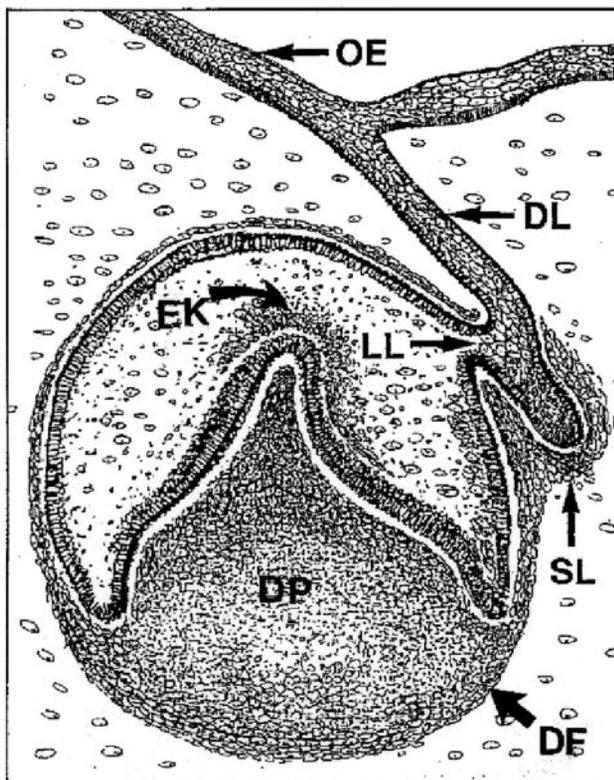

Fig. 2 Formation of the deciduous tooth germs occurs on the labial aspect of the dental lamina (DL). An epithelial bridge (lateral lamina, LL) is seen to connect DL with the bell-shaped tooth germ. EK: enamel knot. The free tip of DL proliferates into the ectomesenchyme as the successional lamina (SL) providing the anlage for a permanent tooth. Dental papilla (DP), dental follicle (DF).

THE LATERAL LAMINA, ENAMEL NICHE AND ENAMEL KNOT

With the formation of the tooth germs for primary teeth on the facial aspect of the dental lamina, part of the dental lamina extends labially as an epithelial bridge connecting the differentiating tooth organ with the dental lamina. This extension of the dental lamina is named the lateral lamina (LL) (Fig. 2). Occasionally, growth forces of the ectomesenchyme adjacent to the lateral lamina produce a cavitation between the lamina and the dental organ, called the enamel niche. Neither the lateral lamina nor the enamel niche is, however, considered to be functionally important. The enamel knot (EK) (Fig. 2) represents a small, closely packed transient population of non-dividing cells located adjacent to the inner enamel epithelium. The EK, previously believed to be unimportant, has achieved prominence as a potential regulatory centre of cell proliferation involved in cusp formation (Vaahtokari et al, 1996; Thesleff and Jernvall, 1997; Jernvall et al, 1998). The EK is believed to be necessary for morphogenesis of the tooth germ to progress from the bud to the cap stage.

ADDITIONAL LAMINAE

The Successional Lamina
After the formation of the bell-shaped enamel organ, the free terminal or tip of the dental lamina begins to proliferate into the ectomesenchyme, lingually (or palatally) to the enamel organ of each deciduous tooth. This newly established growth centre is known as the successional (succedaneous) lamina (SL) (Fig. 2) and is destined to provide the anlage for the permanent teeth replacing the primary predecessors, incisors for incisors, canines for canines, but premolars for primary molars. The process of producing the first permanent teeth (incisors, canines and premolars) occurs from the 5th intrauterine month (central incisor) to the 10th postnatal month (second premolar).

The Accessional Lamina
At $3\frac{1}{2}$ to 4 foetal months (160 mm CRL) the permanent molars, which do not have deciduous predecessors begin to appear. They arise directly from a distal extension of the dental lamina, which grows backwards underneath the oral epithelium. This part of the dental lamina complex is called the accessional lamina (the parent dental lamina or lamina for permanent molars). These segments of the dental lamina elongate

progressively, keeping pace with the lengthening of the arches and maturation of the maxilla and mandible. The earliest sign of the enamel organ of the first permanent molar is seen in the 4th intrauterine month. The second permanent molar appears shortly before birth and the third molar is initiated when the child is about 4-5 years of age. When the tooth germ of the third permanent molar is well defined, the dental lamina may extend further distally and give rise to the epithelial primordium of a fourth – and even a fifth molar (Nordenram, 1968).

Proliferative activity may, however, terminate prematurely so that the accessional lamina and the associated tooth germ for the third molars are not produced. This accounts for the possible absence of the permanent third molars in some individuals. Meyer (1932) and later Ooé (1979) have demonstrated that the first, second and third permanent molar anlage all exhibit a successional lamina, exactly as does the primary tooth primordia. However, these laminae do not develop into a successor but rather show fragmentation resulting in the production of epithelial cell remnants or the structure will disintegrate.

DISINTEGRATION OF THE DENTAL LAMINAE

Shortly after the establishment of the tooth germs the complex pattern of dental laminae begins to fragment or disintegrate due to ectomesenchymal invasion and/or programmed cell death. From the area known as the oro-dental epithelial junction (the zone where the dental lamina joins with the oral epithelium) (Provenza and Seibel, 1986), disorganization or fragmentation of the dental lamina progresses toward the developing enamel organ (PDL) (Fig. 3). Some cells of the laminae persist and tend to aggregate through proliferation into nests, known traditionally as epithelial pearls (Serres' pearls or glands of Serres). The successional as well as the accessional laminae also disintegrate and give rise to epithelial cell remnants.

Dental Lamina-derived Microkeratocysts
Moreillon and Schröder (1982) presented data on the numerical frequency of oral 'dental lamina-derived microkeratocysts' in human embryos (9-22 week of foetal life). They demonstrated an increase in the numbers of Serres' pearls producing microkeratocysts. The cystic change of the cell rests reached a peak at foetal week 22 where as many as 190 microkeratocysts per foetus were encountered. The high number of foetal
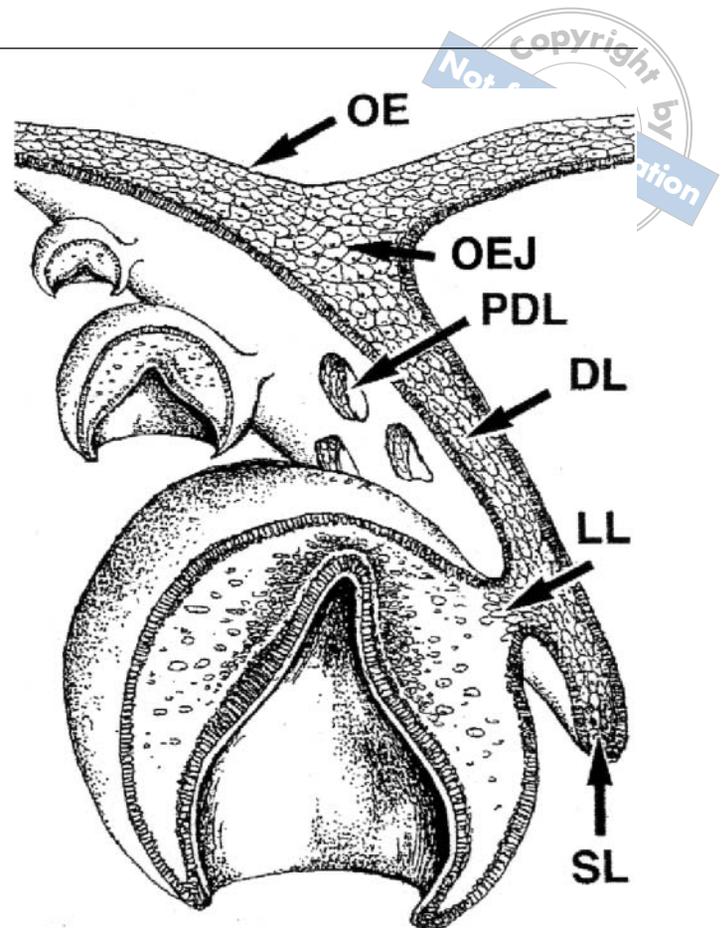

Fig. 3 Initial fragmentation of dental lamina (DL) starting at the oro-dental epithelial junction (OEJ). Several perforations have occurred (PDL). LL: lateral lamina; SL: uccessional lamina; OE: oral epithelium.

microkeratocysts gradually decreased in late foetal and early postnatal life. In newborns, lamina-derived microcysts (gingival cysts of infants or 'Bohn's nodules') were present clinically as grey-white, palpable nodules beneath the mucosal surface of the alveolar ridge crests in at least 70-80% of the cases (Fromm, 1967). Moreillon and Schröder (1982) further found that the mechanism responsible for the progressive reduction of the gingival microkeratocysts was discharge of cyst keratin by way of the cyst wall fusing with the oral epithelium, which opens to release the keratin content.

In a study of the embryogenesis of the gingival cyst derived from the dental lamina, Moskow and Bloom (1983) found that keratin- and parakeratin-containing cysts identical to those described by Moreillon and Schröder (1982), were noted in close proximity to the oral epithelium, whereas deeper located strands, nests and islands of disintegrating dental lamina showed less tendency toward cyst formation. The latter were typically squamous epithelial rests, and single or multiple

islands of PAS-positive clear cells were also encountered. Wysocki et al (1980) have pointed out that the distinctive glycogen-rich clear cells so commonly seen in dental lamina-derived cysts and remnants are never found in reduced enamel epithelium or rests of Malassez. Similarly, the epithelial linings of radicular and dentigerous cysts which are derived from the latter do not contain such clear cells.

Apart from the studies referred to above (Moreillon and Schröder, 1982; Moskow and Bloom, 1983; Wysocki et al, 1980), the extent and distribution within the jaws of dental laminae residues has not been investigated thoroughly in contrast to numerous mainly isolated morphological studies of the rests of Malassez.

RESTS OF MALASSEZ

When dentin matrix formation has started, changes occur in the so-called Hertwig's epithelial root sheath (HERS) a double layer of epithelial cells (inner and outer dental epithelium) that determines the shape of the root. The HERS detaches from the dentin surface, and undergoes partial disintegration as its epithelial cells separate and become displaced away from the newly formed unmineralized dentin matrix. Ectomesenchymal cells from the surrounding dental follicle grow in between the epithelial cells and differentiate into cementoblasts, which begin to deposit cementum matrix when directly exposed to the newly formed root dentin. The fragmentation of the HERS results in the creation of a network of epithelial cells around the root.

Simpson (1965) found that the network of examined premolar periodontium resembled a perforated sheet rather than a net. With the passage of time the amount of epithelium diminished so that the network became wide-meshed and the strands of epithelium thinner. Later, the network breaks up into numerous isolated strands and islands. Finally, after programmed cell death only scattered surviving remnants of isolated epithelial cells or cell clusters were present forming the rests of Malassez. The rate of disintegration is rapid at first but eventually becomes quite slow. It is considered unlikely that adult human periodontal membranes will be completely devoid of epithelial rests of Malassez.

Hodson (1962) studied epithelial residues of the human jaws in autopsies of adult subjects. In edentulous jaws, epithelial nests were found in 58% of the incisor and 14% in the third molar regions. They were located in the 'eruption tracts' including their extensions into the gingiva. Residues were found in patients up to the age of 87 years.

Valderhaug and Nylen (1966) showed electron microscopically that the individual rests of Malassez contained all the necessary components to meet whatever functional demands may be placed upon them through environmental alterations. So, although the term 'cell rest' must be considered an apt one, this does not preclude the possibility that the resting cells can return to a more active state if appropriately stimulated. More recent ultrastructural studies (Hamamoto et al, 1998; Yamasaki and Rinero, 1989; Brice et al, 1991) have essentially been confirmatory. A number of possible functional roles of the epithelial cell rests of Malassez have been suggested in the past, ranging from that of protection of the root surface from resorption, to maintaining the width of the periodontal ligament. Recently, these theories were critically reviewed by Ten Cate (1996), who concluded that as yet no firm evidence exists to support a functional role for these cell rests. Whereas an inflammatory stimulus does not seem to play a role in triggering dental laminae residues to proliferation, inflammation is likely to be a main factor in initiating the proliferative activity of the epithelial rests of Malassez.

EPITHELIAL REMNANTS ORIGINATING FROM THE OUTER ENAMEL EPITHELIUM

Eriguchi (1959) has produced evidence for the existence of yet another source of odontogenic epithelial remnants not previously recognized. In embryos of 230-260 mm CRL the author demonstrated thin epithelial strands of polyhedric cells radiating from the outer enamel epithelium. The strands tend to proliferate and may reach 1.5-1.8 mm in length and thus, almost contacting the ridges of the overlying oral epithelium. They are often accompanied by or intermingle with minute blood vessels. The strands later show fragmentation with the formation of several spherical epithelial pearls that will blend with remnants from the dental laminae. The outer enamel epithelium-derived residues often show keratinisation similar to that found in the dental lamina-induced micro-keratocysts mentioned above. The residues are thought to act as source for the development of odontogenic lesions later in life, similar to those originating from dental lamina remnants. These findings have never been confirmed and convincing evidence is thus lacking.

THE GUBERNACULUM DENTIS

Although the permanent incisors, canines and pre-molars, eventually become isolated in their own bony crypts, they maintain continuity with the connective tissue of the lamina propria of the overlying gingiva. This is achieved through the persistence of an intra-bony canal or corridor called the *gubernaculum dentis* or gubernacular canal, which connects the two (Provenza and Seibel, 1986; Hodson, 1971). This canal is occupied by the gubernacular cord, which comprises fibrous connective tissue containing peripheral nerves, blood and lymphatic channels as well as epithelial cells or cell clusters from the fragmented dental laminae. Thus, the gubernacular cord is the connective tissue link between the crypt (or perifollicular connective tissue) and the oral mucous membrane. It has been proposed that the gubernacular cord provides a specific promoting role or a guiding path for eruption of the permanent teeth (Scott and Symons, 1982). The superficial orifice of the individual gubernacular canals, is situated on the lingual (or palatal) aspect of the crowns of the deciduous teeth, and is readily recognized in dried jaw bones of children (van der Linden and Duterloo, 1976). Dental laminae remnants can be traced as 'pearls on a string' from the gingival lamina propria down to the perifollicular tissue (tooth sac) surrounding the developing permanent tooth (Fig. 4).

RECENT VIEWPOINTS ON THE ORIGIN OF EPITHELIAL ODONTOGENIC NEOPLASMS, HAMATORMAS AND CYSTS

It is widely held that the majority of epithelial residues persist throughout life in the gubernacular canals and periodontal membranes as vital, although by and large inactive ('resting'), single cells or cell clusters. Some of the cell rests seem to be triggered to proliferation by hitherto unknown mechanisms (apart from instances of possible inflammatory stimuli), resulting in production later in life of well-recognized pathological entities.

The origin of epithelial odontogenic neoplasms, hamartomas and cysts is inextricably bound up with a discussion of the parent cells of these lesions. Current viewpoints on the cytodifferentiation and histopathogenesis of these lesions are today still largely based on morphology of, and co-localizations between the above odontogenic lesions and the developing tooth. These comparisons depend on individual judgement at the time of assessment. An approach along the lines
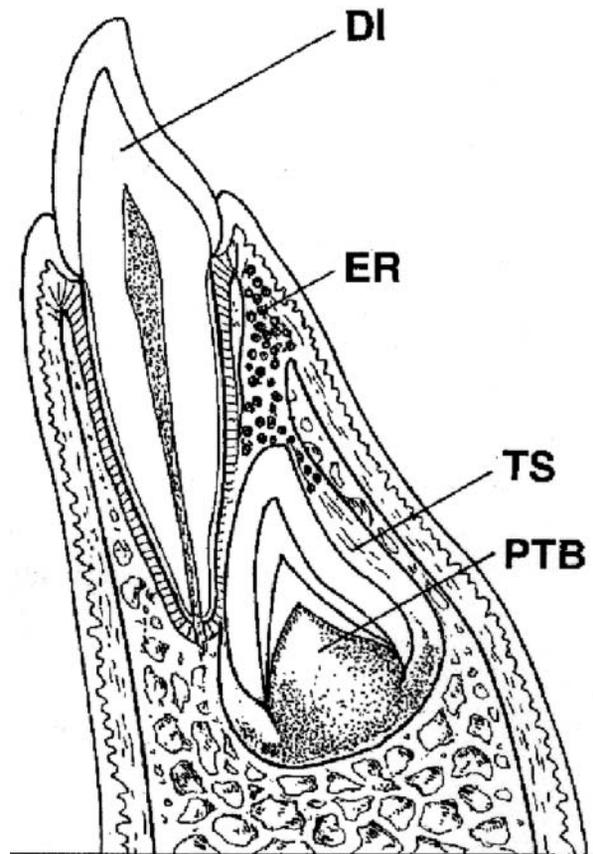

Fig. 4 Epithelial remnants from the dental lamina (ER, shown as tiny circles) localized to the gubernacular canal that links the tooth sac (TS) around the developing permanent successor (PTB) with the lingual gingiva. DI: deciduous incisor. (Drawing modified after Scott and Symons, 1982).

of investigating molecular regulation of the development of both the human teeth and the epithelial odontogenic neoplasms, hamartomas and cysts, is awaited with considerable interest, and will undoubtedly modify or enlarge our knowledge in this field.

Table 1 tabulates 10 selected cases of epithelial, odontogenic neoplasms, hamartomas and cysts, and the most likely origin of these lesions as expressed in the text of the 2nd edition of the WHO classification of odontogenic tumours (Kramer et al, 1992), supplemented with more recent studies (see Reichart and Philipsen, 2004).

Solid/multicystic Ameloblastoma (S/MA)
The S/MA ('classical intraosseous ameloblastoma') is believed to originate from residues of the dental laminae (Melrose, 1999). Takeda and Yamamoto (1990) have found that rare examples (so far only five cases have been reported according to the authors) of so-

Table 1 The likely origins of selected cases of epithelial odontogenic neoplasms, hamartomas and cysts according to morphological studies (Reichart and Philipsen, 2004; Shear, 1992)

	Source of odontogenic epithelium			
	Dental laminae	Oral epithelium	REE[a]	ROM[b]
Lesion				
Ameloblastomas				
S/MA	x			
Peripheral (PA)	x	x		
Desmoplastic (DA)	x			
Unicystic (UA)	–	–	–	–
SOT	x[c]	x[c]		x
CEOT	x			
AOT	x			
KCOT	x	x		
OGEH	x			
Inflam. paradent. cyst (IPC)	x		x	x

[a] reduced enamel epithelium; [b] rests of Malassez; c only peripheral types of SOT
(See text for further details)

called 'small ameloblastomas' located to the mandibular alveolar bone adjacent to 'normal teeth' in the lateral incisor/canine or second premolar/first molar region may arise from rests of Malassez.

Peripheral Ameloblastoma (PA)

The cellular origin of PA is still not fully clarified (Reichart and Philipsen, 2004). When the PA is located entirely within the gingival connective tissue showing no continuity with the oral epithelium, most authors link the origin of PA with remnants of the dental laminae, or if a continuity between tumour and the covering epithelium can be demonstrated, the PA may arise from basal cells of the oral epithelium (although a collision phenomenon cannot be ruled out) (Zhu et al, 1995; Redman et al, 1994; Gurol and Burkes, 1995).

Desmoplastic Ameloblastoma (DA)

A majority of authors consider the DA to be a variant of the S/MA (Reichart and Philipsen, 2004) although differences in tumour localisation, radiographical appearance and biological behaviour exist with significant bearing on the prognosis for DA (Mintz and Velez, 2002; Takata et al, 1999; Melrose, 1999). It is, however, considered most likely that the DA is derived from remnants of the dental laminae as is the S/MA.

Unicystic Ameloblastoma (UA)

The derivation of UA is still actively under debate (Philipsen and Reichart, 1998). The debate has focussed on

whether UA develops *de novo* (Ackermann et al, 1988; Robinson and Martinez, 1977) or arises in an existing odontogenic cyst, particularly a dentigerous cyst (Gardner, 1996; Leider et al, 1985). Based on 33 cases of UA, Li et al (2000) have recently argued against the latter hypothesis. Thus, to date, the origin of UA is unsolved.

Squamous Odontogenic Tumour (SOT)

There are indications that the SOT may arise from rests of Malassez located in the periodontal ligament (Philipsen and Reichart, 1996). The peripheral variant of the SOT may, however, originate from the gingival surface epithelium as a 'dropping off' phenomenon or from remnants of the dental laminae (Baden et al, 1993).

Calcifying Epithelial Odontogenic Tumour (CEOT)

The diverse location of the CEOT within the jaw bones has recently changed the focus on tumour origin from reduced enamel epithelium (Pindborg, 1958) to remnants of the dental laminae or the basal cells of the oral epithelium (Philipsen and Reichart, 2000).

Adenomatoid Odontogenic Tumour (AOT)

Based on the findings described in the above paragraph on the *gubernaculum dentis*, it was strongly suggested (Philipsen et al, 1992) that the AOT is derived from remnants of the dental laminae. The AOT

occurs in two intraosseous variants (follicular and extra-follicular) as well as an extraosseous (peripheral) variant and these three topographical variants all show identical histology. In order to conceptualise a unified source of origin for the diverse location of the AOT, one has to look to odontogenic epithelium with a widespread occurrence through the entire gubernacular canal (Fig. 4). Only one candidate seems to match the requirements, being the epithelial remnants of the dental laminae (Serres' pearls). Again, it must be stressed that hard evidence is not yet at hand.

Keratinising Cystic Odontogenic Tumour (KCOT)

The above term, KCOT, replacing 'odontogenic keratocyst' (OKC), was decided upon at the WHO Consensus Conference held in Lyon, France, in July of 2003 in association with the preparation of the forthcoming volume: *Pathology and Genetics of Tumours of the Head and Neck* (Barnes et al, in press). The change in nomenclature has, however, not changed the long held view that KCOT (OKC) arises from remnants of the dental laminae or from the basal cells of the oral epithelium (Shear, 1992).

Odontogenic Gingival Epithelial Hamartoma (OGEH)

This rare hamartomatous odontogenic lesion (Baden et al, 1968; Philipsen and Reichart, 2004) is agreed upon as originating from residues of the dental laminae.

## Inflammatory Paradental Cyst (IPC)

The pathogenesis of IPC remains, according to a very recent publication (Philipsen et al, 2004) unclarified, and remnants of the dental laminae, the reduced enamel epithelium and rests of Malassez have all been suggested as cells of origin.

CONCLUDING REMARKS

As alluded to earlier, it should be stressed that our present knowledge about the pathogenesis of odontogenic tumours/hamartomas/cysts is solely based on morphological comparisons with the developing tooth, thus allowing only hypothetical or theoretical reflections to be taken. It is expected that the explosion of cytogenetic and molecular genetic information over the past decade will, in the years to come, have a significant impact on our understanding of the biology of the above-mentioned odontogenic lesions.

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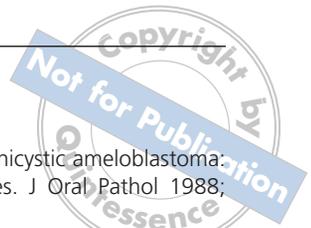
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