KERATINIZING CYSTS

A clinico-pathologic study of odontogenic keratocysts, epidermoid cysts and cholesteatomas.

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PRECIS

The purpose of this study was to critically analyze the clinical and histologic features of selected samples of odontogenic keratocysts, epidermoid cysts derived from the cutaneous tissues of the head and neck and cholesteatomas. An additional aim of the study was to compare the histologic features of the three cyst types.

The material studied derived from the biopsy files of the Department of Oral Pathology and Oral Surgery, University of Adelaide and the Institute of Medical and Veterinary Science, Adelaide, S.A.

The material described in the study was analysized using available clinical and laboratory records and on the basis of a detailed, systematic optical microscopic examination of tissue specimens.

The results of the investigation indicate that there is considerable variation in the detailed histologic features of the odontogenic keratocyst. As well a surprising similarity between odontogenic keratocysts, epidermoid cysts and cholesteatomas is demonstrated particularly in regard to the comparative histology of odontogenic keratocysts and cholesteatomas.

DECLARATION

This research report is submitted in part fulfilment of the requirements for the Degree of Master of Dental Surgery, of the University of Adelaide.

This thesis contains no material which, except where due mention is made, has been accepted for the award of any other degree or diploma in any University. To the best of my knowledge, this thesis contains no material previously published or written by another person, except where due reference has been made in the text.

M. Djamshidi

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INTRODUCTION

A cyst may be defined as an epithelial lined cavity filled with fluid or other material. The epithelial lined cavity is generally circumscribed by a surrounding fibrous connective tissue capsule.

Cysts may occur in bone or soft tissue anywhere in the body. They have long been recognised as clinico-pathologic entities and occur in patients of all ages, all races and of either sex.

Numerous discussions and theories related to clinical and biologic aspects of cysts can be found in the literature.

In recent years a great deal of attention has been paid to a group of odontogenic jaw cysts which are characterised by the presence of a keratinized epithelial cyst lining. Whilst it is accepted that keratinization of any odontogenic cyst type can occur it is generally held that keratinization of the epithelial cyst lining is, along with the presence of certain other histologic findings, a characteristic of the lesion widely referred to as the odontogenic keratocyst.

The odontogenic keratocyst is characterised clinically by its aggressive growth and by its tendency to recur following surgical removal. Similar clinical behaviour is exhibited by another keratinizing cyst type found in the middle ear cavity and bones of the skull. This lesion, although semantic problems exist with regard to its terminology, is widely referred to as a cholesteatoma. Cholesteatomas

are frequently referred to as epidermoid cysts of the middle ear.

A third type of keratinizing cyst found mainly in the cutaneous tissue of the body is the epidermoid cyst. This lesion, although clinically not afforded the attention given to the odontogenic keratocyst and cholesteatoma, is nevertheless an active, keratin producing cyst.

The defining histologic criteria of the odontogenic keratocyst are well known and are generally considered to be pathognomonic. Recent studies of the odontogenic keratocyst have, however, demonstrated that histologic variation can be found in single lesions and when different odontogenic keratocysts are compared.

Toller (1967) has drawn attention to possible similarities between odontogenic keratocysts and cholesteatomas. In addition an occasional reference (Kotton 1972) can be found in the literature where the term cholesteatomas has been used apparently synonomously with the term odontogenic keratocyst. Comparative studies of odontogenic keratocysts and cholesteatomas are lacking.

The aim of this investigation was to:

1. Analyze the clinical and histologic features of selected samples of odontogenic keratocysts, epidermoid cysts and cholesteatomas.
2. Compare the clinical and histologic features of the three cysts.

CHAPTER I

THE ODONTOGENIC KERATOCYST

TERMINOLOGY:

Interest in keratinizing cysts of the jaws was first generated as a consequence of a paper published by Philipsen in 1956. In this paper the term "odontogenic keratocyst" was coined by Philipsen to denote a group of jaw cysts, of odontogenic origin, which were characterised by the presence of a keratinizing epithelium. As pointed out by Pindborg and Hansen (1963) the term odontogenic keratocyst was applied by Philipsen to any odontogenic cyst which exhibited keratinization of its epithelial lining. The use of the term odontogenic keratocyst in an all encompassing context was subsequently extended by Pindborg and Hansen (1963) themselves. These investigators studied a series of odontogenic keratocysts which included examples of radicular cysts, follicular cysts and a group of cysts referred to as residual cysts. In this paper Pindborg and Hansen (1963) drew attention to the fact that a high proportion of their odontogenic keratocysts recurred.

At approximately the same time Shear (1960) published a paper in which he described the histologic features of a keratinizing cyst of the jaws. The term used by Shear to describe these lesions was "primordial cyst".

The possibility that at least some of the odontogenic keratocysts described by Pindborg and Hansen (1963) might belong to the category of cysts described by Shear (1960) as primordial cysts was raised by Toller in 1967. In his paper Toller, as he pointed out "very tentatively" suggested that a group of keratinizing cysts

examined by him in a survey of jaw cysts were identical with primordial cysts. Toller (1967) further suggested that the term odontogenic keratocyst would "become adopted for this condition". His suggestion was subsequently confirmed when Browne (1970, 1971) published detailed papers of a lesion he described as "odontogenic keratocyst". Browne (1970) was careful to point out that he considered his sample of odontogenic keratocysts to be histologically similar to the lesions described by Shear (1960) as primordial cysts.

The concept that the term odontogenic keratocyst as suggested by Toller (1967) and used by Browne (1970,1971) was synonomous with the term primordial cyst as employed by Shear (1960) was apparently recognised by the World Health Organization (1971) when this group published a classification of epithelial cysts of the jaws. This group although apparently favouring the term primordial cyst to describe what Browne (1970,1971) called the odontogenic keratocyst nevertheless conceded that the term "keratocyst" was synonomous. It is perhaps worth noting that while the World Health Organization conceded the term "keratocyst" it did not employ the term "odontogenic keratocyst".

In an historic context it is thus evident that whilst authorities recognised the existence of a distinct jaw cyst having a unique histology there was some disagreement regarding the terminology of this lesion. The same entity was referred to by different investigators by different names viz. "odontogenic keratocyst", "primordial cyst" and keratocyst".

The semantic problems (Robinson 1975) continue to exist regarding this particular lesion is apparent when the terminology employed by

authors publishing the results of more recent studies of thic cyst are examined. For example, papers by Radden and Reade (1973a, 1973b) and Bramley (1974) employed the use of the term "odontogenic keratocyst". Donoff et al (1972a) and Hodgkinson et al (1978) used the term "keratocyst(s)". Shear (1976) in his recent monograph expressed the view that he preferred the term "primordial cyst" rather than the term keratocyst. Further evidence of the semantic problems associated with this cyst is apparent when a modern, standard oral pathology textbook (Shafer, Hine and Levy 1974) is examined. In this widely used text the primordial cyst and the odontogenic keratocyst are classified and described as distinct and separate entities. The description of the histology of each supposedly different lesion however is identical.

It is recognised that the use of the various terms employed by different authors to describe the single entity in question, namely the odontogenic keratocyst, can be justified by the individuals concerned. However to avoid confusion the term odontogenic keratocyst will be employed throughout this study to describe the keratinizing jaw cysts examined in this investigation. The basis for this decision is that the term odontogenic keratocyst does have widely accepted and specific histologic connotations.

CLINICAL FEATURES:

Following the publication of Pindborg and Hansen (1963) great interest was generated in the odontogenic keratocyst. The results of several studies conducted subsequently by a number of investigators are available in the literature. As a consequence the clinical features of odontogenic keratocysts are now well documented.

It is widely accepted that the odontogenic keratocyst can be characterised clinically by certain relatively distinct features. One such clinical characteristic is its well documented tendency to recur following surgical treatment (Pindborg and Hansen 1963, Toller 1967, Rudd and Pindborg 1969, Bramley and Browne 1967, Browne 1970, Donoff et al 1972(a), Hodgkinson et al 1978). It is also well known that odontogenic keratocysts can reach a large size, and are more locally destructive when compared to other cysts of the jaws (Hodgkinson et al 1978). Some investigators (Toller 1967,1972) are of the opinion that the odontogenic keratocyst has a greater likelihood than other jaw cysts to undergo malignant transformation.

Odontogenic keratocysts may be associated with the presence of a variety of other abnormalities in the condition variously known as the Multiple Basal Cell Naevi Syndrome or the Gorlin and Goltz syndrome (Gorlin and Goltz 1960). The major manifestations of the syndrome which is a highly penetrant autosomal dominant condition, are as follows:

a. Multiple basal cell carcinomata of the skin.

b. Multiple cysts of the jaws.

c. Bifid ribs.

d. Dyskeratotic pits of the palms and soles.

e. Calcifications of the falxe cerebri (Jackson and Gardner 1971).

Neurological and genital abnormalities have also been reported in patients with this syndrome (Markovits and Quickert 1972). It is now generally accepted that the jaw cysts in patients with the Gorlin and Goltz syndrome are histologically identical with the lesions referred to as odontogenic keratocysts. The majority of the reported clinical and histologic surveys of odontogenic keratocysts have in fact included keratinizing cysts from the jaws of patients with this disease. Payne (1972), for example, in his survey of 103 odontogenic keratocysts derived from 87 patients included multiple cysts from five of the 87 patients in his sample. Studies reported by Browne (1970, 1971), Radden and Reade (1973b), Brannon (1976,1977) and Hodgkinson et al (1978) similarly included keratocysts from patients with the Gorlin and Goltz syndrome in their respective surveys.

FREQUENCY:

The frequency of odontogenic keratocysts is a parameter which has been detailed in a number of surveys of this lesion. Frequency data from surveys published up to 1976 was reviewed and presented by Shear (1976). These figures demonstrated an apparent frequency for the odontogenic keratocyst in the range of 3.3% to 17.4% of jaw cysts analyzed. Studies by Brannon (1976) and Djamshidi (1976) recorded frequencies of 10.5% and 21.8% respectively in two additional series of odontogenic cysts analyzed.

That there is considerable variation in the reported frequency of odontogenic keratocysts is evident. However when the results of the various surveys are reviewed and analyzed it is evident that frequency data must be interpreted with care. For example, the frequency figure of 3.3% reported by Pindborg et al (1962, cited by

Pindborg and Hansen 1963) is a figure which represented all keratinized odontogenic cysts in their sample. It should be noted that the cysts referred to as odontogenic keratocysts by these particular investigators included examples of keratinized radicular, follicular and residual cysts. While some of the latter would undoubtedly fulfil the criteria of what is now described as the odontogenic keratocyst, it is important to appreciate the fact that the figure of 3.3% reported by Pindborg et al (1962) represented a collective figure rather than a true index of odontogenic keratocyst frequency.

Care must also be taken with regard to the interpretation of frequency data presented by other investigators. Some figures represent the results of analyses of all jaw cysts (viz. odontogenic and non-odontogenic)(Toller 1967, Main 1970a, Killey and Kay 1972). Other investigators (Browne 1970, Payne 1972, Radden and Reade 1973a, Djamshidi 1976 and Shear 1976) derived frequency figures for odontogenic keratocysts from the analysis of jaw cysts of an odontogenic type only.

Besides the variables related to the nature of the cyst samples studied by the various investigators other variables probably reflect in the observed variations regarding odontogenic keratocyst frequency. For example, it seems likely that another variable which is present in surveys of odontogenic keratocyst would be the fact that different oral histopathology laboratories receive varying numbers of odontogenic cyst lesions and other forms of jaw cysts. Retrospective surveys of odontogenic cysts, in particular odontogenic keratocysts, based on such material would reflect this particular bias of the sample.

SITE DISTRIBUTION

Odontogenic keratocysts may occur in both the mandible and maxilla. It is well known that the majority of odontogenic keratocysts are found in the mandible (Browne 1970, Payne 1972, Radden and Reade 1973b, Brannon 1976, Djamshidi 1976, Shear 1976). Although there are slight variations in the reported site distribution figures in the literature it would appear to be well established that approximately 50% of all odontogenic keratocysts are found in the third molar, angle of mandible and ascending ramus area (Browne 1970, Radden and Reade 1973b, Shear 1976, Djamshidi 1976). The remaining 50% of odontogenic keratocysts have been recorded as occurring in sites outside the mandibular third molar/ramus area. Site distribution figures available from the various surveys however do not demonstrate a definite site predeliction for the odontogenic keratocyst other than the third molar ramus area. For example in Browne's (1970) survey of 90 odontogenic keratocysts 15 occurred in the maxilla. Of these 80% (12) occurred in the posterior maxilla while 20% (3) were reported in the anterior portion of this jaw. In contrast Hodgkinson et al (1978) in a survey of 79 odontogenic keratocysts reported that 65% of their sample of maxillary odontogenic keratocysts occurred in the anterior maxilla while only 35% were situated in the posterior maxilla. Other investigators (Radden and Reade 1973b, Djamshidi 1976) reported a more general site distribution for odontogenic keratocysts found in sites outside the third molar/ramus area.

SEX INCIDENCE

The odontogenic keratocyst may occur in patients of either sex. In a series of odontogenic keratocysts Pindborg and Hanson (1963) noted an almost equal sex incidence in their sample. Shear (1976) found that of sixty-five patients presenting with odontogenic keratocysts

54 were of Caucasian descent and 13 were of Negroid origin. Of the Caucasian cases 33 were male and 21 were female whereas in the Negroid sample 11 patients were male and two were female. Payne (1972) and Brannon (1976) found no significant odontogenic keratocyst sex distribution pattern in their investigations. Radden and Reade (1973b) in a survey of odontogenic keratocysts reported that in their sample 34 lesions occurred in males and 19 in females.

AGE DISTRIBUTION

Odontogenic keratocysts have been reported in patients of various age groups. Pindborg and Hansen (1963) reported an age range, at the time of detection of 15 to 75 years. Browne (1971, 1975) and Shear (1976) suggested that odontogenic keratocysts were detected most commonly in the second and third decades. Payne (1972) reported an age range of 7 to 74 years with a peak incidence being found in the second decade. Brannon (1976) in his survey of a large number of odontogenic keratocysts reported an age range of 7 to 93 years with a peak incidence in the second and third decades. Toller (1967) reported a peak incidence in the fourth to fifth decades with an age range at time of detection of 10 to 70 years for the odontogenic keratocyst. Hodgkinson et al (1978) reported a similar peak incidence in the fourth and fifth decades.

HISTOLOGY:

Shear (1960) in his paper describing the lesions he termed "primordial cysts" listed four histologic features which he considered to be the main characteristics of this lesion. These criteria (Shear 1960) were as follows:

1. "A regular, thin lining of stratified squamous epithelium, with no rete pegs".
2. "The presence of a keratinized or parakeratinized layer on the surface of the epithelium. Keratin is frequently present within the cyst cavity".
3. "A relative absence of inflammatory cell infiltration".
4. "The presence of columnar basal cells with either pyknotic or vesicular nuclei".

Pindborg and Hansen (1963) in a paper, widely used as a basic reference, described the microscopic features of a group of lesions they referred to as odontogenic keratocysts. The histologic features of the odontogenic keratocysts described by these investigators were essentially similar to those described by Shear (1960) in relation to primordial cysts. There were, however, additional histologic characteristics mentioned by Pindborg and Hansen (1963). For example,Pindborg and Hansen (1963) described the basal epithelial cell layer of the cyst lining as having a columnar or cuboidal morphology. The same investigators also commented upon the fact that in their material the cells of the stratum spinosum of the cyst lining epithelium frequently exhibited vacuolization. A feature of the cysts described by Shear (1960) namely that the lesions exhibited a relative absence of inflammation was not listed by Pindborg and Hansen (1963).

Although, as was discussed in a previous section, there has, over the years, been debate and confusion regarding the terminology of primordial cysts and keratocysts, it is now generally agreed that the primordial cysts of Shear (1960, 1976) and the odontogenic keratocysts described by many others (Pindborg and Hansen, 1963, Browne 1970, 1971, Payne 1972, Radden and Reade 1973b, Brannon 1976 and 1977) are histologically identical lesions. The histologic criteria described by Shear (1960) and Pindborg and Hansen (1963) have, with minor modification, formed the basis for the more recent studies of this lesion.

EPITHELIAL CYST LINING REGULARITY

One of the major histologic features characteristically associated with the odontogenic keratocyst is the fact that the cyst lining epithelium is consistently described as being thin, flat and regular. Browne (1971) in his survey of 139 odontogenic keratocysts, a study which can be regarded as one of the first highly detailed investigations of a large number of these lesions, confirmed the characteristic regularity of odontogenic keratocyst lining epithelium. Browne (1971) did point out, however, that there was some variation in thickness of cyst lining epithelia in his sample. Variation in epithelial thickness occurred particularly in those cysts which were inflammed and had a history of secondary infection.

Further analysis of the literature revealed a number of interesting findings regarding the question of the regularity of the epithelial lining of odontogenic keratocysts. For example, Shear (1960) in his listing of histologic criteria of primordial cysts stated that the cyst lining epithelium characteristically was devoid of rete pegs. An analysis of his data reveals that one third of the samples did in

fact exhibit the presence of rete pegs. The presence of rete pegs was reported by Shear (1960) to be unrelated to inflammation. Of further significance in this context was a recent paper by Brannon (1977). This investigator in a survey of 312 odontogenic keratocysts reported that 14.2% of the cysts exhibited what was described as irregular acanthosis while 16.1% of the cysts exhibited rete peg formation and/or budding. Irregular acanthosis and budding of odontogenic keratocyst epithelium was also illustrated by Payne (1972) and Radden and Reade (1973b).

While it is evident that it is widely accepted that the epithelial lining of odontogenic keratocysts is generally flat and regular it is also apparent that this particular feature is variable. Epithelial irregularities in the form of areas of acanthosis, rete peg formation and epithelial buds do occur. In addition it is apparent (Pindborg and Hansen 1963, Browne 1971, Radden and Reade 1973b, Brannon 1977, Hodgkinson et al 1978) that although the consensus view is that the odontogenic keratocyst lining epithelium is usually thin there is no real agreement as to what number of cells constitutes "thin".

BASAL EPITHELIAL CELL MORPHOLOGY

A feature of odontogenic keratocyst epithelium which has been commented upon in the literature is the morphology of the basal layer. As indicated previously Shear (1960) described the basal cells of such cysts as being columnar in shape. Pindborg and Hansen (1963) described the basal cells of keratocysts as having either a columnar or a cuboidal morphology. Browne (1971) in his study described the basal cell layer of the cyst lining epithelium as being "characteristically" columnar. Approximately 90% of Browne's sample of cysts exhibited the presence of columnar basal cells. However, in almost direct contrast

to Browne's (1971) findings Brannon (1977) reported that in his survey of 312 odontogenic keratocysts only approximately 14% of lesions exhibited the presence of a basal epithelial cell layer having a columnar morphology. The remaining cysts exhibited a cuboidal to low columnar shape. Since the morphology of the basal cell layer of odontogenic keratocyst epithelium has generally been accepted as a basic, definitive histologic feature, the conflicting findings of Browne (1971) and Brannon (1977) would appear to be of some significance and indicate a need for further analysis of this particular histologic feature of odontogenic keratocysts.

Another feature of the basal cells of the cyst lining epithelia of odontogenic keratocysts which has received comment by several investigators (Browne 1971, Radden and Reade 1973b, Shear 1976 and Brannon 1977) is that the nuclei supposedly have a tendency towards polarization within the cells. Browne (1971) reported a high frequency of polarization of basal cell nuclei in the odontogenic keratocysts comprising his sample. Radden and Reade (1973b) commented upon the fact that some basal cells exhibited an ameloblast type appearance. Brannon (1977) reported a low incidence of reversed nuclear polarity of the nuclei in the basal cells of odontogenic keratocyst lining epithelia and suggested that this phenomenom was a consequence of cell shape. Columnar cells in Brannon's (1977) study exhibited reversed nuclear polarity whereas cuboidal shaped cells, which in his investigation comprised the majority of cysts, did not. Whether the opinion expressed by Browne (1971) that a tendency of odontogenic keratocyst lining epithelia to exhibit polarization of basal cell nuclei is a "characteristic" histologic feature remains open to question.

KERATINIZATION

Another basic histologic criteria for the diagnosis of an odontogenic keratocyst is demonstration of keratinization of the cyst lining epithelium. Shear (1960) described the cyst lining epithelia of his cysts as having a keratinized or parakeratinized surface layer. Pindborg and Hansen (1963) considered that the predominant type of keratin found in odontogenic keratocysts was parakeratin. However analysis of data by Browne (1971), Payne, (1972) and Brannon (1977) revealed that although parakeratinization is frequently found, orthokeratinization and mixed orthokeratinization and parakeratinization patterns may be observed in odontogenic keratocysts. A further point of significance deriving from the data presented by Shear (1960), Browne (1971) and Brannon (1977) is that a granular layer is not a constant histologic finding of orthokeratinization in these lesions. In addition, it is evident (Shear 1960, Browne 1977) that a granular layer can in fact be found in a number of parakeratinized cyst linings.

The reasons for and the significance of the presence of different types of keratin in odontogenic keratocysts would appear to be topics which remain unclear. Brannon (1977) suggested that "keratocysts" containing orthokeratin perhaps had an origin different from "keratocysts" exhibiting parakeratinization. It was also considered (Rud and Pindborg 1969, Payne 1972, Brannon 1977) that the type of keratin found in odontogenic keratocysts might be significant in terms of explaining the propensity for recurrence exhibited by this lesion. A definite relationship between keratin type and cyst recurrence does not appear to have been demonstrated.

Hansen and Kobyasi (1970) and Hansen (1970) on the basis of ultrastructural studies of keratinizing jaw cysts suggested that the process of keratinization in odontogenic keratocysts, whilst being essentially similar to keratin production occurring elsewhere, was not as stable as that occurring in other sites such as the skin and oral mucosa. Wysocki and Sapp (1975), on the basis of a combined transmission and scanning electron microscopic studies suggested that parakeratinized odontogenic keratocyst lining epithelia differed from orthokeratinized linings and that differences in the type of keratin found could be related to variations in cellular activity.

INFLAMMATION IN ODONTOGENIC KERATOCYSTS

A relative absence of inflammation in odontogenic keratocysts is generally accepted as one of the major histologic criteria defining one of these lesions. Histologic evidence of inflammation in the walls of odontogenic keratocysts has, nevertheless been presented by a number of investigators (Shear 1960, 1976, Browne 1971, Radden and Reade 1973b, Brannon 1977, Hodgkinson et al 1978).

Although inflammation in odontogenic keratocysts is known to occur there is surprisingly little detailed information available regarding this topic. Shear (1960) in a reference to inflammation in his cyst sample described the presence of a mild to moderate chronic inflammatory cell infiltrate in a number of cyst capsules. As well the same investigator reported the presence of inflammatory cells, predominantly polymorphonuclear leucocytes, within the lining epithelia of six cysts. Intraepithelial inflammatory cells were, according to Shear (1960) confined to areas devoid of keratin. Later studies by Pinsborg and Hansen (1963), Browne (1971) and Brannon (1977) also associated an absence of keratin in cyst lining epithelia with

inflammation, in particular capsular inflammation.

The nature of inflammatory changes in odontogenic keratocysts were more fully described by Browne (1971). Although Browne (1971) stated that the capsules of cysts in his sample were "mostly free from inflammatory cell" infiltrations, 88 of 139 cysts exhibited the presence of focal, sometimes mural collections of chronic inflammatory cells while 18 lesions exhibited the presence of a diffuse capsular chronic inflammatory cell infiltration. The latter category of inflammatory change was considered by Browne (1971) to be a feature of odontogenic keratocysts having a history of secondary infection (Soskolne and Shear 1967, Radden and Reade 1973b).

The severity and distribution of inflammatory cell infiltrates in odontogenic keratocysts were extensively described by Brannon (1977). In a series of 312 cysts studied by this investigator 209 exhibited signs of inflammation of one type or another. The severity and distribution of inflammatory cell infiltrates in the cysts exhibiting signs of inflammation were categorised into five groups according to the histologic pattern of inflammation observed and associated findings in the cysts. Although, as was mentioned previously, it has been suggested that inflammatory changes noted in odontogenic keratocysts are of secondary (Shear 1960) or a secondary infective origin (Soskolne and Shear 1967, Browne 1971, Radden and Reade 1973a) further investigation of inflammatory changes in these lesions would appear to be of value in terms of further clarifying questions related to the true incidence and significance of such changes in odontogenic keratocysts.

SEPARATION OF CYST LINING EPITHELIUM

A histologic finding which has been recorded by a number of investigators in relation to descriptions of odontogenic keratocyst

morphology is the phenomenon of separation of the cyst lining epithelium from the capsular tissues. This phenomenon involving separation of some areas of the cyst lining epithelium was reported by Browne (1971, Donoff et al (1972a), Radden and Reade (1973b) and Brannon (1977). The latter investigator reported an incidence of 94%.

The reasons for the observed separation of the epithelial lining of odontogenic keratocysts from the capsular tissues and whether or not the separation has significance remains unclear (Wilson 1978). Browne (1971) on the basis of an examination of PAS stained tissues considered that the basement membrane in odontogenic keratocysts was poorly developed and that this was a fact related to the separation of the epithelium from the vapsular tissues. He also noted that in areas of cysts where the epithelium had separated the basement membrane remained attached to the epithelium. This finding was subsequently confirmed at an electron microscopic level by Wilson (1978). Donoff et al (1972a) offered an explanation for the separation of odontogenic keratocyst lining epithelium based on the fact that since the epithelium/connective tissue interface in these lesions is frequently flat there was a greater likelihood of simple mechanical separation occurring during histologic tissue processing procedures. As an alternative explanation Donoff et al (1972a) suggested that the epithelial separation was the consequence of enzymatic activity albiet of an unknown type.

EPITHELIAL DISCONTINUITIES

Toller (1966a) in an analysis of odontogenic cysts reported that discontinuities in the epithelial lining of non-keratinizing cysts was observed more frequently than in keratinizing lesions. In a later paper the same investigator (Toller 1967) also referred to this features of odontogenic keratocysts and added it to a list of "additional characteristics" of these lesions. As is the case with several histologic

features of odontogenic keratocysts the significance of the observation that these lesions frequently possess a complete epithelial lining is unclear. Toller (1967, 1972) however, suggested that epithelial discontinuities in dodontogenic cysts may be related to modes of cyst growth and that the differences observed in keratinizing and non-keratinizing jaw cysts could be related to different mechanisms of cyst enlargement.

MITOTIC ACTIVITY OF THE CYST LINING EPITHELIUM

Another feature of the epithelial lining of odontogenic keratocysts which has received a degree of attention in the literature is the basophilia exhibited by the basal epithelial cells of the cyst lining (Shear 1960, Browne 1971). Shear (1960) was of the opinion that the morphologic characteristics of the basal cells in the epithelium of odontogenic keratocysts suggested cellular activity. That the epithelium of odontogenic keratocysts exhibited signs of greater biologic activity than other jaw cysts was later confirmed by the studies of Main (1970a) and Toller (1971). Main (1970a) in his study showed that the "mitotic value" for his sample of odontogenic keratocysts approximated that of ameloblastoma epithelium and dental lamina epithelium. Toller (1971) on the basis of an *in vitro* study employing tritiated thymidine concluded that the mitotic activity of odontogenic keratocyst epithelium was approximately seven times that of apical cysts. Browne (1971) although deriving a lower mitotic value than Main (1970a) also confirmed the latter investigator's finding that the mitotic activity in odontogenic keratocysts was higher than in other cysts. In addition, Browne (1971) observed that only approximately 10% of mitotic figures counted in the epithelial lining of keratocysts were present in the basal layer, the remainder being in suprabasal cells. The tendency for suprabasilar mitosis in odontogenic keratocyst epithelium was more recently recorded by Brannon (1977). The observed degree of mitotic activity within

odontogenic keratocyst epithelium was related to mechanisms of primary cyst growth (Main 1970a, Browne 1971) and recurrence (Toller 1971) of this lesion. The signficiance of mitotic activity in odontogenic keratocyst epithelium is dealt with in further detail in the section of this review dealing with the pathogenesis of this lesion.

MICROCYSTS AND EPITHELIAL CELL RESTS

The capsule of odontogenic keratocysts is characteristically described as being thin. The capsular tissues of odontogenic keratocysts comprise collagenous fibrous connective tissue. The most striking feature of odontogenic keratocyst capsules and associated soft tissues is the frequent finding at the time of histologic examination of variable numbers of microcysts and epithelial cell rests and islands. The microcysts, variously described as "daughter" cysts or "satellite" cysts (Keith 1973) found in association with odontogenic keratocysts are, as the term microcyst suggests, small discrete cysts.

Browne (1971) in his study recorded a 30% incidence of microcysts in his sample of odontogenic keratocysts. This investigator classified microcysts into three categories depending on their morphology. Some microcysts were described by Browne (1971) as having a similar morphology to the main cyst while others presented a variable epithelial morphology. Brannon's (1977) in his investigation of a large number of odontogenic keratocysts recorded a microcyst incidence of 22% and confirmed Brown'e (1971) finding of histologic variability. The data of Browne (1971) and Brannon (1977) suggests that microcysts are found more frequently in association with mandibular odontogenic keratocysts. It would appear however that this association could probably be explained on the basis of the known frequency of odontogenic keratocyst occurrence in the third molar region of the mandible.

The result of studies by Browne (1971), Keith (1973),

Radden and Reade (1973b), Shear (1976) and Brannon, (1977) suggests that microcysts are more frequently found in cases of multiple odontogenic keratocysts and in cysts from patients with Gorlin and Goltz syndrome. The parameters of age and microcyst occurrence have so far been shown to be unrelated (Browne 1971).

The exact origin of microcysts and cell rests found in association with odontogenic keratocysts remains somewhat unclear. Soskolne and Shear (1967) were of the opinion that microcysts arose from remnants of the dental lamina, the latter being originally in the form of epithelial islands. Stoelinga and Peters (1971) suggested microcysts could, in addition, arise from epithelial islands derived from the oral mucosa. A third possibility regarding the origin of microcysts was suggested by Payne (1972). This investigator was of the opinion that microcysts could derive from epithelial islands arising as a consequence of "budding" proliferation from the main cyst lining epithelium.

The clinical significance of epithelial cell rests and microcysts in odontogenic keratocyst capsules is of considerable importance and is discussed later in another section of this review dealing with the question of cyst recurrence.

MISCELLANEOUS HISTOLOGIC FEATURES

Histologic features which have been occasionally reported occurring in association with the epithelial and connective tissue components of odontogenic keratocysts include, melanocytic pigmentation of the epithelium, the presence of ciliated cells within the epithelium, sebaceous glands and the presence of hyaline bodies and calcifications (Browne 1971, Brannon 1977). In addition the

occasional presence of cholesterol clefts and hyalinization of capsular connective tissue particularly that subjacent to the epithelium have been noted.

The occurrence of melanocytic pigmentation of odontogenic keratocyst epithelium is reportedly very rare. Browne (1971) reported two cases in a series of 139 cysts while Brannon (1977) recorded one case in a series of 312 odontogenic keratocysts. All three cases reported involved cysts removed from people of West Indian or Negroid origin.

Two investigators (Browne 1971, Brannon 1977) recorded the presence of mucous cells within a small number of odontogenic keratocysts lining epithelia. Browne's (1971) statement that "literally only one or two cells" exhibited this form of metaplasia would strongly suggest that this particular histologic feature is of little significance other than in the context of histologic comparison of this lesion with other odontogenic cysts where mucous metaplasia is known to occur with greater frequency.

Hyaline bodies described as Rushton bodies were reported with a frequency of 9.4% and 11.2% respectively by Browne (1971) and Brannon (1977). The latter investigator did not detail the site of occurrence of the hyaline bodies in his series of cysts. Browne (1971) however, recorded that in the case of 11 out of 13 cysts the Rushton bodies were found within the epithelium overlying inflammatory foci in the capsule. The presence of hyaline bodies in odontogenic keratocysts was related to the presence of inflammation by both Browne (1971) and Brannon (1977). Morgan and Johnson (1974) found that Rushton bodies in an odontogenic keratocyst exhibited some ultrastructural differences

from those observed in non-keratinizing odontogenic cysts.

Calcifications in the form of mineralisations occurring in association with hair pin shaped structures and in the form of structureless masses were reported in 13% of odontogenic keratocysts studied by Browne (1971). Dystrophic calcifications were recorded in 17% of cysts in Brannon's (1977) study. In addition, Brannon (1977) reported calcifications occurring in association with epithelial cell rests. Data presented by Browne (1971) and Brannon (1977) could be interpreted in such a way to suggest that calcifications occur with greater frequency in cases of multiple keratocysts, although not necessarily multiple keratocysts found in association with the Gorlin-Goltz syndrome. Brannon (1977) considered that the presence of dystrophic calcifications in odontogenic keratocysts could reflect some form of metabolic disturbance related to calcification generally.

Hyalinization of capsular tissues (Browne 1971) in the form of dense, acellular, collagenous areas usually situated immediately subjacent to the cyst lining epithelium is not an infrequent finding in odontogenic keratocysts. The presence of capsular hyalinization was related by Browne (1971) to the parameter of patient age. This view was supported by the findings of Brannon (1977). As pointed out by Browne (1971) hyalinization of cyst capsular tissues has been recorded in other varieties of odontogenic cysts.

Toller (1967) was of the opinion that a relative absence of cholesterol was a characteristic of odontogenic keratocysts. Browne (1971) and Brannon (1977) reported incidence figures for cholesterol in odontogenic keratocysts of 13.7% and 12.5% respectively. Browne

(1971) in his survey reported figures which indicated that in the majority of cases cholesterol cleft presence was associated with the presence of inflammation and/or haemosiderin. Browne (1971) favoured the latter source as being the factor most likely associated with cholesterol formation in odontogenic keratocysts. Brannon (1977) suggested that the presence of cholesterol in odontogenic keratocysts was unlikely to be associated with inflammation. Brannon's (1977) data indicated however that over half of his sample of odontogenic keratocysts in fact exhibited signs of inflammation. In view of the controversy surrounding the question of the origin of cholesterol in odontogenic cysts in general (Shear 1976) the significance of cholesterol in odontogenic keratocysts would appear to be a matter which at this time remains unclear.

CYST LUMEN CONTENTS

The luminal contents of odontogenic keratocysts have, in recent years, been the subject of several investigations and papers. A proportion of this work was aimed at attempts to elucidate the mechanisms of cyst growth. Mechanisms of cyst growth are referred to elsewhere in this review. At a purely histologic level, desquamated keratin, degenerate epithelial cells, inflammatory cells, cholesterol and bacteria have been reported as comprising part of the constituents of odontogenic keratocyst lumens (Browne 1976). In paraffin embedded material although desquamated keratin is frequently observed in the lumens of odontogenic keratocysts large amounts of keratin were only reported to occur in a proportion of lesions (Shear 1960, Soskolne and Shear 1976, Browne 1971, Brannon 1977). In the absence of large quantities of keratin the cavities of odontogenic keratocysts may appear relatively empty when examined histologically.

In recent years the nature of the contents of odontogenic keratocysts has aroused interest in relation to the question of clinical, preoperative diagnosis. In an electrophoretic study on odontogenic cyst fluids, Toller (1970a) found that the odontogenic keratocysts had a low soluble protein content relative to other odontogenic cysts. On the basis of his finding Toller (1972) suggested that an analysis of cyst lumen fluids was a useful clinical diagnostic tool. Similar findings regarding the low soluble protein content of odontogenic keratocysts were recorded by Browne (1976) who, in addition, found that odontogenic keratocysts exhibited the presence of high albumen levels relative to other cysts and lower gamma globulin levels than radicular cysts. Browne (1976) concurred with Toller's (1970a) view that electrophoresis of cyst fluids was useful diagnostic procedure. Browne (1976) on the basis of findings in the portion of his study involving cytological analysis of odontogenic keratocyst contents also agreed that preoperative cytological examination of smears was a useful diagnostic tool (Kramer and Toller 1973).

NEOPLASIA AND ODONTOGENIC KERATOCYSTS

A histologic feature of odontogenic keratocysts which was recorded by a number of investigators is the finding of histologic evidence of neoplasia. Toller (1967) expressed the opinion that keratinizing jaw cysts had a greater tendency than nonkeratinized cysts to undergo carcinomatous transformation. This opinion was based on an analysis of 13 cases of intracystic jaw carcinoma. Toller (1967) found that six of the 13 cases of cyst related carcinoma were associated with cysts having a keratinized epithelial lining. Analysis of the literature, however reveals in fact a paucity of properly documented cases of squamous cell carcinoma arising specifically from the epithelium of odontogenic keratocysts.

Rudd and Pindborg (1969) reported finding one case of squamous cell carcinoma in a series of 21 odontogenic keratocysts. However, because of the fact that these particular investigators used the term odontogenic keratocysts in a broad context, namely that it applied to any type of odontogenic cyst exhibiting keratinization, it is difficult to establish whether this case of carcinoma was truly associated with an odontogenic keratocyst. Ward and Cohen (1963) reported a case of squamous cell carcinoma arising in a jaw cyst. According to Browne and Gough (1972) the case reported by Ward and Cohen (1963) possibly represented an instance of carcinoma truly arising in an odontogenic keratocyst. Browne and Gough (1972) themselves reported three cases of squamous cell carcinoma arising in association with jaw cysts. Although the cyst lining in these cases exhibited keratinization Browne and Gough (1972) were very careful to point out that their cases were not odontogenic keratocysts. These investigators suggested that the finding of keratin metaplasia in odontogenic cysts rather than the keratinization found in odontogenic keratocysts was of greater significance with respect to the question of carcinomatous transformation of jaw cyst epithelium. Shear (1976) demonstrated a case of squamous cell carcinoma supposedly arising from the epithelium of an odontogenic keratocyst and Hodgkinson et al (1978) reported one case of squamous cell carcinoma in a series of 79 odontogenic keratocysts. However as pointed out by Hodgkinson et al (1978) their particular case of squamous cell carcinoma could have represented an instance of squamous odontogenic tumour rather than carcinoma.

In addition to carcinoma a small number of ameloblastomas (Byrd et al 1973, Brannon 1977) and instances of epithelial atypia and dysplasia have been reported (Rud and Pindborg 1969, Toller 1972,

Radden and Reade 1973b, Shear 1976, Brannon 1977).

The reported instances of epithelial atypia or dysplasia within the linings of odontogenic keratocysts are relatively few in number. The terms epithelial atypia and epithelial dysplasia do have connotations of neoplasia. Data available in the literature does not provide a sufficient base from which to draw conclusions regarding the question of whether or not atypia is more frequently found in odontogenic keratocysts or the question of whether or not it heralds carcinomatous transformation.

THE PATHOGENESIS OF THE ODONTOGENIC KERATOCYST

The histogenesis of odontogenic keratocysts, their aetiology and the biologic mechanisms of growth and enlargement are topics about which relatively little is known in spite of the recent upsurge in interest regarding these lesions.

Shear (1960) in his original paper on primordial cysts suggested that these lesions developed in place of a normal tooth or a supernumerary tooth. The mechanism of cyst initiation proposed by Shear (1960) was that cyst development was initiated as a consequence of cystic breakdown of the stellate reticulum of the enamel organ. A significant corollary inherent in this theory was that odontogenic keratocysts were considered to arise from dental lamina derived epithelium at a stage where, although some differentiation of cells had occurred, no apposition of mineralised tissue matrix had occurred. In other words the epithelium of odontogenic keratocysts is derived from embryologically young epithelium which at the time of cystic transformation has not fulfilled its predestined functions.

Shear's (1960) theory regarding the origin of odontogenic keratocysts was subsequently modified by Soskolne and Shear (1967) on the basis of a histologic examination of a larger series of these lesions including a number of patients with the Gorlin-Goltz syndrome. Soskolne and Shear (1967) postulated that in addition to deriving from preappositional enamel organ epithelium, odontogenic keratocysts could derive directly from dental lamina tissue. This latter suggestion arose from observation that in multiple keratocysts from patients with the Gorlin-Goltz syndrome dental lamina epithelium could be seen in close proximity to the main cysts

and microcysts present.

That odontogenic keratocysts could originate from dental lamina epithelium either in a pre-odontogenesis or a post-odontogenesis phase (Bartlett et al 1973) was a theory which gained wide acceptance (Stoelinga 1976). However, Stoelinga (1976) himself on the basis of an examination of human and non-human primate material and on the basis of results of previous observations on odontogenic keratocysts (Stoelinga and Peters 1973, Stoelinga et al 1973, Stoelinga et al 1975) suggested an alternative theory related to odontogenic keratocyst histogenesis. This investigator stated that "..the remnants of dental lamina are unlikely to be the principle origin of keratocysts" and suggested that odontogenic keratocysts could derive directly from mature oral epithelium. The mechanism of odontogenic keratocyst formation from oral epithelium as proposed by Stoelinga (1976) involved the suggestion that cysts could arise from epithelial islands which originated as epithelial hamartomata from the oral epithelium or as a consequence of a "dropping off" of cells from the basal layer of the oral epithelium. Whilst arguing strongly that the chief source of epithelium in odontogenic keratocysts was the mature oral epithelium Stoelinga (1976) did however concede that these lesions, particularly in the tooth bearing areas of the jaws, could be derived from dental lamina epithelium.

Browne (1971) and Brannon (1977) in their histologic surveys of odontogenic keratocysts reported the finding which has received relatively little attention in the literature but which would appear nevertheless to be of significance with respect to the question of odontogenic keratocyst histogenesis. These investigators found that a small number of odontogenic keratocysts in their respective samples

exhibited a true, histologically demonstrable dentigerous relationship to tooth crowns. While this observation suggested that in some cases at least odontogenic keratocysts could arise from reduced enamel epithelium (that is, post functional enamel organ epithelium) this view was refuted by Main (1970a) and Browne (1971). Both Main (1970a) and Browne (1971) were of the opinion that such cysts occurred as a consequence of tooth "eruption" into pre-existing odontogenic keratocysts. Such lesions were classified by Main (1970a) as "envelopmental" odontogenic keratocysts. In view of the more recent reports of this phenomenon by Brannon (1977) and the in vivo work described by Bartlett et al (1973) where it was demonstrated that post-appositional enamel organ epithelium could undergo keratinizing cystic change it would appear that the reduced enamel epithelium cannot be entirely ruled out as being a possible occasional source of odontogenic keratocyst epithelium.

A number of experiments concerned with the experimental production of jaw cysts have been reported in the literature. Studies conducted by Riviere et al (1971), Atkinson (1972 and 1976) and Bartlett et al (1973) involved the transplantation of mouse embryonic dental organs to sites other than the jaws, whilst a study reported by Soskolne et al (1976) involved the transplantation of rat gingival epithelium to intramandibular bone. All groups of investigators demonstrated that keratinizing cysts could, with varying degrees of success, be shown to derive from the various tissue sources, namely enamel organ epithelium (Riviere et al 1971, Atkinson 1972, 1976, Bartlett et al 1973) or oral mucous membrane epithelium (Soskolne et al 1976). Both Bartlett et al (1973) and Soskolne (1976) in their respective papers noted that the lesions produced by them in their respective model system bore some similarities to odontogenic keratocysts.

While the study of Soskolne et al (1976)

interpreted as being circumstantially supportive of Stoelinga's (1976) views regarding odontogenic keratocyst derivation from oral mucosal epithelium, the studies of Atkinson (1972,1976) and Bartlett et al (1973) do not directly prove or disprove the previously described hypothesis regarding the tooth associated epithelial origin of odontogenic keratocysts. Both studies did, however, as pointed out previously,demonstrate the potential of enamel organ epithelium to undergo keratinizing cystic change, albiet at a stage of tooth development where enamel apposition had already begun (c.f. Shear's 1960 theory).

In summary, it would appear from the literature that although there is some agreement concerning the possible histogenesis of odontogenic keratocysts it has not been clearly established whether or not these lesions all derive from one histogenic source or several. At the present time dental lamina epithelium, preappositional enamel organ epithelium, functionally appositional organ epithelium, reduced enamel epithelium and mature oral mucosal epithelium would all appear to represent potential histogenic sources for odontogenic keratocysts.

The fact that the exact histogenesis of odontogenic keratocysts remains uncertain would appear to reflect in the paucity of factual data in the literature concerning the aetiology of this lesion. Information available on this topic was reviewed by Browne (1975). As pointed out by Browne (1975) there is no evidence that odontogenic keratocysts arise as a consequence of inflammatory stimulation of odontogenic epithelium. Although a developmental origin for these lesions is widely accepted there is no scientific data available which identifies specific aetiologic factors involved in the initiation of odontogenic keratocysts. However, there is circumstantial evidence

to suggest a genetic predisposition inherent in some individuals. This evidence was derived from studies of patients with the Gorlin-Goltz syndrome where there is a known autosomal dominant mode of transmission associated with this disease and where multiple odontogenic keratocysts are known in many instances to form part of the manifestations of this syndrome. Whether all odontogenic keratocysts, single or multiple, found in patients reflect an inherent predisposition, whether or not odontogenic keratocysts represent an expression of neoplastic potential (Toller 1967, 1972) or hamartomatous potential subsequent to the presence of some form of inherent genetic predisposition (Browne 1975) are questions which remain unclear.

The mechanisms of odontogenic cyst growth and the factors associated with the mechanisms of cyst growth have been investigated by a number of researchers. Aspects of cyst growth related to osmotic and hydrostatic pressure characteristics of odontogenic cysts were studied by James (1926), Toller (1948, 1966b, 1970a) and Susuki (1975). An analysis of odontogenic cyst contents by means of electrophoresis was the subject of investigations by Toller (1970b) and Browne (1971, 1976). Studies investigating the biologic activities of odontogenic cyst lining epithelia as measured by their respective mitotic activities were reported by Main (1970a), Browne (1971) and Toller (1971). The topic of odontogenic cyst growth and enlargement was also reviewed in papers by Toller (1967,1972), Main (1970b) and Browne (1975).

The results of the various studies concerning mechanisms of cyst growth would appear to have resulted in the general acceptance of the fact that odontogenic keratocysts are probably different in some ways to other odontogenic cysts. The exact manner in which odontogenic keratocysts differ from other cyst types in the way they enlarge would

however appear to be a problem still awaiting solution.

Toller (1967, 1972) suggested that certain features of odontogenic keratocysts, for example, their aggressive clinical behaviour and the demonstrated mitotic activity of their lining epithelia (Main 1970a, Toller 1971, Browne 1971) were consistent with the view that the enlargement of these lesions reflected an inherent biologic tencency on the part of the lining epithelium towards active and persistent proliferation. This inherent tendency of odontogenic keratocysts lining epithelium was considered to be confined to odontogenic keratocysts rather than being a property of all odontogenic cyst epithelial linings. A similar view was shared by Main (1970b).

Whether the inherent proliferative activity of odontogenic keratocyst lining epithelium is an expression of neoplastic activity (Toller 1976, 1972) or inherent hyperplastic activity (Main 1970b) is unclear although the latter investigator argued strongly for the concept of mural hyperplastic growth. Browne (1975) concluded that the available evidence did not support the view that odontogenic keratocysts were cystic neoplasms. Instead, Browne (1975) argued that odontogenic keratocysts were hamartomatous thus perhaps implying that these lesions possessed an inherent capacity for active, proliferation at least during the period od childhood and adolescence. That odontogenic keratocysts continue to grow, albiet at an unknown rate, after puberty was explained by Browne (1975) on the basis of considerations related to the known histologic features, permeability and osmotic and hydrostatic pressure characteristics (Toller 1970a) of odontogenic keratocysts. Browne (1975) proposed that a combination of both inherent epithelial proliferation and hydrostatic pressure effects were involved in odontogenic keratocyst enlargement.

Although, as was mentioned earlier, there is wide agreement that odontogenic keratocysts do differ in some way from other odontogenic cysts regarding mechanisms of cyst enlargement whether or not mural epithelial growth (Main 1970b), osmotic pressure factors (Toller 1970b) or a combination of factors can account for these differences would appear to be matters which require further study. The need for further investigation of this problem would appear to be further highlighted by the findings of Donoff et al (1972b), Harris et al (1973) and Harris and Goldhaber (1973) regarding the related phenomenon of odontogenic cyst mediated bone resorption.

ODONTOGENIC KERATOCYST RECURRENCE

Shear (1960) in his discussion of the lesion he referred to as the "primordial cyst" stated that these lesions were simple odontogenic cysts and while they could grow to a large size they did not recur following enucleation. Pindborg and Hansen (1963), however, in their study of odontogenic keratocysts drew attention to the fact that a number of the lesions they studied were characterised by the fact that they had recurred following surgical treatment. The recurrent nature of the entity now referred to as the odontogenic keratocyst was subsequently confirmed by many investigators (Toller 1967, Browne 1970, Payne 1972, Pearsson 1973, Brannon 1976, Hodgkinson et al 1978) in surveys of this lesion. Instances of unusual recurrence of odontogenic keratocysts in jaw bone grafts were recorded by Edwards and McMillan (1971), Pearsson (1973) and Attenborough (1974).

The reported recurrence rates of odontogenic keratocysts vary widely. Data on this topic obtained by a review of the literature was presented by Shear (1976). Figures presented by Shear (1976) show a reported recurrence rate for odontogenic keratocysts extending from 11% to 62%.

The basis for the tendency of odontogenic keratocysts to recur are largely unknown. Various investigators have, nevertheless, hypothesized possible reasons for this phenomenon. The various theories relate to certain clinical and histological features of odontogenic keratocysts.

As pointed out by Browne (1970) one theory of odontogenic keratocyst recurrence suggested that recurrence of this lesion could

be accounted for by the subsequent growth of satellite cysts left behind at the time of surgery. In a subsequent paper (Browne 1971) the same investigator stated that there was no statistical correlation between the presence or absence of satellite cysts and the rate of recurrence in his series of odontogenic keratocysts.

The validity of Browne's (1971) statement can however be questioned for two reasons. First, the material analysed by Browne (1971) did not comprise material which had been consistently serially sectioned. It is possible therefore that satellite cysts may have been missed during histological examination. Secondly, Browne's (1971) study did not take into account the fact that small daughter cysts and epithelial cell rests may be present within surrounding bone and related soft tissues (Bramley 1974). These small structures may be undetectable clinically or radiographically. Whether or not satellite cysts or epithelial cell rests are responsible for the recurrence of odontogenic keratocysts remains uncertain.

Fickling (1965) proposed that the clinically friable nature of odontogenic keratocysts coupled with difficult surgical access at the time of operation could result in remnants of cyst wall including epithelium being left behind in the surgical wound. These remnants could in theory subsequently proliferate and reform a new cyst. Scholefield (1971) hypothesized that small numbers of epithelial cells could be detached from the cyst lining epithelium and subsequently proliferate in the wound. Support for these theories was generated as a result of studies which indicated that odontogenic keratocyst epithelium was mitotically active (Main 1970a, Toller 1971) and that the epithelium of odontogenic keratocysts was freely detachable from the capsule (Donoff et al 1972a). Both Main (1970a) and Toller (1971)

reported that the epithelium of odontogenic keratocysts consistently exhibited a mitotic index greater than other jaw cysts. The mitotic activity approximated that of ameloblastoma and dental lamina epithelium. Main (1970a) drew attention to the fact that the relatively high mitotic rate in odontogenic keratocysts could possibly be related to parameters such as size and multilocular growth within bone. Both Main (1970a) and Toller (1971) also suggested that the biologically active nature of odontogenic keratocyst epithelium, as evidenced by its mitotic rate, could be related to the phenomenon of cyst recurrence. At the present time however although it is recognised that the epithelium of odontogenic keratocyst does appear to have a greater biologic activity in terms of inherent proliferative capabilities than other jaw cysts there would appear to be no direct evidence available at this time to substantiate the claim that odontogenic keratocyst remnants left behind in the jaws following surgery are responsible for recurrences. Furthermore, Browne (1970) demonstrated that in his analysis of a series of odontogenic keratocysts there was no direct correlation between occurrence of cysts and the parameters described by Fickling (1965).

Cell rests in the form of remnants of dental lamina (Soskolne and Shear 1967), cell rests of possible oral mucosal origin (Stoelinga and Peters 1973) have also been suggested as being responsible for odontogenic keratocyst recurrence. Soskolne and Shear (1967) expressed the view that patients with the Gorlin-Goltz syndrome had a predisposition to form cysts from the dental lamina. Shear (1976) subsequently expressed the view that the keratinizing cysts in patients who did not have this syndrome were possibly also of dental lamina origin. Stoelinga and Peters (1973) suggested that odontogenic keratocysts could arise from epithelial cell rests generated as hamartomas from

overlying oral mucosa. The theoretical implication arising from the suggestion is that recurrent odontogenic keratocysts could arise not because fragments of the cyst were left behind but because new lesions were generated as a consequence of subsequent proliferation of the basal cells of the mucosal epithelium. These cell islands would subsequently give rise to new cysts. Odontogenic keratocysts clinically manifested as a recurrence would similarly be expected to arise from pre-existing mucosal epithelial cell rests not removed at the time of surgery. Whether or not adult oral mucosa in some individuals does have the capability of producing mucosal cell rests of a non-odontogenic type throughout life or whether in fact the cell rests described by Stoelinga and Peters (1973) were rests of dental lamina remains open to question.

A further possibility regarding the question of odontogenic keratocyst recurrence could be related to cell rests and microcysts derived from proliferation of the basal cells of odontogenic keratocyst lining epithelium. The relationship between odontogenic keratocyst epithelial budding (Payne 1972) and recurrence would appear to remain uncertain. Bramley (1974) did not find any relationship between these two parameters. Brannon (1977) on the other hand on the basis of his survey of a large number of keratocysts supported Payne's (1972) concept.

There are thus several hypotheses available in the literature which relate to the question of odontogenic keratocyst recurrence. At the present time it would seem that direct data supporting any of these hypotheses is lacking.

CHAPTER II

THE EPIDERMOID CYST

TERMINOLOGY AND CLINICAL FEATURES:

The "epidermoid cyst" variously referred to as the "epithelial cyst" (Love and Montgomery 1943), "keratinous cyst" or "keratoma cyst" (Wilson-Jones 1966) or "epidermal cyst" (Lever and Schaumburg-Lever 1975) is a benign keratin producing cyst. Throughout this thesis the term epidermoid cyst is employed and care has been taken to distinguish epidermoid cysts from dermoid cysts.

Epidermoid cysts may occur in patients of either sex and there would not appear to be a particular sex predilection. Epidermoid cysts have been reported occurring in patients of various age groups but they apparently occur more commonly after the second decade of life (Love and Montgomery 1943).

Epidermoid cysts generally present as slow growing intradermal or subcutaneous lesions. On occasion they have also been reported occurring within bony structures (Yachnin and Summerill 1941). Epidermoid cysts occur most commonly on the face, neck and trunk as single or multiple lesions. Patients presenting with multiple epidermoid cysts usually present with fewer than 10 cysts (Love and Montgomery 1943).

Epidermoid cysts may be found as one of the abnormalities associated with Gardner's syndrome (Gardner and Richards 1953) and have been reported to occur in patients suffering from the multiple basal cell naevi syndrome (Gorlin and Pindborg 1964).

Epidermoid cysts may recur after surgery and although epidermoid cysts are benign lesions malignant transformation of the epithelial lining of these lesions has been reported in the literature (McDonald 1963, Wilson-Jones 1966). The reported incidence of malignant transformation in skin cysts was reported by Wilson-Jones (1966) as ranging from 0.5% to 9.2%. Lever and Schaumburg-Lever (1975) were of the opinion that a number of the previously diagnosed malignancies associated with epidermoid cysts represented psuedo-carcinomatous hyperplasia rather than neoplastic transformation.

Three cases of epidermoidal (sic) cysts occurring in the oral region were reported by Tores and Higa (1970). Two of these lesions were soft tissue lesions whilst one was recorded as having occurred within the mandible. Modern oral pathology texts, for example, Shafer, Hine and Levy (1974) do not distinguish epidermoid cysts from dermoid cysts and there is in fact little detailed information available on intra-oral epidermoid cysts in the literature.

HISTOLOGY

Although much has been written about epidermoid cysts surprisingly little detailed information exists in the literature regarding the histology of these lesions. Descriptions of epidermoid cyst histology such as those found in dermatology text books (Lever and Schaumburg-Lever 1975), are brief and are confined to a superficial discussion generally pointing out the histologic similarities of epidermoid cyst lining epithelium to epidermis. There is little detailed reference to features such as the nature of and variations found in the cyst lining epithelia, the appearance of the capsular tissues or the nature of inflammatory changes which may be associated with this lesion. The paucity of data contrasts markedly with the literature on odontogenic keratocysts.

Love and Montgomery (1943) described the histologic features of epidermoid cysts. These authors considered that epidermoid cysts were characterised by the presence of a cyst lining showing a complete cycle of keratinization, a prominent stratum corneum and granular layer and marked keratinization. Other features recorded by Love and Montgomery (1943) included epithelial rete peg formation, a relative paucity of inflammation, the presence of cholesterol and pigmentation in the basal epithelial cells. Lever and Schaumburg-Lever (1975) described the cyst linings of epidermoid cysts as being "true epidermis" and noted that young cysts usually had a thicker epithelium than old cysts. The latter were described as having epithelial linings of only 1-2 flattened layers of epithelial cells.

The optical microscopic, electron microscopic and histochemical features of epidermoid cysts were studied in more detail by McGavran

and Binnington (1966). These investigators showed that the epithelial lining of these lesions was composed of four readily recognizable cell layers, namely a basal cell layer, a spinous zone, a granular layer and a keratinized layer. McGavran and Binnington (1966) concluded that the process of cell maturation and keratin production in epidermoid cysts was identical to that seen in the skin. They also reported that melanocytes were rarely seen in the epithelium of epidermoid cysts in Caucasian individuals whereas melanin pigmentation was common in Negroids.

The topic of malignant transformation of the epithelial lining of epidermoid cysts was discussed by Love and Montgomery (1943), Wilson-Jones (1966) and Lever and Schaumburg-Lever (1975). The incidence figures for malignant transformation, chiefly in the form of squamous cell carcinoma and basal cell carcinoma, in skin cysts were reported by Wilson-Jones (1966) as ranging from 0.5% to 9.2%. Both Wilson-Jones (1966) and Lever and Schaumburg-Lever (1975) were of the opinion that although the true incidence of malignant transformation in epidermoid cysts is not known, this phenomenon is rare and that many of the reported cases in the literature represented instances of over diagnosis or misdiagnosis. Lever and Schaumburg-Lever (1975) considered that many of the reported cases of malignancy in epidermoid cysts were in fact instances of psuedo-carcinomatous hyperplasia.

PATHOGENESIS

The epithelial lining of epidermoid cyst was described by Ettinger and Manderson (1973) as being potentially derived from three basic sources. These sources were as follows:

1. Implanted surface epithelium.
2. Embryonic epithelial cell rests, or epithelium derived from the deeper layer of the surface epithelium.
3. Adnexal structures such as hair follicles and the ducts of sebaceous glands.

That the epithelial lining of epidermoid cysts can arise from these potential sources would appear to be a generally held view (McGavran and Binnington 1966).

The formation of epidermoid cysts of an implantation type were described following hernial repair by Strahan (1951). Epidermoid cysts thought to be of an implantation type were reported in the phalanges by Yachnin and Summerill (1941) and in the lip by Torres and Higa (1970) and Ettinger and Manderson (1973).

That epidermoid cysts could arise as a consequence of implantation of epidermis was demonstrated experimentally by a variety of investigators (Zimecher 1931, Peer and Paddock 1937, Baker and Mitchell 1965, Thompson cited by Toller 1967). Pioneer experimental work involving the production of epidermoid cysts from implanted epidermis and skin was carried out by Kauffman (1884) and Schumenger (1884).

While it is clear that implantation type epidermoid cysts can form from implanted epithelium a number of questions would still appear to remain concerning lesions of this type. For example experimental

implantation type epidermoid cysts were reported by Baker and Mitchell (1965) and Toller (1967) to be of a small size. It is known that epidermoid cysts can in fact reach a large size clinically. In addition the work of Thompson (1967, cited by Toller) indicated that epidermoid cysts of an implantation type tended to show regressive changes after a few months. Since as indicated previously, it is well known that epidermoid cysts can reach a size larger than 1-2mm. and therefore must by some mechanism enlarge it would appear that further study of these lesions is required in order to fully qualify their pathobiologic characteristics.

Information regarding the other histogenic sources of the epithelium found in epidermoid cysts namely embryonic cell rests, epithelial islands derived from the surface epithelium or the epithelium association with adnexal structures is scanty. Review of papers such as those published by Love and Montgomery (1943). Wilson-Jones (1966) and Ettinger and Manderson (1973) showed that whilst there is general agreement regarding the supposed histogenic origins of epidermoid cysts there is little direct scientific evidence that the various proposed sources of epithelium are in fact involved in the genesis of epidermoid cysts.

Some direct evidence that human epidermoid cysts could arise as a consequence of proliferation of the surface epithelium and also adnexal structures was provided by the study of Epstein and Kligman (1957). What could be interpreted as indirect evidence that epidermoid cysts could arise by proliferation of surface ectoderm and hair follicles was provided by the same authors in a previous study, Epstein and Kligman (1956) in an experimental investigation of the histogenesis of Milia. Milia are generally separated from

epidermoid cysts clinically but histologically they are regarded as being identical (Lever and Schaumburg-Lever 1975).

The aetiology of epidermoid cysts, aside from the trauma associated implantation types, would appear to be similarly obscure, although as pointed out by Ettinger and Manderson (1973) it is generally held that trauma in one form or another is aetiologically associated with the development of epidermoid cysts from all the suggested histogenic epithelial sources. Obstruction of the sebaceous gland ducts as a result of the accumulation of keratin was described as being an aetiologic factor associated with the formation of epidermoid cysts by Love and Montgomery (1943). The known association of epidermoid cysts and/or milia (Gorlin and Pindborg 1964) with the multiple basal cell naevi syndrome would also suggest that in some cases at least genetic aetiologic factors are operating in the genesis of these lesions. In the case of milia, Epstein and Kligman (1956) were of the opinion that these lesions were essentially hamartomas implying the presence of some inherent proliferative tendency on the part of the skin and adnexal epithelium of some individuals.

In contrast to odontogenic cysts information regarding these mechanisms of epidermoid cyst growth is scarce. Baker and Mitchell (1965) pointed out that the presence of an adequate blood supply was essential for the initial development and maintenance of implantation type epidermoid cysts. Their study however only extended over a short time period. Enlargement of epidermoid cysts was postulated by Zimecher (1931) to be the result of "pressure" build up in the cyst lumen as a consequence of keratin and epithelial debri accumulation. There does not appear however to be any literature directly

testing this hypothesis in relation to epidermoid cysts. Epstein and Kligman (1957) considered that inflammation played little part in the enlargement of epidermoid cysts.

CHAPTER III

THE CHOLESTEATOMA

TERMINOLOGY

As pointed out by Friedmann (1974) the term "cholesteatoma" is one which has been associated over the years with a considerable amount of confusion, largely as a consequence of a failure to separate two histologically distinct lesions which, at a clinical level, may occur, either singly or together.

The term "cholesteatoma" was first introduced by Muller (cited by Friedmann 1974) in 1838 to describe a cholesterol containing lesion having a laminated structure and an epithelial capsule which he apparently directly related to cholesterol containing granulomas found in inflammed middle ear. That cholesterol was a main component of the former was disputed by Virchow (1855) (cited by Friedmann 1974), who proposed that the term "pearly tumour" was a more appropriate description.

In an effort to remove the connotation of neoplasia inherent in the use of the term cholesteatoma, Young (1950) suggested that the term "cholesteatosis" was more appropriate. Tumarkin (1958) pointed out however that the term cholesteatosis encompassed two different entities, namely "epidermosis: and "cholesterol granuloma". For the histologic diagnosis of the former the presence of epidermis was required whereas the cholesterol granuloma was described as being a lesion composed simply of cholesterol crystals, giant cells and granulation tissue.

Although it seems generally accepted that cholesteatomas are of two histologic types, a survey of relatively recent literature reveals that semantic problems still exist. For example Young (1950) in a

review paper entitled "Aural cholesteatoma - or cholesteatosis" described the lesions as cysts of an epidermoid type. Similar use of the term cholesteatoma was employed by Ruedi (1957) and Abramson (1969). Friedmann (1974) suggested that in order to avoid confusion the term "epidermoid cholesteatoma" should be used to describe those cholesteatomas having an epidermoid cyst like structure. More recent papers by Wingert et al (1978), Beales (1978) and Sade (1978) however still use the term cholesteatoma to describe what Friedmann (1974) suggested be called epidermoid cholesteatoma.

In this study the group of lesions investigated comprised a series of keratinizing cyst lesions removed from the middle ear cavity and adjacent bony structures. Although it is recognised that the term cholesteatoma is associated with semantic difficulties this term is used throughout this thesis to describe the lesions investigated.

CLINICAL FEATURES

The site of occurrence of cholesteatomas is usually described as being the middle ear cavity and adjacent bony structures. As pointed out by Friedmann (1974) many cholesteatomas are thought to arise in the attic region and this site is generally regarded as an important site of occurrence of this lesion (Tumarkin 1958, Beales 1978, Sade 1978).

Cholesteatomas may occur in patients of either sex. Holmes (1938) found that in the survey of 303 cholesteatomas that 43% of these lesions occurred in patients under 20 years of age with 11% of these patients being under the age of 10 years. Friedmann (1974) in a later review of 562 cases of cholesteatoma found that although there was a wide age distribution ranging from childhood to old age the peak age incidence (399 cases) occurred between the ages of 20 and 59 years.

Cholesteatomas are considered to be clinically significant lesions because of the important auditory problems and complications that may be associated with their presence. More importantly in the context of this thesis cholesteatomas exhibit two characteristics, namely progressive bone destruction (Abramson 1969) and recurrence following surgery (Tumarkin 1958) which are shared by the odontogenic keratocyst.

HISTOLOGY

Although much has been written about the clinical features and aetiology/pathogenesis of cholesteatomas little detailed reference to the histology of these lesions could be found in the literature. That cholesteatomas are in histologic terms equated with epidermoid cysts (Young 1950, Abramson 1969, Beales 1978, Sade 1978) could possibly explain the paucity of literature on this subject.

The histologic structure of cholesteatomas was described and illustrated by Friedmann (1974). The lumen of cholesteatomas is characterised by the presence of thick laminated keratin or keratin scales, "often with a generous admixture of pus". The cyst lining epithelium would appear to consist of a relatively thin keratinizing squamous epithelium. The surrounding connective tissues adjacent to the epithelium were described by Friedmann (1974) as "fibrous granulation tissue of variable thickness". The two pathognamonic histologic features of cholesteatomas were considered by the same author to be the presence of laminated keratin and/or the presence of the squamous epithelial cyst lining.

Although not specifically mentioned by Friedmann (1974) an examination of his illustrations reveals that inflammation of capsular tissues, separation of the lining epithelium from surrounding tissues and occasional hyperplasia of the epithelium can be observed in some cholesteatomas.

THE PATHOGENESIS OF CHOLESTEATOMAS

A number of theories described as theories of pathogenesis of cholesteatomas (Beales 1978, Sade 1978) exist in the literature. No single theory would however appear to be universally acceptable at this time. The theories of pathogenesis of cholesteatomas are concerned chiefly with the question of histogenesis of these lesions and to a lesser extent with aetiologic considerations. The mechanisms of enlargement of cholesteatomas is a subject which has received little attention in the literature although an understanding of this topic would seem to be important if the pathogenesis and biologic nature of this lesion are to be better understood.

There would appear to be four main theories concerned with the question of pathogenesis of cholesteatomas. These theories are as follows:

1. The congenital theory.

Cawthorne and Griffith (1961), Derlacki and Clemis (1965) and Perone and Schuknecht (1975) believed that cholesteatomas could arise as a consequence of proliferation of embryonal cell rests of squamous epithelium in the developing temporal bone. Cholesteatomas formed in this way were considered to be essentially developmental cysts and the clinical signs and symptoms associated with infection and inflammation of these lesions were considered to be secondary phenomena. However, histological investigations by Ruedi (1958) and Friedmann and Osborn (1966) on a large number of temporal bones could not demonstrate any evidence of embryonic cell rests in this particular site. These investigators concluded that only a very few cases of cholesteatoma could be regarded as being congenital in origin. This view was re-iterated by Friedmann (1974) who in addition pointed out that even those few cases of cholesteatomas which could in theory

arise as developmental lesions could in fact represent developmental epidermoid cysts which developed in the temporal bone and which as they grew came to involve the middle ear and thus presented as cholesteatomas.

2. The Immigration theory.

Many investigators are of the opinion that cholesteatomas arise as a consequence of ingrowth of keratinised epidermis from the external auditory meatus or from the outer surface of the tympanic membrane. This is the oldest and most widely accepted of the theories concerning the pathogenesis of cholesteatomas (Holmes 1938, Harris 1962, Friedmann 1955 and 1974, Beales 1978).

The immigration/migration theory postulates that keratinised squamous epithelium gains access to the middle ear either by direct migration through a pre-existing tympanic proliferation (Seaman and Newell 1971) or as a consequence of proliferation of the basal epithelium of the outer surface of an intact tympanic membrane or external auditory meatus (Friedmann 1955, Ruedi 1958).

Although ear drum perforations are commonly found in association with cholesteatomas there is little direct evidence which proves that squamous epithelium from the meatus or outer surface of the tympanic membrane actually migrates through such a perforation to form a cholesteatoma. Acceptance for the pre-existing perforation source of the cholesteatoma epithelium would appear it seems to have been based largely on the frequently observed clinical association of eardrum perforation with cholesteatomas. As suggested by Sade (1978) however tympanic perforations could be a consequence of rather than a causative factor associated with cholesteatoma formation.

That cholesteatomas could arise as a consequence of proliferation of squamous epithelium directly from the external auditory meatus and tympanic membrane epithelium in the absence of tympanic perforation was demonstrated by Friedmann (1955) and Ruedi (1957, 1958). On the basis of experimental animal studies (Friedmann 1955, Ruedi 1958) and observations on human material (Ruedi 1957) these investigators demonstrated that the outer epithelium of the tympanic membrane and the epithelium of the external auditory meatus, particularly that found superiorly (Ruedi 1957) was capable of giving rise to cholesteatomas and that the epithelium in these sites exhibited proliferative activity in the presence of inflammation. The types of epithelial proliferative activity noted by these investigators included hyperplasia and the formation of epithelial islands and microcysts directly from the lining epithelia of intact tympanic membranes and the meatus.

The aetiologic factors associated with the immigration/migration theory of cholesteatoma formation do not appear to have been fully elucidated. As was just mentioned the studies of Friedmann (1955) and Ruedi (1957, 1958) demonstrated that cholesteatoma development was associated with pre-existing or concurrent inflammation consequent to infection (Friedmann 1955) or foreign body irritation (Ruedi 1958). Tumarkin (1958) also expressed the view that a necessary pre-requisite for the development of an attic cholesteatoma was the invagination of Shrapnell's membrane. This invagination was suggested by Tumarkin (1958) to be a consequence of reduced middle ear pressure brought about by childhood ear infection and reduced pneumatization. Although not necessarily agreeing on the question of the pathogenesis of cholesteatomas several authors hold the view that the Shrapnell's membrane area of the ear is an important anatomical site with respect

to cholesteatoma occurrence (Ruedi 1957, Tumarkin 1958, Beales 1978, Sade 1978, Wingert et al 1978).

3. The Implantation Theory.

Juers (1965) suggested that epithelial tissue could be implanted to the middle ear cavity and the bones of the skull following trauma. He proposed that cholesteatomas could arise as a result of subsequent proliferation and growth of this epithelium.

Whilst traumatic implantation of epithelium would appear to be generally included among the list of potential sources of epithelium giving rise to cholesteatomas (Friedmann 1974, Wingert et al 1978) it would seem that this particular theory is afforded little significance (Wingert et al 1978). An inference which could be drawn from papers by Friedmann (1974) and Sade (1978) is that such implantation type lesions are best regarded as simple implantation type epidermoid cysts.

4. The Metaplasia Theory.

Tumarkin (1954) believed that cholesteatomas could arise as a consequence of squamous metaplasia of the epithelium of a middle ear cleft lining mucosa. Tumarkin (1958) would later appeared to have changed his views. Although recognition of this theory is afforded in the literature it would seem that it has received little attention from investigators. Karma (1972) stated that "cholesteatomatous aetiology cannot be explained on a metaplastic basis". Sade (1978) in a review of attic cholesteatomas re-iterated the fact that although squamous metaplasia of the middle ear mucosal epithelium is not uncommon the metaplasia that does occur does not generally involve the production of a keratinizing epithelium. He further pointed out that the mere presence of such epithelium did not in itself demonstrate an origin

for cholesteatomas.

Of interest with regard to the metaplasia theory of cholesteatoma origin are the recent findings of Sade (1978). This investigator demonstrated the presence of squamous epithelial islands and buds in attic mesenchyme derived from the normal middle ear cavity lining epithelium. Sade (1978) suggested that these metaplastically derived islands could, theoretically, give rise to cholesteatomas.

It is well known that cholesteatomas, as they grow, can erode contiguous bony structure and give rise to serious complications. The exact mechanisms associated with the growth and enlargement of cholesteatomas would however appear to be unclear.

Ruedi (1957) in a review of the topic of cholesteatoma enlargement pointed out that the majority of investigators considered that cholesteatoma enlargement was a consequence of keratin accumulation and that bone resorption subsequently occurred due to inflammatory irritation and pressure. Cholesteatoma enlargement was thus considered to be a passive process. This view was re-iterated by Friedmann (1974). Ruedi (1957) himself, however, on the basis of a study of human material suggested that growth of cholesteatomas was an active process reflecting inherent proliferative activity of the "matrix".

Abramson (1969) pointed out that there was no direct experimental proof that bone resorption was a result of keratin accumulation and subsequent pressure generation within cholesteatomas. In his study Abramson (1969) demonstrated collagenolytic activity within the lining of cholesteatomas and suggested that enzymatic mechanisms might be

responsible for the erosion of surrounding bone. Whilst demonstrating collagenolytic activity in cholesteatomas Abramson's (1969) study did not further clarify the question of the nature of the mechanisms of cholesteatoma enlargement. It is perhaps worth noting that Donoff et al (1972b) demonstrated collagenolytic activity within the walls of odontogenic keratocysts.

In summary, it would appear that the pathogenic mechanisms associated with cholesteatoma, histogenesis, formation and enlargement are poorly understood. The paucity of literature available on the histology of these lesions was surprising and it would seem to indicate a need for more detailed investigation of this particular lesion.

CHAPTER IV

MATERIALS AND METHODS

MATERIAL

1. SELECTION OF ODONTOGENIC KERATOCYSTS:

The odontogenic keratocysts examined in this study were selected from the histopathology files in the Department of Oral Pathology and Oral Surgery, The University of Adelaide. The time period covered in the survey extended from 1961 to 1978. Specimens received by the Department of Oral Pathology and Oral Surgery for the purposes of histological assessment are forwarded by dental practitioners and medical practitioners in private practice, by various clinics of the Royal Adelaide Hospital and Queen Elizabeth Hospital in Adelaide and the School Dental Service of South Australia.

The majority of odontogenic keratocysts used in the present study derived from an odontogenic cyst sample which was retrospectively analyzed by the present author (Djamshidi 1976) in a previous study. All cysts analysed in the 1976 study were re-embedded, re-cut and re-stained. Sections of seven micron were cut and stained with haematoxylin and eosin (Appendix I) for routine observation. It was found, however, during the selection procedures associated with the 1976 study that the determination of keratin was subject to observer error. Subsequently sample sections of keratinized skin and oral mucosa and a selection of non-keratinized and keratinized odontogenic cysts were stained with a variety of keratin stains (Appendices II-VI). Following examination of the specimens stained for keratin by the various techniques it was decided that the Kreyberg method provided the most satisfactory technique for the assessment of keratin in the histologic material.

However, because of the unavailability of one of the constituent chemicals used in the original Kreyberg stain and for technical reasons related to staining times it was subsequently decided to utilise a modification of the Kreyberg method (Appendix VII).

From a total sample of 415 odontogenic cysts surveyed in the 1976 study 115 were diagnosed as keratinizing cysts. Twenty-seven of these cases were diagnosed as fulfilling the criteria of dentigerous or inflammatory cysts. Inflammatory cysts were so designated on the basis of a clinical history of a direct association with a non-vital tooth. Truly dentigerous lesions were so classified on the basis of histologic examination. Lesions designated as dentigerous keratinizing cysts were so categorized on the basis of an examination of a decalcified tooth with all or part of the cystic lesion being present in a truly dentigerous relationship to the tooth crown.

The remaining 88 cysts were classified as odontogenic keratocysts on the basis that they presented histologic features similar to those reported by Shear (1960). In these lesions there was evidence of a thin, regular layer of keratinized squamous epithelium and the presence of a basal cell layer having a cuboidal or columnar morphology in whole or in part.

For the purposes of the present study an additional ten odontogenic keratocysts were selected from the biopsy files covering the period January 1976 to July 1978 in the Department of Oral Pathology and Oral Surgery.

A total of 98 specimens thus comprised the odontogenic kerato-

cyst material available for study in the present investigation. The majority (75) of these lesions were solitary odontogenic keratocysts. Twenty-three of the odontogenic keratocysts comprised multiple cysts removed from eight patients. Two of the latter were diagnosed as having the Gorlin-Goltz syndrome.

2. SELECTION OF EPIDERMOID CYSTS AND CHOLESTEATOMAS:

The majority of epidermoid cysts and cholesteatomas were selected from the files of the Department of Pathology, Institute of Medical and Veterinary Science of South Australia. A small number of lesions were received directly from private practitioners. Following a review of the departmental files of the Institute of Medical and Veterinary Science and examination of specimens received from private practitioners, 50 specimens of epidermoid cysts from the head and neck region and 30 specimens of cholesteatoma from the middle ear cavity and adjacent bony structures were chosen for analysis.

The term epidermoid cysts was applied to that group of cysts with an epidermis-like epithelium lining a cavity filled with keratinous material (Lever and Schaumburg-Lever 1975). This definition excluded dermoid cysts. The term cholesteatoma was applied to that group of cystic lesions of the middle ear cavity and adjacent bony structures which exhibited the presence of a keratinized epithelial lining of the cyst lumen (Freidmann 1974).

METHODS:

1. PREPARATION OF HISTOLOGIC MATERIAL:

Subsequent to collection of the odontogenic keratocyst, epidermoid cyst and cholesteatoma samples material for definitive investigation in the present study was prepared as follows:

a. Sections of paraffin embedded material were cut at 7 microns using a Leitz rotary microtome. Because the material utilised in this study consisted of material which had previously undergone processing and cutting procedures for the purpose of diagnosis the material was incomplete as regards the possibility of obtaining serial sections. Consequently, in order to obtain as representative a sample as possible of the histology of the individual cysts it was decided to cut a number of sections from different regions of each lesion. A total of eight sections were then selected as representative samples of each cyst.

b. Selected sections were then stained with haematoxylin and eosin (Appendix I) or for keratin using the modified Kreyberg method (Appendix VII).

2. ASSESSMENT OF CLINICAL AND HISTOLOGIC MATERIAL:

Histologic examination of material in this study was carried out using an Olympus BH optical microscope. Photomicrographs were taken using a Leitz Ortholux unit and Pan X film.

The histologic features of the odontogenic keratocysts, epidermoid cysts and cholesteatomas examined in this study were assessed on the basis of an examination on the eight sections obtained

from each specimen. The observations pertaining to each cyst were then collated and scored after an overall examination of the eight sections. Observations were scored on a prepared working chart. Each specimen was assessed according to a number of criteria as indicated below. The order of the criteria was made in an attempt to provide a comfortable progression from one feature to the next. Features assessed were as follows:

1. Age

Age was determined from examination of available clinical and laboratory records.

2. Sex

The sex of patients was determined from examination of clinical and laboratory records.

3. Size

The size of cysts was determined on the basis of radiologic examination or comment from the surgeon involved. Cysts were classed as small when the diameter did not exceed 1cm. Cysts exceeding 1cm in gross diameter were classified as large.

4. Cyst number

The number of cysts in each patient was determined from radiologic examination, clinical records, comments from surgeons, and histologic assessment. If there was more than one cyst present that case was classified as an example of multiple cysts.

5. Site

A system similar to that described by Radden and Reade (1973a) was utilised to determine the site of distribution of odontogenic keratocysts examined. The site of epidermoid cysts was obtained from available clinical and laboratory records. All cholesteatomas examined in this study comprised lesions which were simply designated as having been found in the middle ear cavity or surrounding bony environments.

6. Epithelial thickness

Epithelial thickness of the cyst linings was assessed by approximate counting of the epithelial cell layers. Each cyst was then categorised into one of four groups as follows:

Group 1: Epithelium 1-5 cells thick,

Group 2: Epithelium 6-10 cells thick,

Group 3: Epithelium 11-15 cells thick,

Group 4: Epithelium 16+ cells thick.

7. Epithelial Regularity

The epithelium was classified as being regular when there was little variation in the thickness of the epithelial lining. Conversely epithelial cyst linings exhibited obvious variation in thickness were classed as irregular.

8. Separation of Epithelium from Capsule

Positive separation of the epithelium from the surrounding connective tissue capsule was determined and scored on the basis of obvious histologic evidence.

9. Rete pegs

Rete pegs were defined as obvious undulating down-growths of the epithelium into the connective tissue capsule.

10. Budding

Budding of the epithelium was defined as localised and isolated proliferation of the basal cells of the epithelium into the underlying connective tissue.

11. Basal cell morphology

Basal cell morphology was classified into three groups namely columnar, cuboidal and mixed. If the vertical axes of the cells were longer than the horizontal axes then basal cells exhibiting this characteristic were classified as columnar basal cells. If the vertical axes of the cells were equal to or shorter than the horizontal axis

the basal cell layer was classified as cuboidal. A combination of the two existing in one specimen was specified as a mixed basal cell morphology.

12. Angle of the basal cells to the basement membrane

The angulation of the basal cells to the basement membrane was classified as straight in which case the central axes of the cells were perpendicular to the basement membrane and acute in which case the vertical axes of the cells were at an angle to the basement membrane. If a combination of straight and acute existed in one specimen that specimen was classified as mixed.

13. Nuclear polarity

The location of basal cell nuclei with respect to the basement membrane was classified into three categories which for the purposes of the scoring sheet were termed "away", "towards", and "mixed". If there was visible space between nuclei and basement membrane this was termed "away". If nuclei were located close to the basement membrane that was classed as "toward". In cases where the nuclei were located centrally or where a combination of the two categories existed then this pattern was classified as "mixed".

14. Prickle cell layer

The prickle cell layer was defined as several rows of polyhederal epithelial cells located between the basal cell layer and the flattened superficial cell layers of the superficial cell layers of the cyst lining epithelium.

15. Vacuolisation of the prickle cell layer

Vacuolisation was scored as positive when there was evidence of intercellular oedema or vacuolisation of the epithelial cells.

16. Oedema of the prickle cell layer

Oedema was defined as a widening of intracellular spaces in the prickle cell layer of the cyst lining epithelium.

17. Keratin type

The type of keratin present was categorised as follows:

a. parakeratin was defined as keratin in which epithelial cell nuclei had been retained.

b. Orthokeratin was defined as keratin free of retained nuclei.

c. Mixed keratinization was defined as a combination of parakeratin and orthokeratin in the one specimen.

18. The continuity of the keratin layer

The continuity of the keratin layer was assessed by observation of the superficial keratin layer in the cyst lining of each specimen.

19. Individual cell keratinization

Individual cell keratinization was defined as keratinization of single cells or small groups of epithelial cells beneath the superficial keratin layer.

20. Keratohyalin granules

Keratohyalin granules were defined as the dark staining intracellular granules located in the epithelial cells immediately subjacent to the superfical keratin layer.

21. Cholesterol

The presence of cholesterol was assessed according to the presence or absence of lenticular shaped clefts within the cyst capsules or lumens.

22. Inflammatory cells in the epithelium

The presence of inflammatory cells within the epithelial cyst linings was classified as being either "acute" in which case polymorphonuclear leucocytes were present or "chronic" in which lymphocytes and other chronic inflammatory cells could be detected. If a combination of both acute and chronic cells existed that specimen was classified as "mixed" with respect to the presence of inflammatory cells within the epithelium.

23. Relationship of inflammatory cell infiltration to epithelial morphology.

Signs of epithelial degeneration associated with intra-epithelial inflammatory cell infiltrates were classified into two categories. Degeneration was scored as "mild" if there were no obvious changes in the arrangement of cells within the cyst lining epithelium or "severe" in which case there were obvious signs of cellular degeneration and disorganisation associated with the presence of inflammatory cells within the epithelium.

24. Distribution of inflammatory cells within the epithelium.

The distribution of inflammatory cells within the epithelial cyst linings were classified as being "localised" in which case inflammatory cells were present in only a small or focal areas of the epithelium or "diffuse". In the latter instance inflammatory cells were diffusely scattered within the epithelium.

25. Atypia.

Epithelial atypia was related to the presence of the following features:

a. mitotic activity,

b. increased nucleo-cytoplasmic ratio,

c. hyperchromatic nuclei,

d. hyperplasia of the basal cell population,

e. dyskeratosis in the form of single cell keratinization or keratin pearl formation,

f. cellular and nuclear pleomorphism.

26. Metaplasia.

The term metaplasia was defined as the transformation of some portion of the cyst lining epithelium to a non-squamous type.

27. Melanocytes.

Melanocytes were defined as cells containing melanin pigment-

ation located in the basal cell layers of the cyst lining epithelium.

28. Calcified material.

For purposes of assessing the material calcified material was defined as being any localised area of calcification located either within the epithelium or within the surrounding connective tissue capsule. Definite bone or osteoid was excluded from this definition.

29. Inflammatory cells in the capsule.

The presence of inflammatory cells within capsules was scored as follows:

If only polymorphonuclear leucocytes were present then that cyst was classified as "acute". If lymphocytes and other chronic inflammatory cells could be demonstrated then that lesion was classified as being "chronic". If a combination of both acute and chronic cells existed then the lesion was classified as being "mixed". The distribution of the inflammatory cell infiltrates were, as in the case of epithelial infiltrates, also scored according to whether or not the inflammatory cell infiltrate was focal or diffuse. The degree of inflammation was also classified as being either mild or severe. This latter parameter was scored on the basis of a subjective analysis regarding the nature and distribution of the inflammatory cell infiltrate present in each case.

30. Homogeneous zone.

A homogenous zone was defined as a relatively acellular zone of capsular tissue located immediately subjacent to the basal cell layer of the cyst lining epithelium.

31. Microcyst.

A microcyst was defined as a very small epithelial lined cavity located within the connective tissue surrounding the main cyst lumen.

32. Epithelial cell rests.

Epithelial cell rests were defined as solid islands of epithelium of varying sizes scattered throughout the connective tissue capsule and surrounding connective tissues associated with each cyst examined.

CHAPTER V

RESULTS

CLINICAL DATA

AGE DISTRIBUTION

A:. Odontogenic Keratocysts.

The diagnosed odontogenic keratocysts examined in this study occurred within an age range of 7-76 years (Figure 1). The age was undetermined with respect to 15 individuals. The age distribution was noted to peak in the third decade. A relatively high incidence was also noted within the second and sixth decades.

B: Epidermoid cysts.

The diagnosed epidermoid cysts occurred within an age range of 9-78 years (Figure 2). The age was unrecorded with respect to cysts obtained from four female patients. Age distribution was noted to peak in the third decade. However a high incidence was also noted within the fourth and sixth decades.

C: Cholesteatomas.

The diagnosed cholesteatomas occurred within an age range of 6-88 years (Figure 3). The age was unrecorded with respect to two male individuals. The age distribution was noted to have a peak incidence in the fourth decade. A relatively high incidence was also noted within the third and fifth decades.

SEX DISTRIBUTION

A: Odontogenic Keratocysts.

The diagnosis of odontogenic keratocyst was made in specimens obtained from 34 females and 33 males (Figure 1). The sex of the patient was unknown in the case of 8 specimens. One female and one male had systemic abnormalities acknowledged as representing features

of the Gorlin Goltz syndrome.

B: Epidermoid cysts.

The diagnosis of epidermoid cysts was made from specimens obtained from 27 females and 23 males (Figure 2).

C: Cholesteatomas.

The cholesteatomas examined were obtained from 16 females and 14 males (Figure 3).

CYST SIZE

A: Odontogenic keratocysts.

Forty odontogenic keratocysts examined were classified as large lesions and 21 as small cysts. The size of 37 specimens could not be determined with any degree of certainty.

B: Epidermoid cysts.

Twelve epidermoid cysts were classified as large and 33 as small. The size of five specimens was uncertain.

C: Cholesteatomas.

Five cholesteatomas were classified as large lesions and 18 as small cysts. The size of seven specimens could not be determined.

SITE DISTRIBUTION

A: Odontogenic Keratocysts.

As indicated in the Materials and Methods section a site distribution scoring system similar to that utilised by Radden and Reade (1970a) was employed in the present study to determine site incidence data regarding the odontogenic keratocyst sample.

Using this system it was found that odontogenic keratocysts examined involved 122 areas in the mandible and maxilla. Ninety four (77%) of these sites were in the mandible and 28 (23%) were in the maxilla (Figure 4). The site of 15 cysts, 5 in males and 10 in females, was not able to be determined with accuracy.

The most commonly involved sites in the jaws were the mandibular, third molar and ramus areas. Together these areas or zones accounted for 46 (33%) of the total sites score. In the maxilla the cannine area was most commonly involved followed by the third molar area.

B: Epidermoid cysts.

The distribution of the epidermoid cysts examined is shown in Figures 5 and 6. The site distribution was unrecorded in two cases.

C: Cholesteatomas.

The cholesteatomas examined in this study were described in clinical and laboratory records as being located in the middle ear cavity and/or temporal bone. A more exact distribution could not be obtained in the case of cholesteatomas.

Odontogenic Keratocysts (Age Distribution)

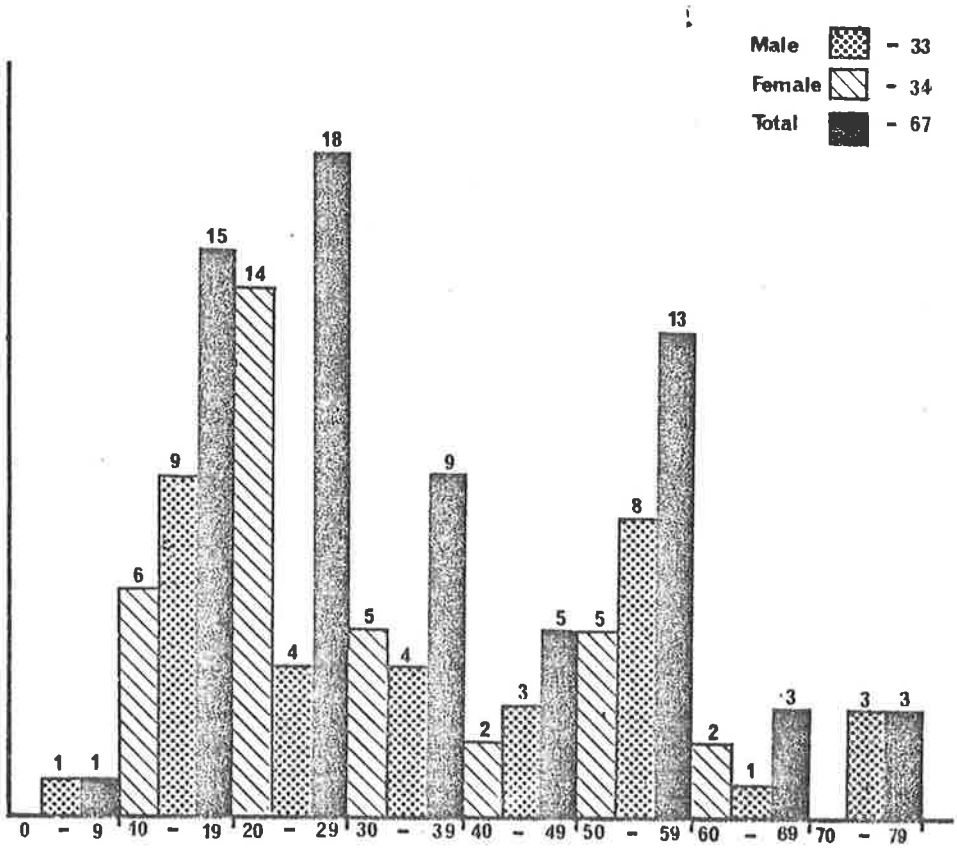


Figure 1

Epidermoid Cysts (Age Distribution)

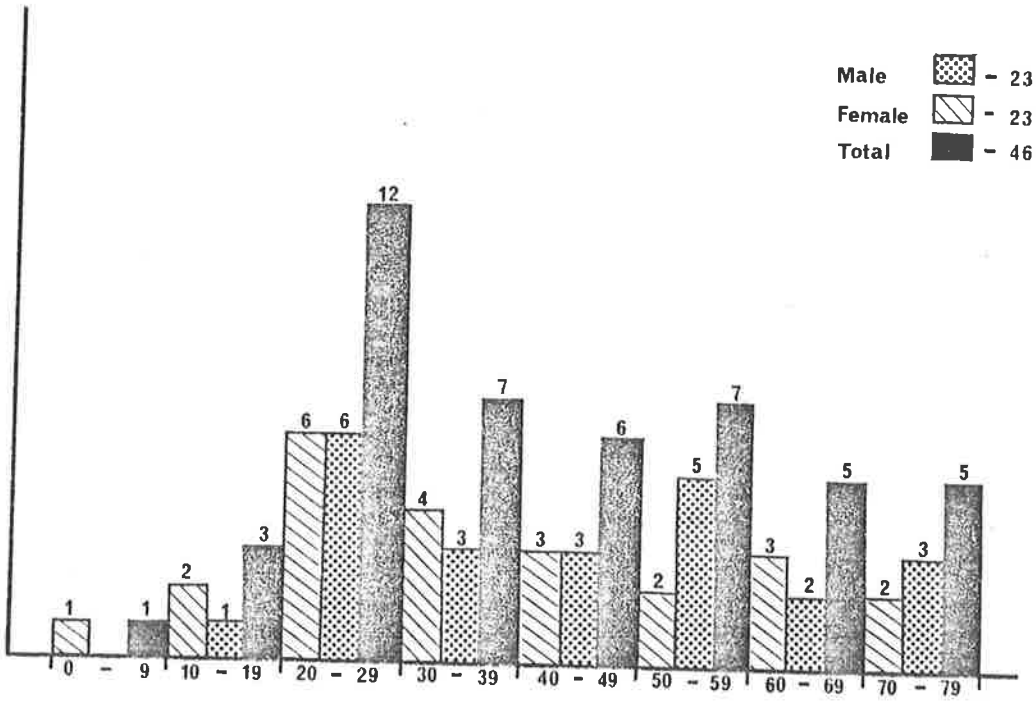


Figure 2

Cholesteatomas (Age Distribution)

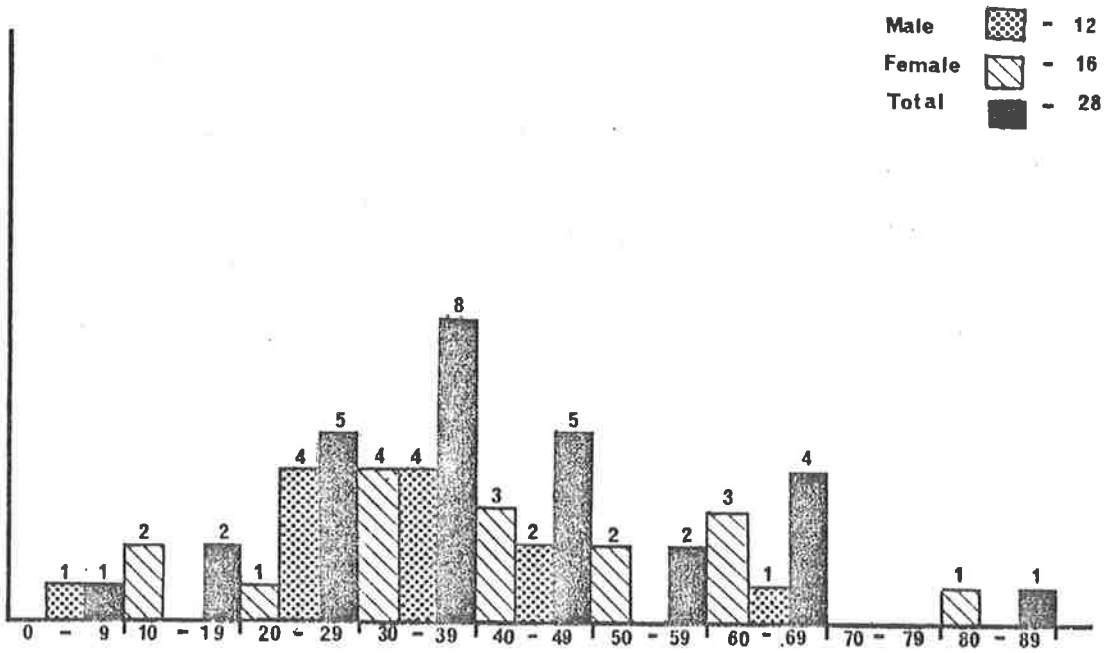


Figure 3

Odontogenic Keratocysts (Area Distribution)

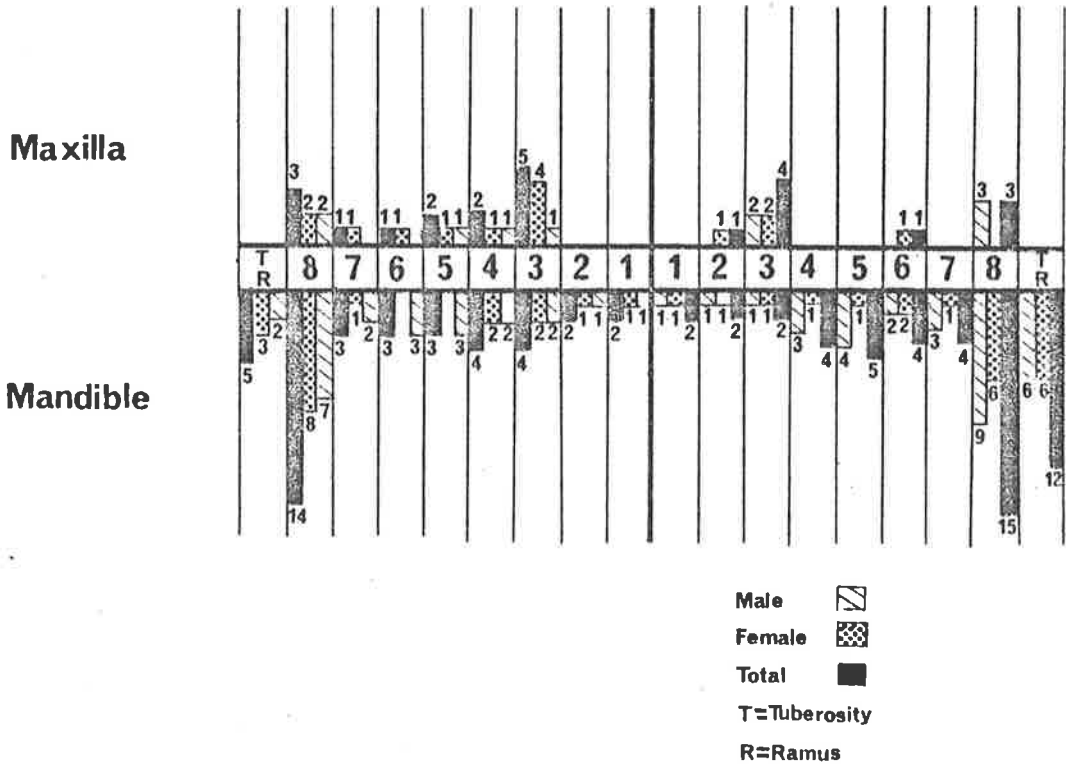
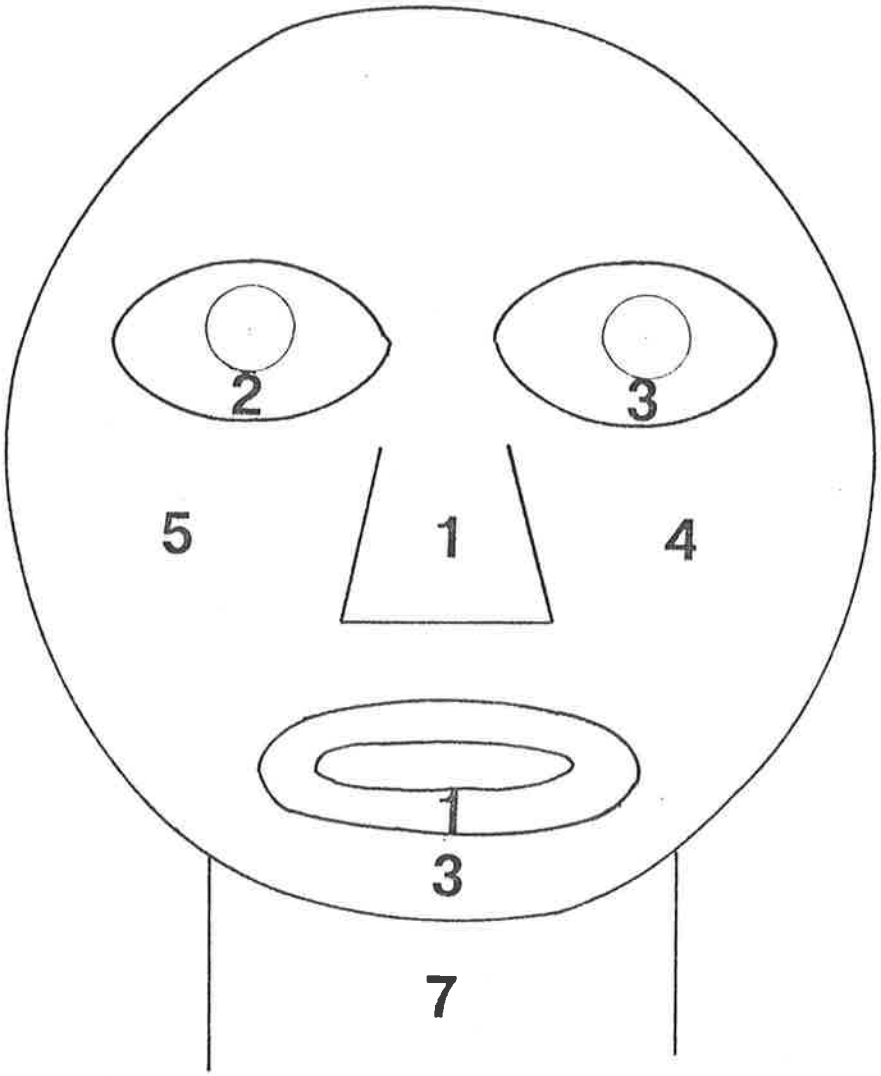


Figure 4

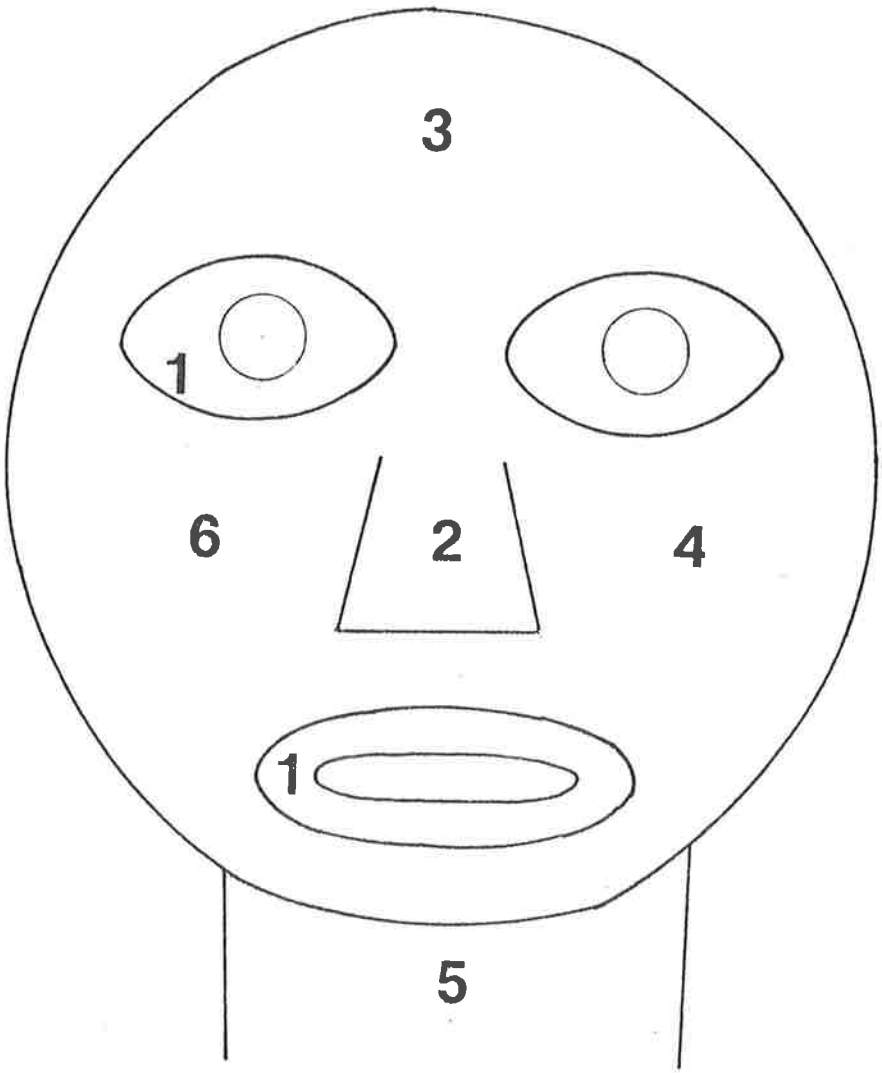
Epidermoid Cysts (Area Distribution Female)



Total - 26

Figure 5

Epidermoid Cysts (Area Distribution - Male)



Total - 22

Figure 6

HISTOLOGIC OBSERVATIONS

EPITHELIAL THICKNESS

a. Odontogenic Keratocyst.

Fiftythree specimens (55%) of odontogenic keratocysts possessed and epithelial lining having a thickness of approximately 1-5 cells (Figure 7). Fortyone specimens (42%) were considered to have an epithelial lining 6-10 cells thick. Three specimens (3%) were recorded as having an 11-15 cell thick epithelial lining and one specimen (1%) a 16+ cell thick epithelial cyst lining.

b. Epidermoid cysts.

Eighteen cysts (36%) possessed an epithelial lining having a thickness of 1-5 cell layers. Thirty (60%) epidermoid cysts were considered to have a lining 6-10 cells thick (Figure 9), and two specimens (4%) an epithelial lining 11-15 cells thick.

c. Cholesteatomas.

Four cholesteatomas (13%) possessed epithelial linings 1-5 cells thick. Twentyfive specimens (83%) had linings 6-10 cells thick (Figure 10) and one specimen (3%) had an epithelial lining 11-15 cells thick.

EPITHELIAL REGULARITY

a. Odontogenic Keratocysts.

Regular epithelium was observed in 31 specimens (32%) of odontogenic keratocyst (Figures 11 and 12). Irregular epithelium was found in 67 (68%) of the odontogenic keratocysts examined (Figures 13, 14 and 15).

b. Epidermoid cysts.

Regular epithelium was observed in 27 (54%) epidermoid cysts (Figures 9 and 16). Irregular epithelium was observed in 23 specimens (46%)

c. Cholesteatomas.

Regular epithelium was observed in 22 (73%) of the cholesteatomas examined (Figures 10 and 17). Irregular epithelium was observed in eight specimens (27%).

SEPARATION OF THE EPITHELIUM FROM THE CAPSULE

a. Odontogenic Keratocysts.

Separation of the cyst lining epithelium from the subjacent connective tissue was observed in 59 (60%) of the odontogenic keratocysts examined (Figures 12 and 18). In 39 specimens (40%) there was no evidence of separation of epithelial cyst lining from the adjacent connective tissues.

b. Epidermoid cysts

Separation of the epithelium from the adjacent connective tissue was observed in 31 (62%) of the epidermoid cysts. In 19 specimens (38%) there was no evidence of separation of the epithelium from the adjacent connective tissues.

c. Cholesteatomas.

Separation of the epithelium from the subjacent connective tissue was observed in 26 (87%) cholesteatomas (Figure 19). There was no evidence of separation in four specimens (13%).

RETE PEGS

a: Odontogenic Keratocysts.

Regular rete pegs were observed in two (2%) of the odontogenic keratocysts studied (Figure 15). The rete peg formation noted was observed only in some portions of the specimens. Irregular rete pegs were observed in 17 (17%) of the odontogenic keratocysts (Figure 14). The

presence of irregular rete pegs was associated with prominent capsular inflammation. Seventynine specimens (81%) did not show any evidence of rete peg formation.

b. Epidermoid cysts.

Regular rete pegs were observed in three (6%) of the epidermoid cysts sampled. Irregular rete pegs were observed in 10 (20%) specimens. Thirtyseven specimens (74%) did not show any evidence of rete peg formation.

c. Cholesteatomas.

No evidence of rete peg formation was observed in any of the epithelial linings of the cholesteatoma sample investigated.

BUDDING

a: Odontogenic Keratocysts.

Budding of the basal layer was observed in 16 specimens (16%) (Figure 20). Budding of the basal layer was absent in 82 (84%) of the odontogenic keratocysts examined.

b. Epidermoid cysts.

Budding of the basal layer was observed in three (6%) of the epidermoid cysts. Budding of the basal layer was absent in 47 (94%) specimens.

c. Cholesteatomas.

Budding of the basal layer was observed in 3 (10%) of the cholesteatomas. Budding of the basal layer was absent in 27 (90%) specimens.

MORPHOLOGY OF THE BASAL CELLS

a. Odontogenic Keratocyst.

Columnar basal cells were observed in five (5%) odontogenic keratocysts (Figure 8). Cuboidal basal cells were observed in 35 (36%) of the odontogenic keratocysts examined (Figure 7). A mixture of columnar and cuboidal basal cells was observed in 58 (59%) specimens.

b. Epidermoid cysts.

Columnar basal cells were observed in 6 (12%) of the epidermoid cysts studied. Cuboidal basal cells were observed in 10 (20%) of the cysts. A mixture of columnar and cuboidal basal cells was observed in 34 (68%) of the specimens (Figure 9).

c. Cholesteatomas.

Columnar basal cells were observed in four (13%) of the cholesteatomas (Figure 10). Cuboidal basal cells were observed in 14 (47%) specimens. A mixture of columnar and cuboidal basal cells was observed in 12 (40%) of the cholesteatomas.

ANGULATION OF THE BASAL CELLS TO THE BASEMENT MEMBRANE

a. Odontogenic Keratocysts.

Basal cells were observed having a perpendicular orientation to the basement membrane in 37 (38%) of the odontogenic keratocysts (Figure 8). A combination of perpendicular and acute angulation was observed in 46 (47%) specimens. The angulation of the basal cell layer to the basement membrane could not be assessed in 15 (15%) of the odontogenic keratocysts.

b. Epidermoid cysts.

Perpendicular orientation of the basal cells to the basement membranes was observed in 15 (30%) of the epidermoid cysts (Figure 9). A combination of perpendicular acute angulation was observed in 35 (70%) specimens.

c. Cholesteatomas.

Perpendicular orientation of basal cells to the basement membrane was observed in six (27%) of the cholesteatomas examined (Figure 10). A combination of perpendicular and acute angulation was observed in 24 (73%) specimens.

NUCLEAR POLARITY

a. Odontogenic Keratocysts.

Polarization of nuclei away from the basement membrane was observed in 11 (11%) of the odontogenic keratocysts (Figure 21). Twenty specimens (20%) show polarization of nuclei towards the basement membrane (Figure 22). In 52 specimens (53%) a mixed nuclear polarity was evident. Polarization of nuclei could not be assessed in 15 (15%) specimens.

b. Epidermoid cysts.

Polarization of nuclei away from the basement membrane was observed in three (6%) of the epidermoid cysts. Six specimens (12%) showed polarization of nuclei towards the basement membrane. In 31 specimens (82%) a mixed nuclear polarity was present.

c. Cholesteatomas.

Polarization of nuclei away from the basement membrane was observed in 5 specimens (17%). Twelve specimens (40%) showed polar-

ization of nuclei towards the basement membrane. In 13 specimens (33%) a mixed nuclear polarity was evident.

CONTINUITY OF THE PRICKLE CELL LAYER

a. Odontogenic Keratocysts.

The prickle cell layer was observed as a continuous layer in 60 (61%) of the odontogenic keratocysts (Figure 8). An absence of a continuous prickle cell layer in some portions of the epithelium was observed in 38 (39%) of the odontogenic keratocysts studied (Figure 7).

b. Epidermoid cysts.

The prickle cell layer was observed as a continuous layer in 37 (74%) of cysts (Figure 9). An absence of the prickle cell layer in some areas of the epithelium was noted in 13 (26%) of specimens.

c. Cholesteatomas.

The prickle cell layer was observed as a continuous layer in 25 (83%) of the cholesteatomas (Figure 10). An absence of a prickle cell layer in some portions of the epithelium was observed in five (17%) specimens.

VACUOLIZATION OF THE PRICKLE CELL LAYER

a. Odontogenic Keratocyst.

Vacuolization of the prickle cell layer was observed in 38 (39%) of odontogenic keratocysts (Figure 22). The remaining 60 (61%) of specimens did not show any evidence of vacuolization.

b: Epidermoid cysts.

Vacuolization of the prickle cell layers was observed in 14 (38%) of the epidermoid cysts. The remaining 36 specimens (32%) did not exhibit

evidence of vacuolization of the prickle cell layer.

c: Cholesteatomas.

Vacuolization of the prickle cell layers was noted in eight (27%) cholesteatomas. The other 22 specimens (33%) did not show evidence of prickle cell vacuolization.

OEDEMA OF THE PRICKLE CELL LAYER

a: Odontogenic keratocyst.

Oedema of the prickle cell layer was observed in 21 (21%) odontogenic keratocysts. Oedema was absent in 77 (79%) of the specimens.

b: Epidermoid cysts.

Oedema of the prickle cell layer of the epithelium was observed in 7 (14%) of the specimens. Oedema was not observed in 43 (86%) of the epidermoid cysts.

c: Cholesteatomas.

Oedema of the prickle cell layer was observed in 4 (13%) of the specimens studied. Oedema was not observed in 26 (87%) cholesteatomas.

KERATIN TYPE

a: Odontogenic Keratocysts.

Complete parakeratinization was found in 48 (49%) of the odontogenic keratocysts examined (Figures 7 and 8). Orthokeratinization was observed in seven (7%) of the lesions(Figure 23). Mixed keratinization was observed in 43 (44%) of the specimens.

b: Epidermoid cysts.

Complete parakeratinization was observed in nine (16%) of the

epidermoid cysts. Orthokeratinization was observed in 26 (52%) of the epidermoid cysts (Figure 9) and mixed keratinization in 16 (32%) specimens.

c: Cholesteatomas.

Complete parakeratinization was found in two (7%) of the cholesteatomas examined. Orthokeratinization was observed in eight (27%) specimens (Figure 10), and mixed keratinization in 20 (67%) of the cysts.

CONTINUITY OF THE KERATIN LAYER

a: Odontogenic Keratocysts.

A keratin layer was found to be continuous in 35 (36%) of the odontogenic keratocysts. A discontinuous keratin layer was observed in 63 (64%) specimens.

b: Epidermoid cysts.

The keratin layer was found to be continuous in 44 (88%) of the epidermoid cysts studied. A discontinuous keratin layer was observed in six (12%) of the epidermoid cysts.

c: Cholesteatomas.

The keratin layer was found to be continuous in 18 (60%) of cholesteatomas. A discontinuous keratin layer was observed in 12 (40%) of the specimens.

INDIVIDUAL CELL KERATINISATION

a: Odontogenic Keratocysts.

Individual cell keratinization or keratin pearl formation was

observed in three (3%) of the odontogenic keratocysts (Figure 24). The remaining 95 (97%) of specimens did not show any evidence of keratinization below the surface keratin layer.

b: Epidermoid cysts.

Individual cell keratinization was not observed in the epithelial lining of any of the epidermoid cysts studied.

c: Cholesteatomas.

Individual cell keratinization was not observed in any of the epithelial linings of the cholesteatomas examined.

KERATOHYALIN GRANULES

a: Odontogenic Keratocysts.

Keratohyalin granules were observed in 23 (23%) of the specimens examined (Figure 23). Keratohylin granules were absent in 75 (77%) of the specimens.

b: Epidermoid cysts.

Keratohyalin granules were observed in 46 (92%) of the epidermoid cysts studied (Figure 9). Keratohyalin granules were not observed in four (8%) specimens.

c: Cholesteatomas.

Keratohyalin granules were observed in 27 (90%) of the cholesteatomas (Figure 10). Keratohyalin granules were absent in three (10%) specimens.

CHOLESTEROL

a: Odontogenic Keratocysts.

Cholesterol clefts were observed in two (2%) of the odontogenic

keratocysts studied (Figure 25). The other 96 (98%) of specimens did not show any evidence of cholesterol.

b:Epidermoid cysts.

No evidence of cholesterol was found in any of the 50 specimens examined.

c: Cholesteatomas.

No evidence of cholesterol was observed in any of the 30 specimens in the sample.

INFLAMMATORY CELLS IN THE EPITHELIUM

a: Odontogenic Keratocysts.

The presence of acute and/or chronic inflammatory cells were observed in some portion of the epithelium in 61 (62%) of the odontogenic keratocysts sample '(Figure 14). An absence of inflammatory cells was observed in 37 (38%) of the odontogenic keratocysts. The presence of inflammatory cells within the epithelium was associated with the presence of inflammatory cells within the capsular tissues.

b: Epidermoid cysts.

The presence of acute and/or chronic inflammatory cells was observed in the epithelium of 13 (26%) specimens. An absence of inflammatory cells was observed in 37 (74%) epidermoid cysts.

c: Cholesteatomas.

The presence of acute and/or chronic inflammatory cells was observed in the epithelium of 14 (47%) cholesteatomas studied. An absence of inflammatory cells was noted in 16 (53%) specimens.

SEVERITY OF INFLAMMATION IN THE EPITHELIUM

a. Odontogenic Keratocysts.

Mild inflammatory cell infiltration was observed in 43 (43%) of odontogenic keratocysts (Figure 26). Severe inflammation was found in 18 (18%) of the specimens (Figure 14). Disorganization of the epithelial lining and proliferation of epithelium was observed in association with severe inflammatory cell infiltrations.

b. Epidermoid cysts.

A mild inflammatory cell infiltration was observed in five (10%) of the epidermoid cysts. A severe inflammatory cell infiltation was noted in eight (16%) specimens.

c. Cholesteatomas.

A mild inflammatory cell infiltration was observed in 10 (33%) specimens. A severe inflammatory cell infiltration was found in 4 (13%) cholesteatomas.

DISTRIBUTION OF INFLAMMATORY CELLS IN THE EPITHELIUM

a. Odontogenic Keratocysts.

Localised areas of inflammatory cells were observed in 59 (59%) of the odontogenic keratocysts studied. A diffuse inflammatory cell infiltration was observed in 2 (2%) specimens.

b. Epidermoid cysts.

Localised areas of inflammatory cells were observed in seven (14%) of the epidermoid cysts. A diffuse inflammatory cell infiltration was observed in six (12%) specimens.

c: Cholesteatomas.

Localised areas of inflammatory cells were observed in 12 (40%) cholesteatomas. A diffuse inflammatory cell infiltration was observed in 2 (7%) specimens.

ATYPIA

a: Odontogenic Keratocysts.

Atypia of the epithelial lining was observed in 6 (6%) of the odontogenic keratocysts examined. The atypia noted included basal cell hyperplasia, evidence of increased mitotic activity, hyperchromatism, loss of polarity and increased nucleo-cytoplasmic ratios. In all cases the atypia noted was focal and in the majority of cases was classed as being of a mild degree. One cyst however (Figures 28 and 29) showed severe, focal epithelial atypia.

b: Epidermoid cysts

No evidence of epithelial atypia was found in the epidermoid cyst group.

c: Cholesteatomas.

No evidence of epithelialatypia was noted in the cholesteatomas.

METAPLASIA

No evidence of epithelial metaplasia could be found in any of the odontogenic keratocysts, epidermoid cysts or cholesteatomas.

MELANOCYTES

a: Odontogenic Keratocysts.

Melanocytes were observed in six (6%) of the odontogenic keratocysts studied (Figure 30).

b: Epidermoid cysts.

Melanocytes were observed in 19 (38%) of the epidermoid cysts.

c: Cholesteatomas.

Melanocytes were observed in the epithelium of two (7%) cholesteatomas.

CALCIFIED MATERIAL IN THE EPITHELIUM

No evidence of calcified material was found in the epithelial linings of any of the odontogenic keratocysts, epidermoid cysts or cholesteatomas examined.

CALCIFIED MATERIAL IN THE CAPSULE

a: Odontogenic Keratocysts.

Calcified material was observed in the capsules of seven (7%) of the odontogenic keratocysts (Figures 35 and 36). The most commonly found calcification was in the form of globular dystrophic type calcification.

b: Epidermoid cysts.

No evidence of calcified material was found in the capsules of any of the epidermoid cysts examined.

c: Cholesteatomas.

There was no evidence of calcified material in any of the cholesteatomas studied.

INFLAMMATORY CELLS IN THE CAPSULE

a: Odontogenic Keratocysts.

Acute and/or chronic inflammatory cells were observed in the

capsules of 83 (83%) of the odontogenic keratocysts (Figures 13, 14, 26 and 27).

b: Epidermoid cysts.

The presence of acute and/or chronic inflammatory cells was noted in the capsules of 26 (52%) specimens.

c: Cholesteatomas.

The presence of acute and/or chronic inflammatory cells was noted in the capsular tissues of 18 (60%) cholesteatomas (Figure 17).

DEGREE OF INFLAMMATION IN THE CAPSULE

a: Odontogenic Keratocysts.

A mild degree of inflammation was observed in 56 (57%) odontogenic keratocysts (Figures 13 and 15). Severe inflammation was found in 27 (28%) of the odontogenic keratocysts sampled (Figure 14).

b: Epidermoid cysts.

A mild degree of inflammation was observed in13 (26%) of the epidermoid cysts. Severe inflammation was found in 11 (22%) of the specimens.

c: Cholesteatomas.

A mild degree of inflammation was observed in 14 (47%) of the cholesteatomas. Severe inflammation was found in 4 (13%) of the specimens.

DISTRIBUTION OF INFLAMMATORY CELLS IN THE CAPSULE.

a: Odontogenic Keratocysts.

Localised areas of inflammatory cells were observed in 52 (53%) odontogenic keratocysts (Figures 13 and 27). Diffuse inflammatory

cell infiltrations were observed in 31 (32%) of the odontogenic keratocysts.

b: Epidermoid cysts.

Localised areas of inflammatory cells were observed in 17 (34%) specimens. A diffuse inflammatory cell infiltration was observed in nine (18%) epidermoid cysts.

c: Cholesteatomas.

Localised areas of inflammatory cells were observed in 14 (47%) cholesteatomas. A diffuse inflammatory cell infiltration was observed in four (13%) specimens (Figure 17).

HOMOGENEOUS ZONE

a: Odontogenic Keratocysts.

A homogeneous zone was observed in 62 (63%) of odontogenic keratocysts (Figure 18). This feature was absent in 23 (23%) specimens and in 13 specimens (13%) this feature could not be assessed because of the presence of inflammatory cells in the capsule and/or epithelium.

b: Epidemoid cysts.

A homogeneous zone was observed in the capsular tissues of 39 (78%) epidermoid cysts. This feature was absent in 11 (22%) specimens.

c: Cholesteatomas.

A homogenous zone was observed in 18 (60%) of the cholesteatomas. This feature was absent in 12 (40%) specimens.

EPITHELIAL CELL RESTS

A:Odontogenic Keratocysts.

Epithelial islands in the form of small cell rests and larger epithelial islands were observed in 49 odontogenic keratocysts (50%) (Figures 31 and 32). In eight of these specimens cell islands were observed in close relationship to overlying oral epithelium which had been included in the surgical specimen (Figure 33).

b: Epidermoid cysts.

Epithelial cell rests were observed in two (4%) of the epidermoid cysts sampled (Figure 16).

c: Cholestatomas.

Epithelial cell rest like structures were observed in two (7%) cholesteatomas.

MICROCYSTS

a: Odontogenic Keratocysts.

Microcysts were observed in 40 (44%) specimens (Figures 13 and 37). In six of these specimens microcysts were observed in close relationship to the overlying oral epithelium.

b: Epidermoid cysts.

Microcysts were observed in 4 (8%) epidermoid cysts (Figure 34).

c: Cholesteatomas.

Microcysts were observed in one (3%) specimen.

Figure 7.

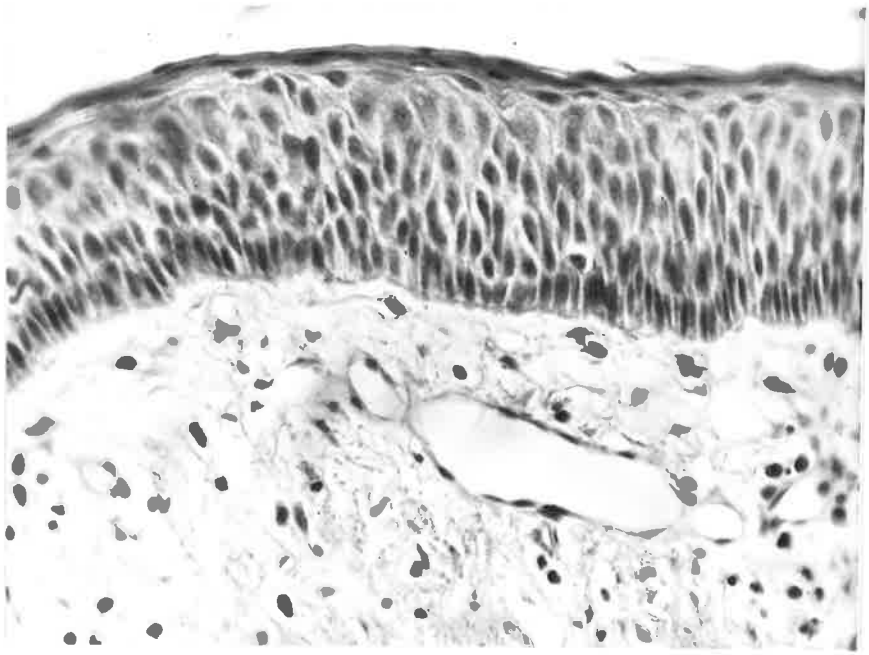


Figure 8.

Fig. 7: Odontogenic Keratocyst.

Note the thin parakeratinized epithelial cyst lining, approximately 5 cells thick, which is devoid of a well defined prickle cell layer. The basal cells exhibit a cuboidal morphology.

Haematoxylin and Eosin (H&E)

Original magnification x250.

Fig. 8: Odontogenic Keratocyst.

Cyst exhibiting the presence of a cyst lining 6-10 cells thick. The epithelium has a well defined prickle cell layer. The basal epithelial cells exhibit a columnar morphology and ar orientated perpendicular to the basal lamina. The epithelium is parakeratinized.

H & E. Original magnification x250.

Figure 9.

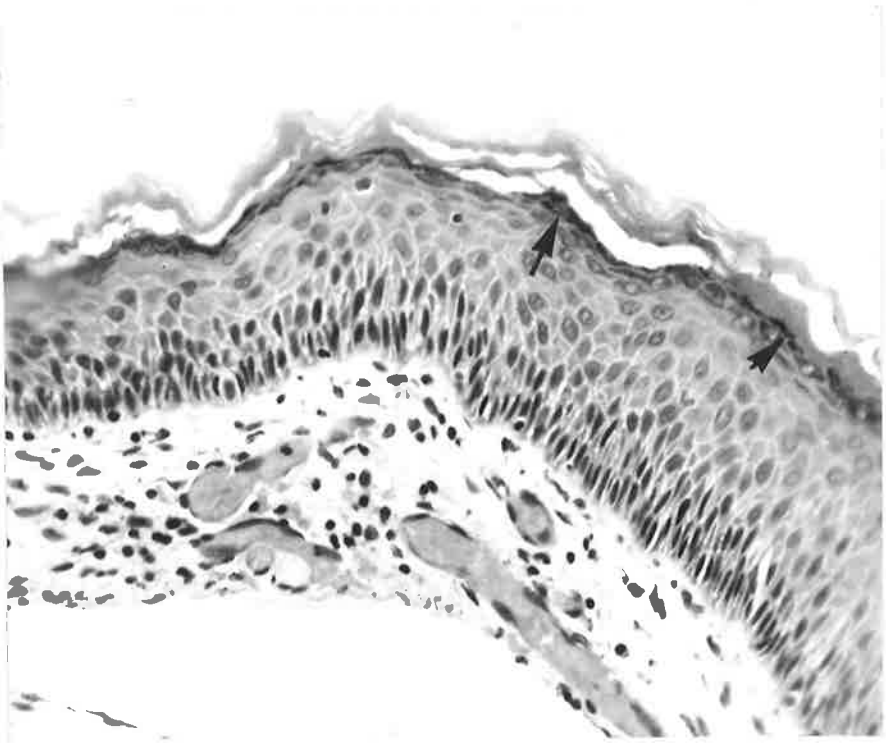


Figure 10.

Fig. 9: Epidermoid cyst.

Note the regular epithelial cyst lining which is approximately 6-10 cells thick. A well defined prickle cell layer is present. The basal cells of the epithelium exhibit a mixed columnar (arrow) and cuboidal morphology and are orientated perpendicular to the basal lamina. The cyst lining epithelium is orthokeratinized and exhibits the presence of a granular layer (small arrows). H & E. Original magnification x250.

Fig. 10: Cholesteatoma.

Note the regular epithelial cyst lining approximately 6-10 cells thick. A well defined prickle cell layer is present.
The basal cells of the epithelium exhibit a columnar morphology and are orientated perpendicular to the basement membrane. The cyst lining is orthokeratinized and exhibits the presence of a granular cell layer (arrows).
H & E.Original magnification x250.

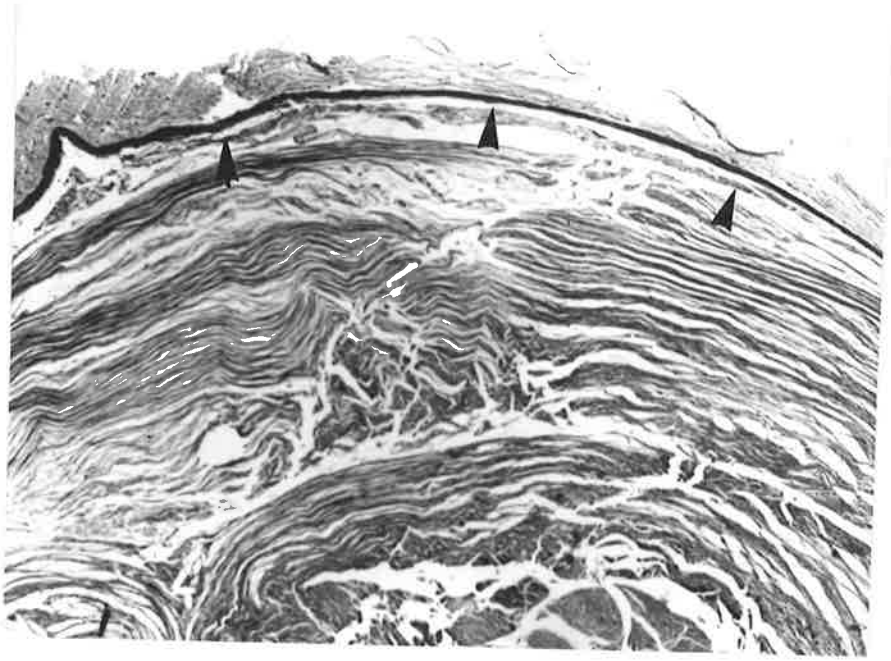


Figure 11.

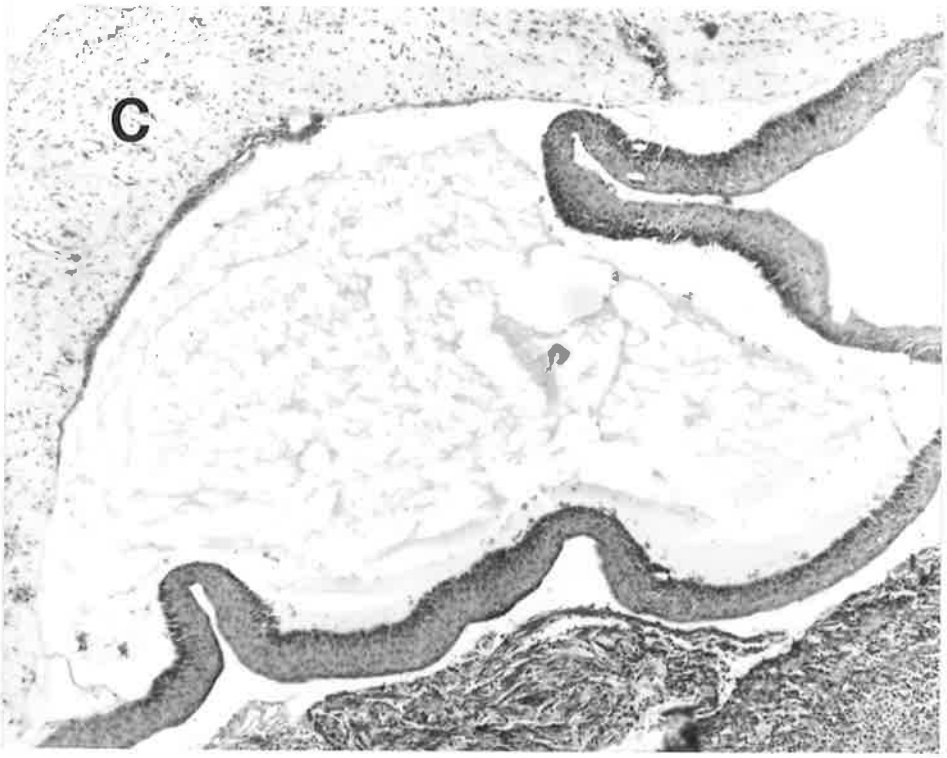


Figure 12.

Fig. 11: Odontogenic Keratoyst.

Low power photomicrograph of an odontogenic keratocyst. Note the keratin filled lumen and the uniformly regular cyst lining (arrows).

H & E. Original magnification x40.

Fig. 12: Odontogenic Keratocyst.

Note the regular cyst lining epithelium which has separated from the capsular tissues (c).

H & E. Original magnification x40.

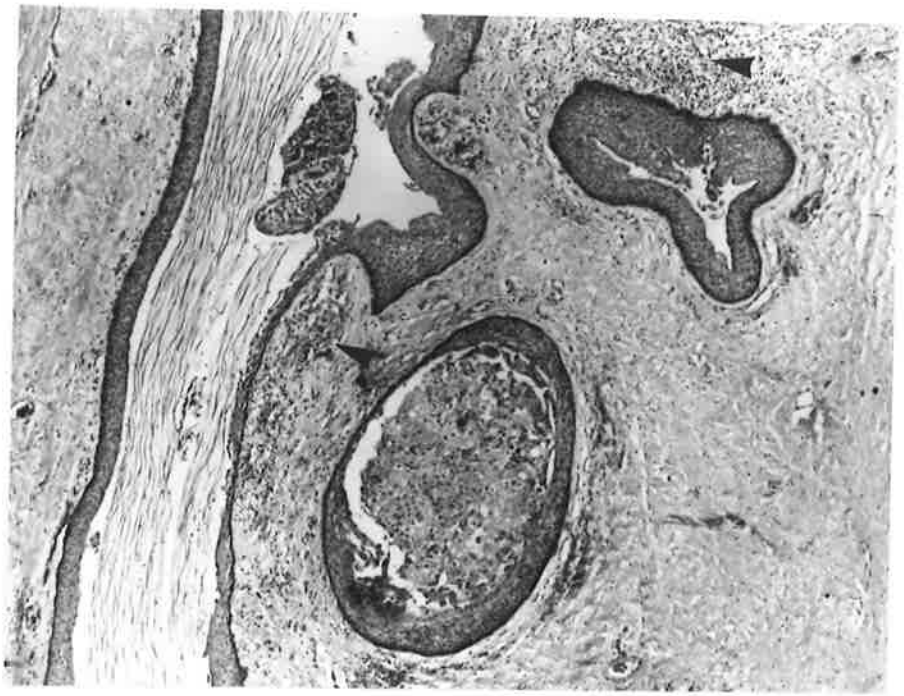


Figure 13.

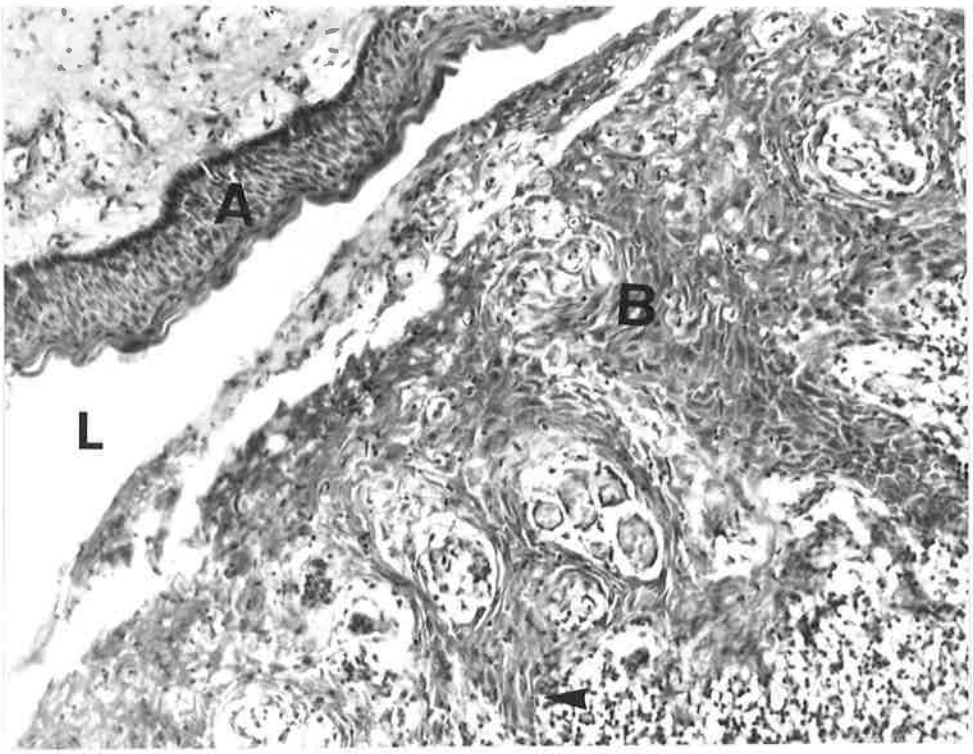


Figure 14.

Fig. 13: Odontogenic Keratocyst.

The irregular epithelium lining the main cyst lumen. Two microcysts are present in the capsular tissues. The capsular tissues exhibit a mild degree of focal inflammation (arrows).

H & E. Original magnification x40.

Fig. 14: Odontogenic Keratocyst.

Low power photomicrograph of a collapsed odontogenic keratocyst demonstrating the presence of a typical cyst lining epithelium in one area (A) and an area of cyst lining epithelium (B) which has undergone hyperplastic degenerative change in association with an inflammatory cell infiltrate and inflammation of the capsular tissues. Although the apparent thickness of the epithelium in the hyperplastic area is exagerated by a tangential plane of section the epithelium does show a tendency towards irregular rete-peg formation (arrow).

L - cyst lumen.

H & E. Original magnification x100.

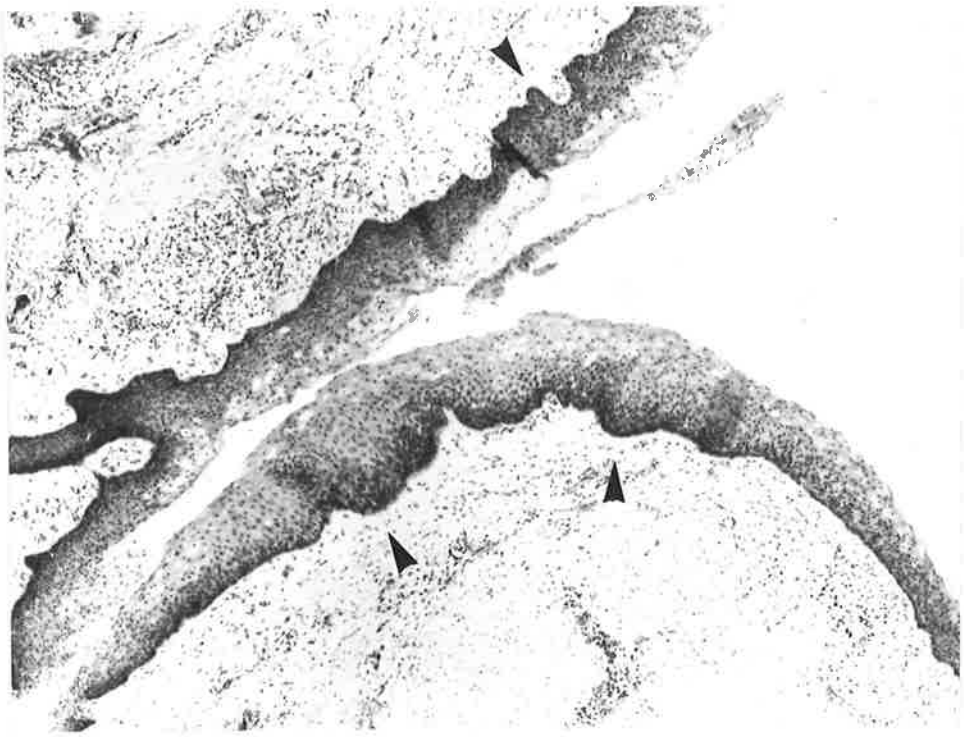


Figure 15.

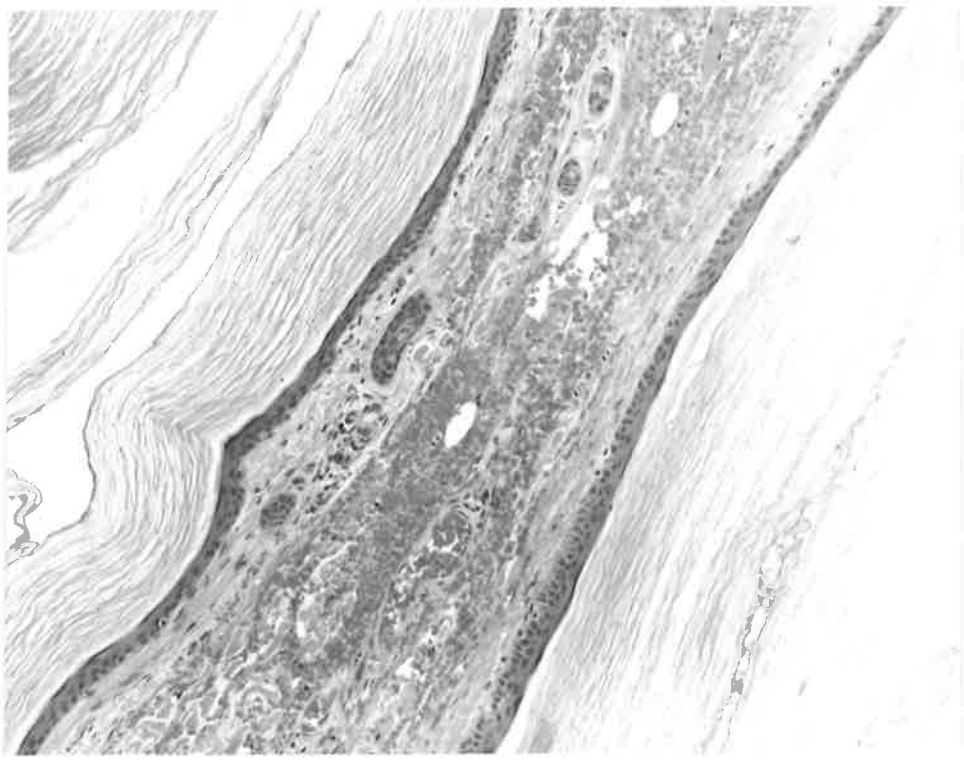


Figure 16.

Fig. 15: Odontogenic Keratocyst.

Note the irregular cyst lining epithelium which is characterised by variation in thickness and the formation of rete pegs (arrows). The capsular tissues exhibit the presence of a mild inflammatory cell infiltration.

H & E. Original magnification x100.

Fig. 16: Epidermoid cyst.

Low power photomicrograph of portion of two epidermoid cysts sharing a common capsule in some areas. The cyst lining epithelium is thin and regular.

Note the epithelial cell rests in the capsular tissues.

H & E. Original magnification x100.

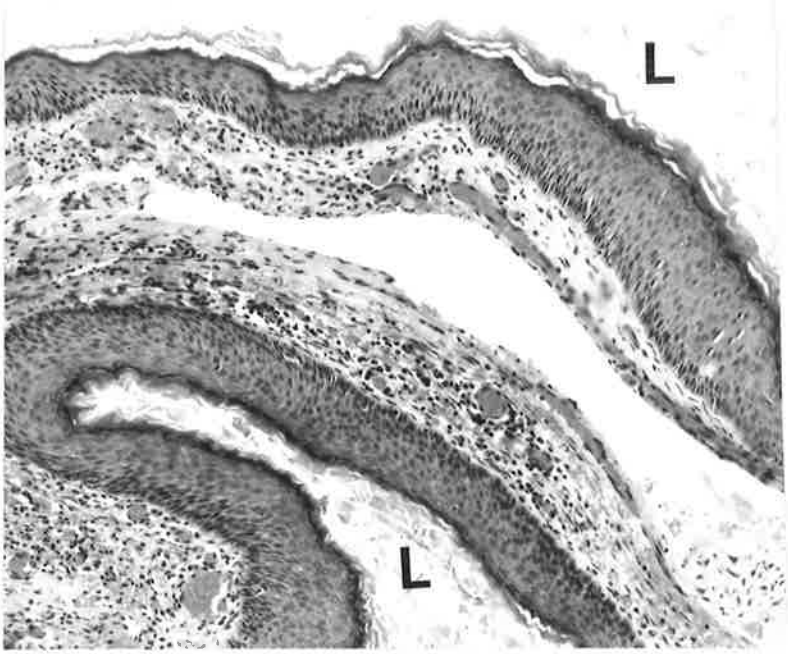


Figure 17.

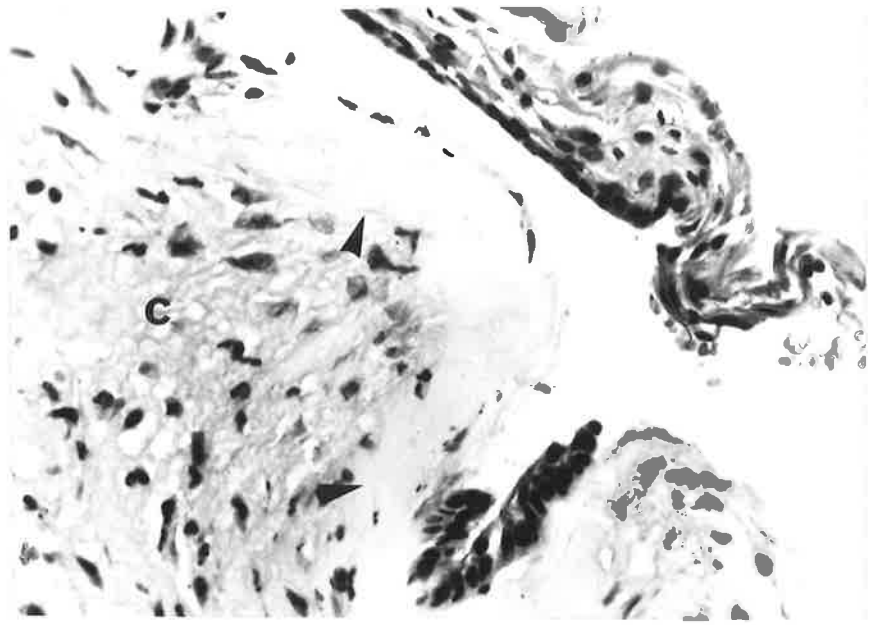


Figure 18.

Fig. 17: Cholesteatoma.

Low power photomicrograph of a cholesteatoma.
Note the generally regular epithelium, the thin capsular tissues and the presence of a mild, diffuse inflammatory cell infiltrate in the capsule. The histologic similarity of this lesion to an odontogenic keratocyst is evident.
H & E. Original magnification x100.

Fig: 18: Odontogenic keratocyst.

Note the separation of the cyst lining epithelium from the capsular tissues (c). The photomicrograph also illustrates the phenomenon of marked hyalinization (arrows) of capsular tissues subjacent to the epithelium.
H & E. Original magnification x250.

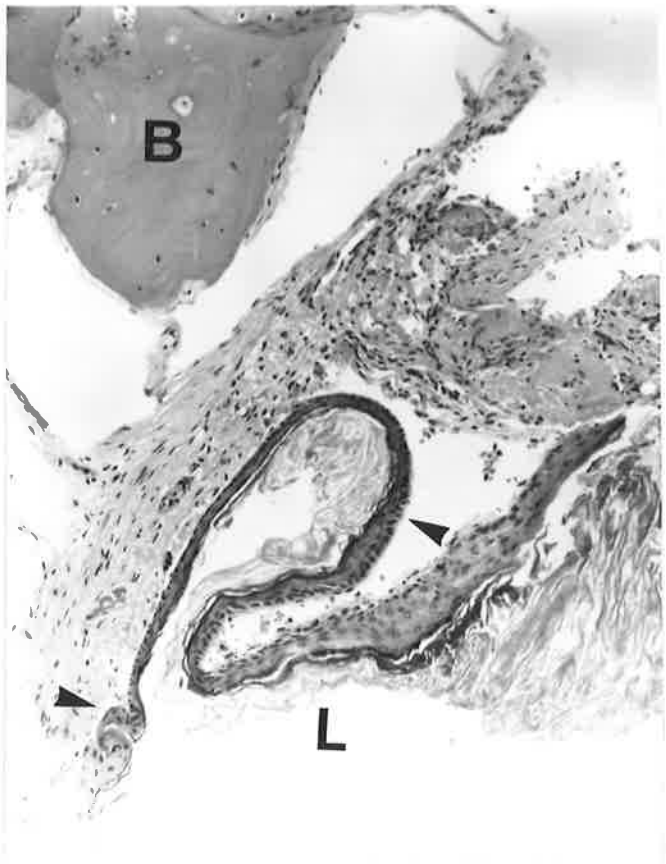


Figure 19.

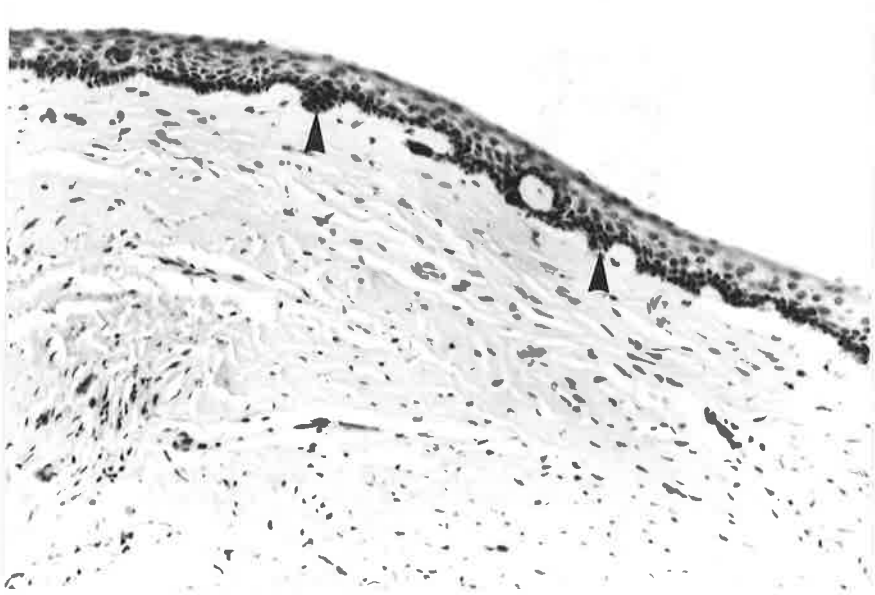


Figure 20.

Fig. 19: Cholesteatoma.

Note the separation (arrows) of the cyst lining epithelium from the capsular tissues. B - Bone. L - cyst lumen.

H & E. Original magnification x100.

Fig. 20: Odontogenic Keratocyst.

Note the hyperplasia of the basal epithelial cells giving rise to small epithelial buds (arrows).

H & E. Original magnification x100.

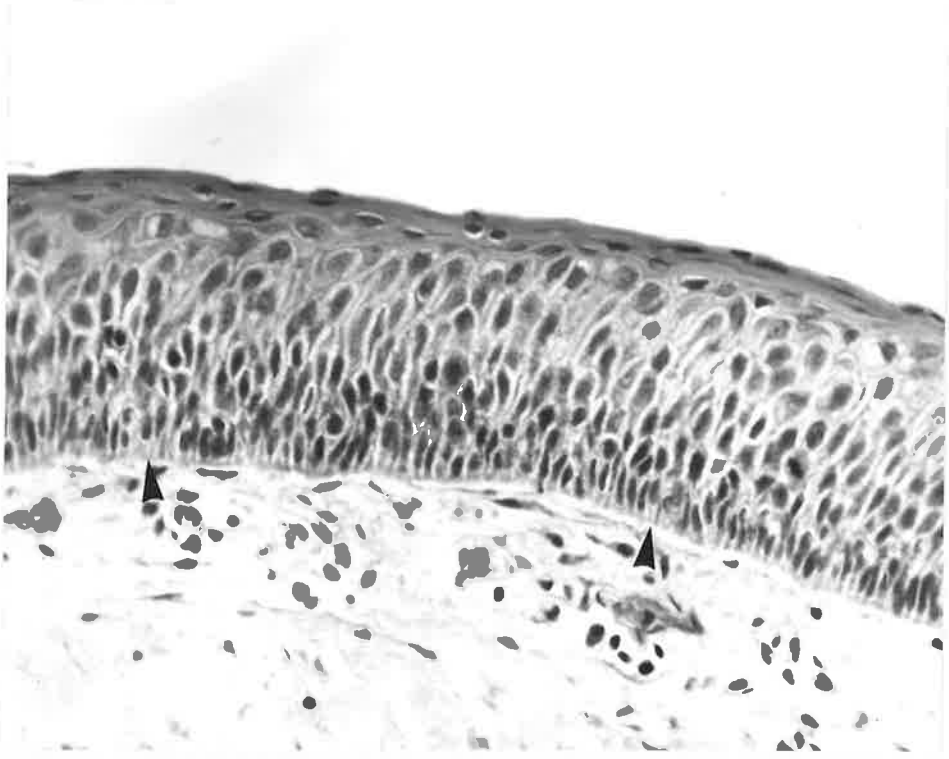


Figure 21.

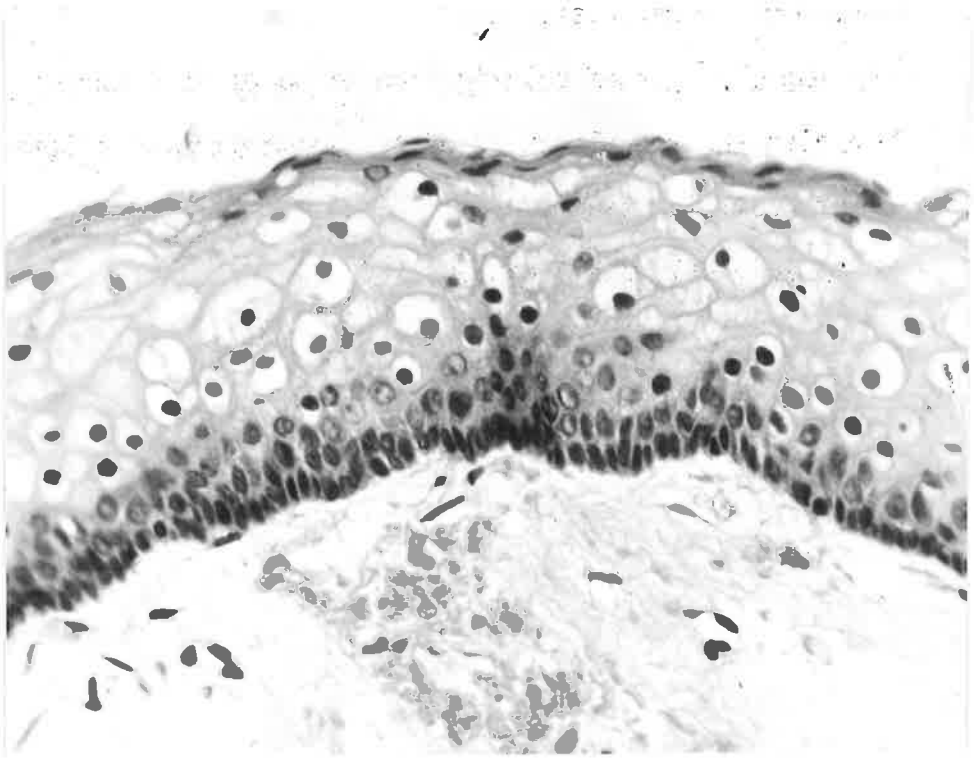


Figure 22.

Fig. 21: Odontogenic Keratocyst.
Note the polarization of the columnar basal cell nucleii away from the basememt membrane (arrows).
H & E. Original magnification x250.

Fig. 22: Odontogenic Keratocyst.
Note the abscence of polarization of basal cell nucleii.
Note also the vacuolization of the epithelium as evidenced by intracellular oedema.
H & E. Original magnification x250.

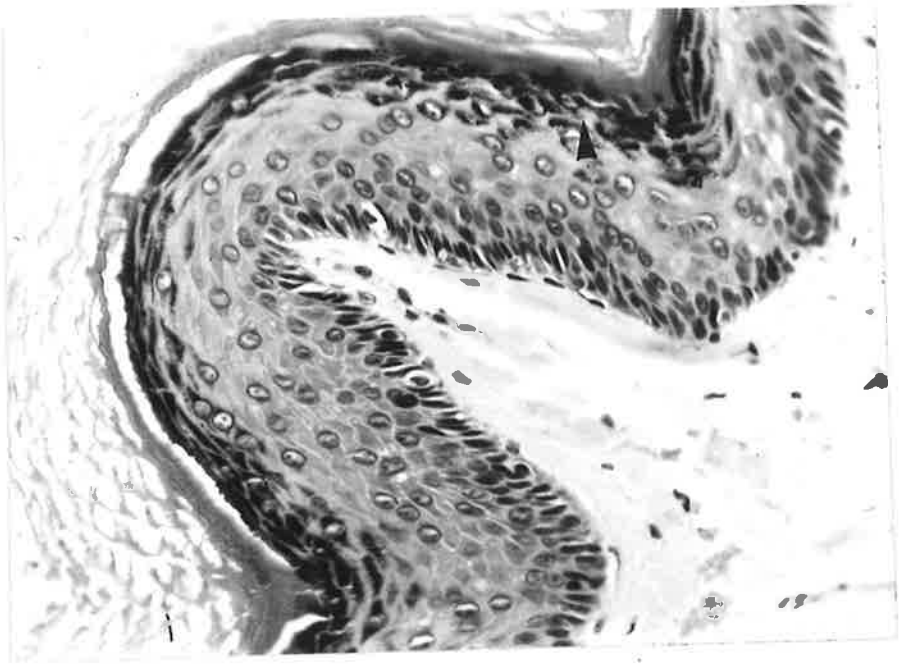


Figure 23.

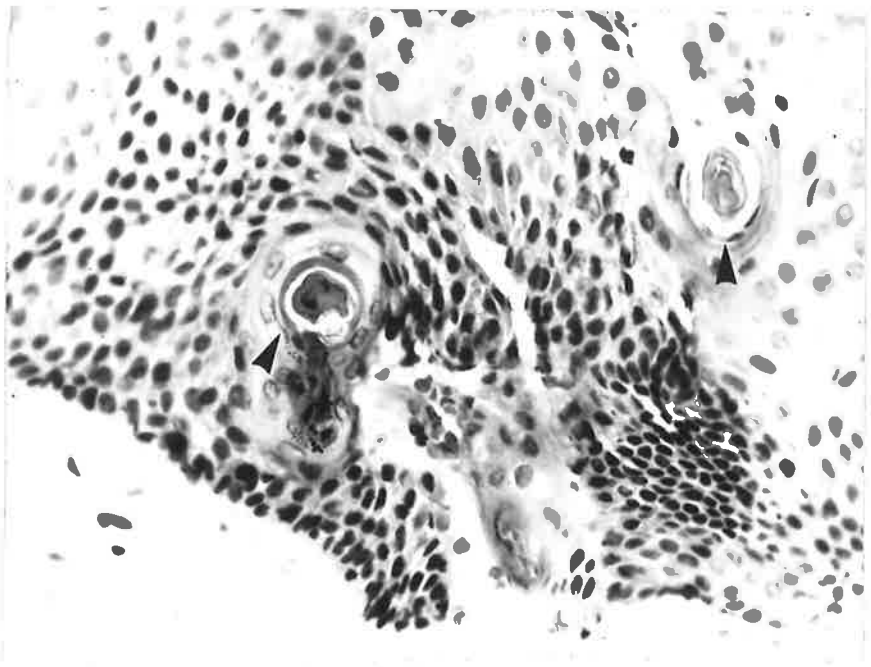


Figure 24.

Fig. 23: Odontogenic Keratocyst.

Note the prominent orthokeratin and granular cell layer associated with the epithelium.

Note the resemblence of the epithelium to that of a cholesteatoma (Figure 10).

H & E. Original magnification x250.

Fig. 24: Odontogenic Keratocyst.

Note the superficial and deep (arrows) keratin pearl formation in the epithelium of this specimen.

Note the hyperchromatism and apparent hyperplasia of the basal type cells. These features are typical of those which were considered to constitute mild atypia in this study.

C - Capsule.

H & E. Original magnification x250.

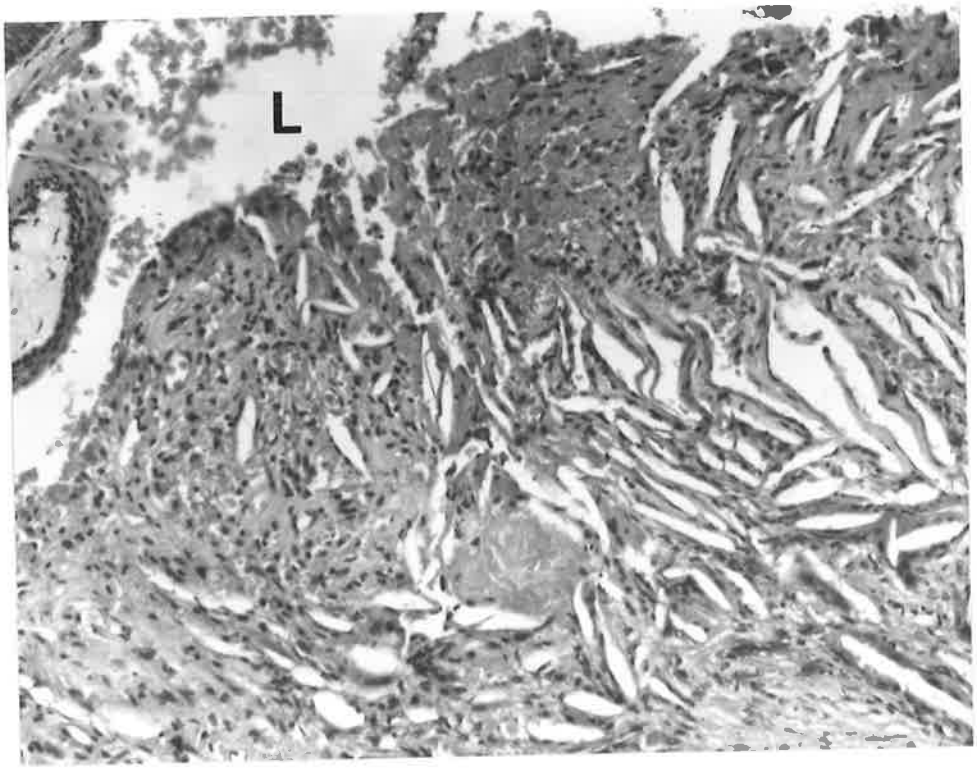


Figure 25.

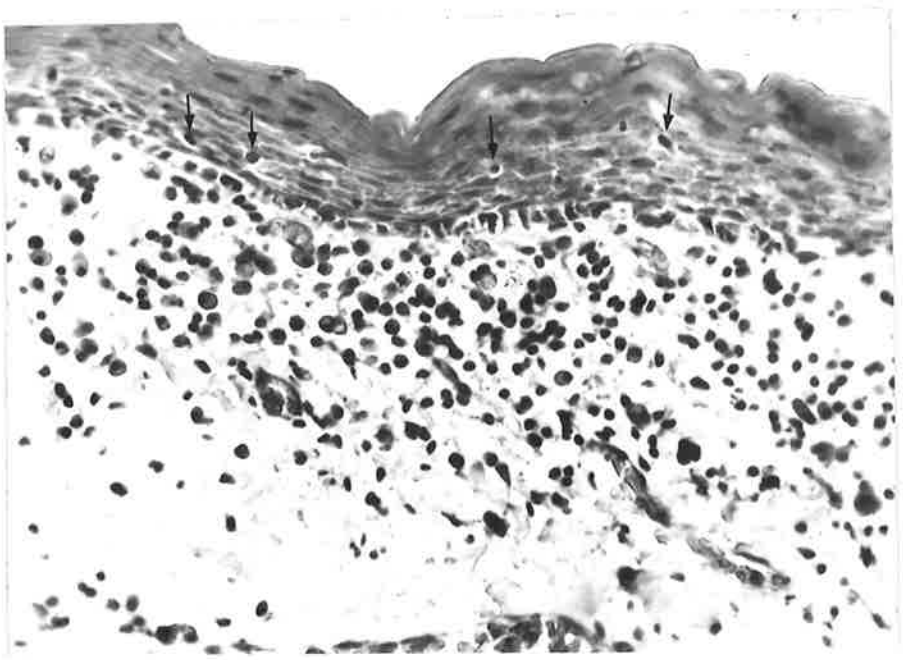


Figure 26.

Fig. 25: Odontogenic Keratocyst.

Photomicrograph illustrating a portion of a mural, cholesterol-cleft containing inflammatory associated proliferation of capsular tissue.

L - cyst lumen.

H & E. Original magnification x100.

Fig. 26: Odontogenic Keratocyst.

Chronic inflammatory cells in the form of lymphocytic and plasma cells can be seen in the capsular tissues. A few inflammatory cells (arrows) can be seen within the epithelium.

H & E. Original magnification x250.

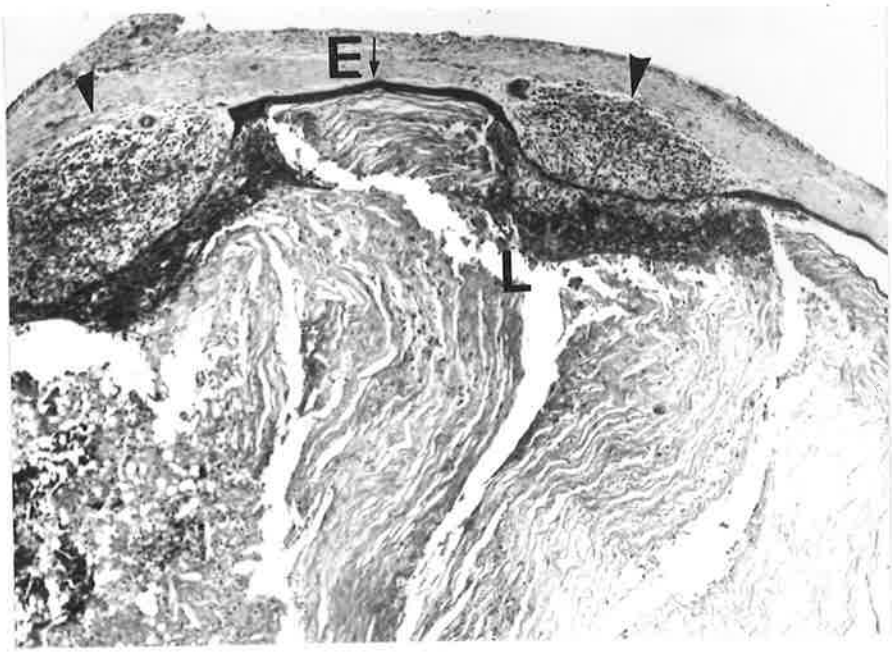


Figure 27.

Fig. 27: Odontogenic Keratocyst.

Focal areas of inflammation (arrows) are evident in the capsular tissue. The capsular inflammation is associated with alteration of the epithelium (E - arrow).

L - cyst lumen.

H & E. Original magnification x40.

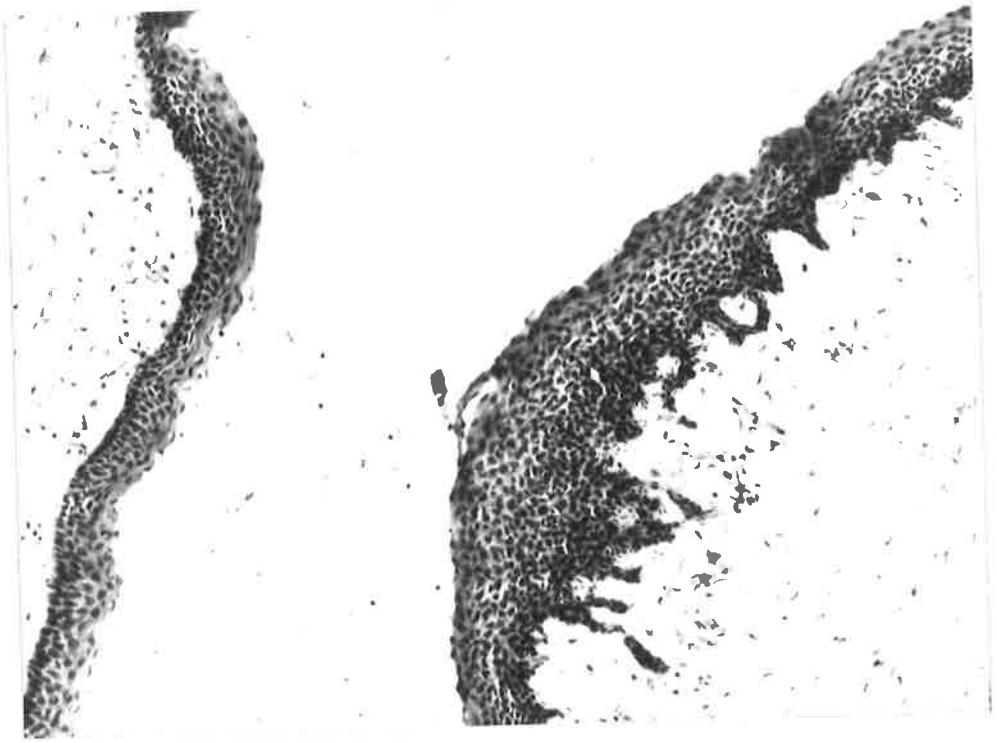


Figure 28.

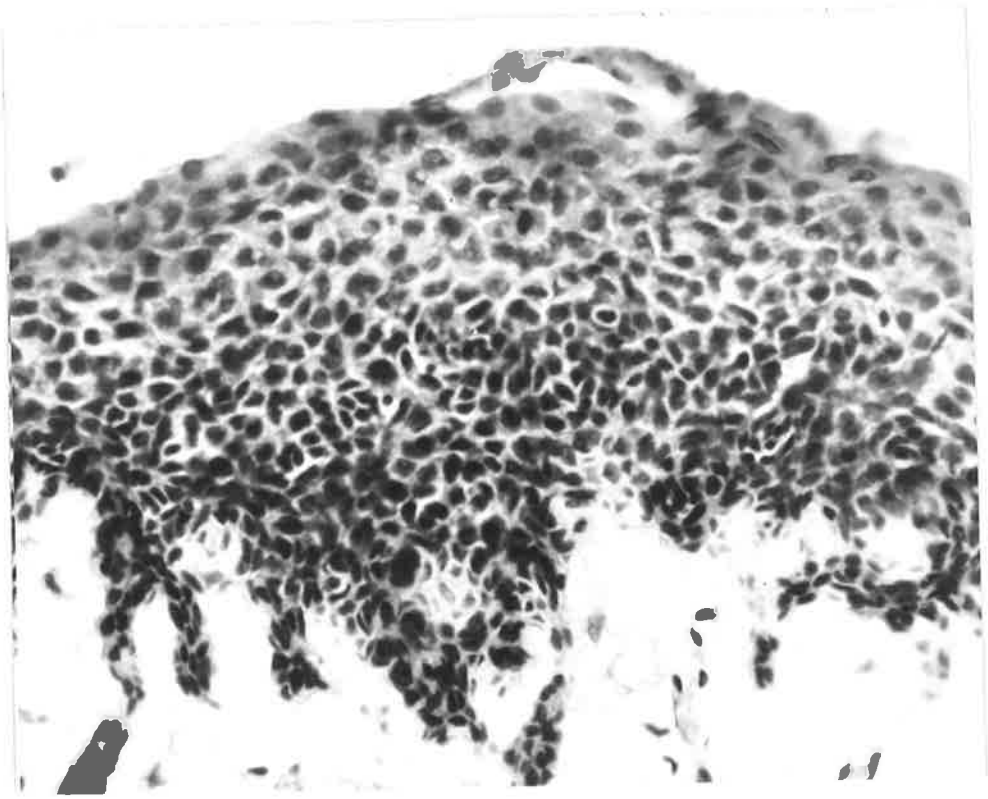


Figure 29.

Fig. 28: Odontogenic Keratocyst.

Low power photomicrograph of a portion of an odontogenic keratocyst. The epithelium in the lower section of the photomicrograph exhibits signs of moderate-severe atypia and proliferation in the absence of inflammation. The epithelium in the upper portion of the photomicrograph exhibits a morphologic feature within normal limits.
H & E. Original magnification x100.

Fig. 29: Odontogenic Keratocyst.

High power view of the atypia epithelium illustrated in Figure 28. Note:

1. The thickening of the epithelium and downwards proliferation of basal type cells.
2. Hyperplasia of basal type cells.
3. Hyperchromatism.
4. Cellular pleomorphism.
5. Nuclear pleomorphism.

H & E. Original magnification x250.

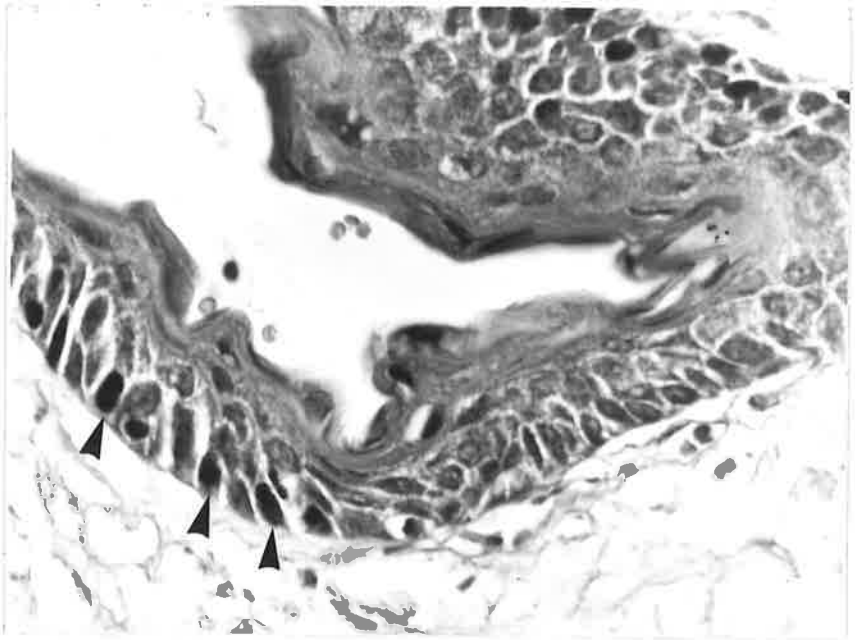


Figure 30.

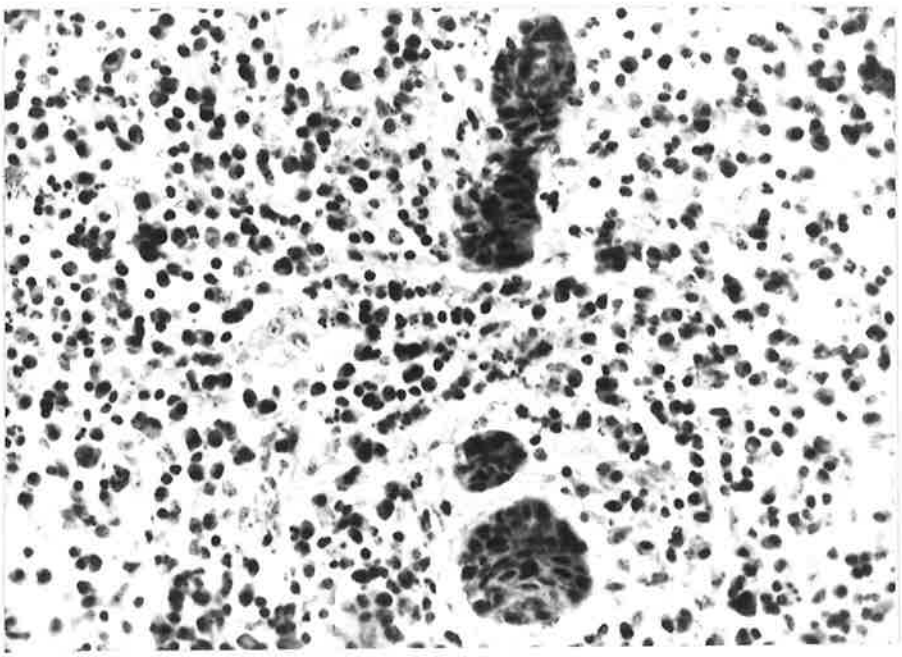


Figure 31.

Fig. 30: Odontogenic Keratocyst.

Portion of an epithelial lining of an odontogenic keratocyst demonstrating the presence of melanocysts (arrows) in the basal layer. The Masaan-Fontana stain was positive for melanin.

H & E. Original magnification x250.

Fig. 31: Odontogenic Keratocyst.

Epithelial cell islands can be seen in a markedly inflammed region of capsular tissue.

H & E. Original magnification x250.

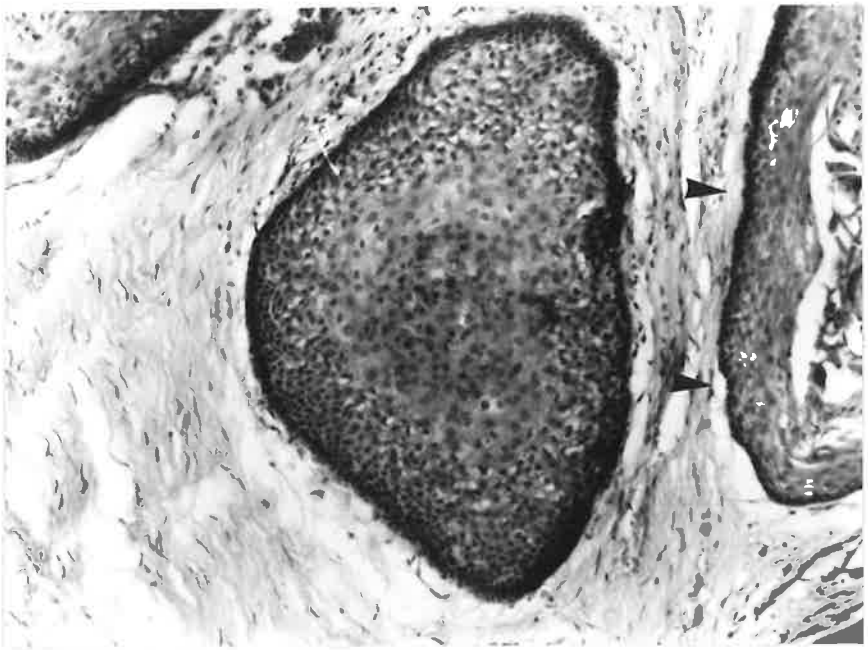


Figure 32.

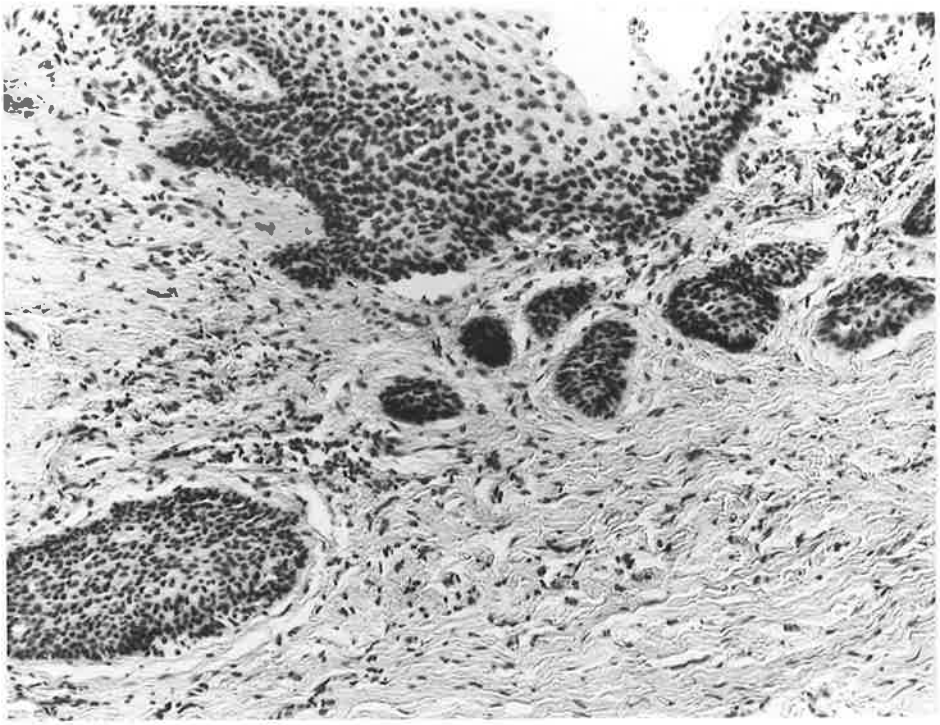


Figure 33.

Fig. 32: Odontogenic Keratocyst.
A large squamous epithelial island can be seen in the capsular tissues. Adjacent to the epithelial island a similar structure (arrows) which appears to be undergoing cystic change can be observed.
H & E. Original magnification x100.

Fig. 33: Photomicrograph illustrating an area of mucosal tissue continguous with an odontogenic keratocyst.
Note the epithelial islands subjacent to the mucosal epithelium.
H & E. Original magnification x100.

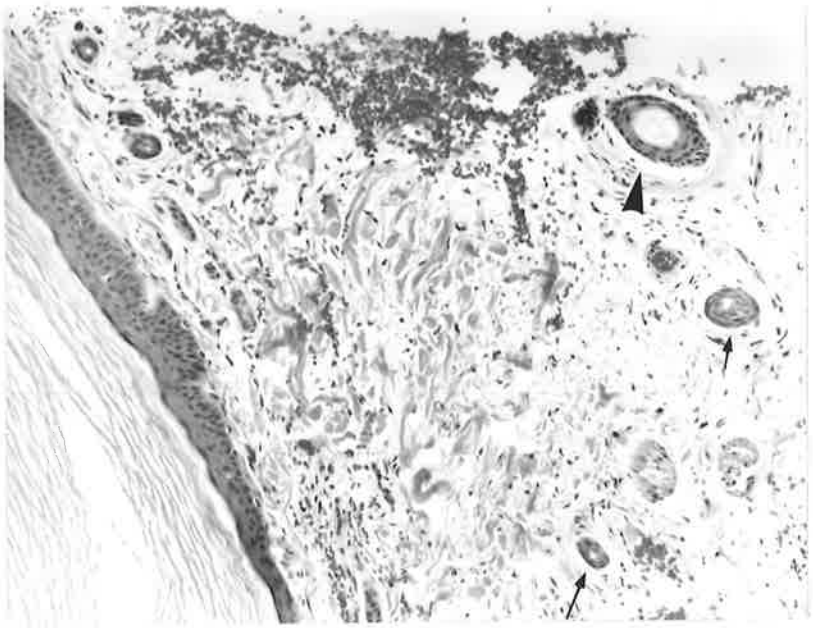


Figure 34.

Fig. 34: Epidermoid cyst.

Portion of an epidermoid cyst exhibiting the presence of a small microcyst (arrow) and small epithelial island-like structure (small arrows) in the capsular tissue.

H & E, Original magnification x100.

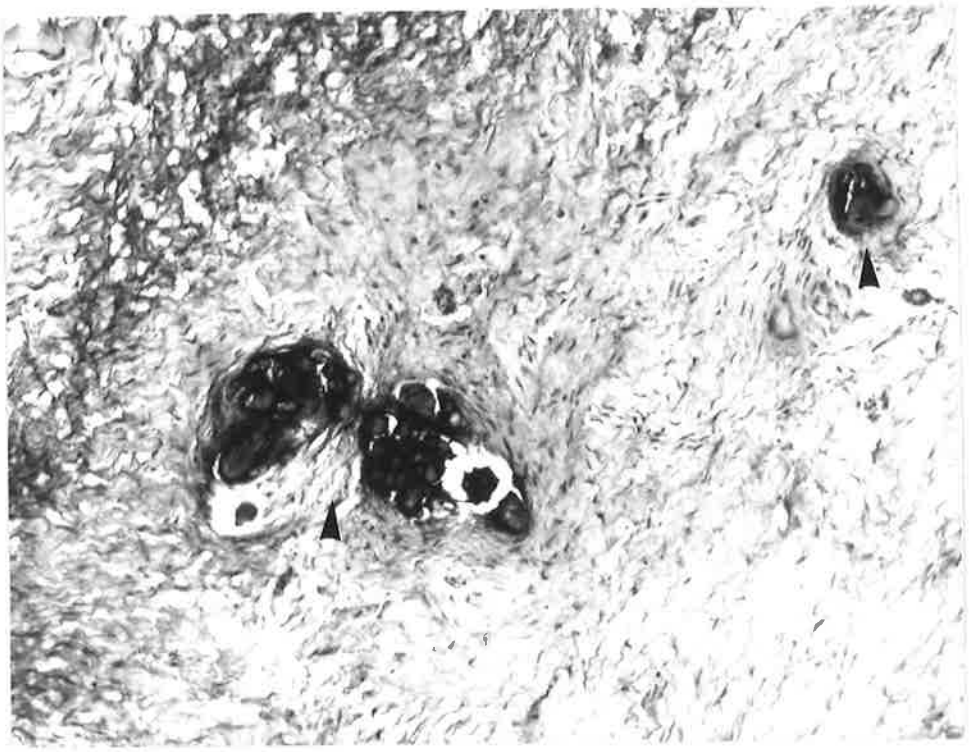


Figure 35.

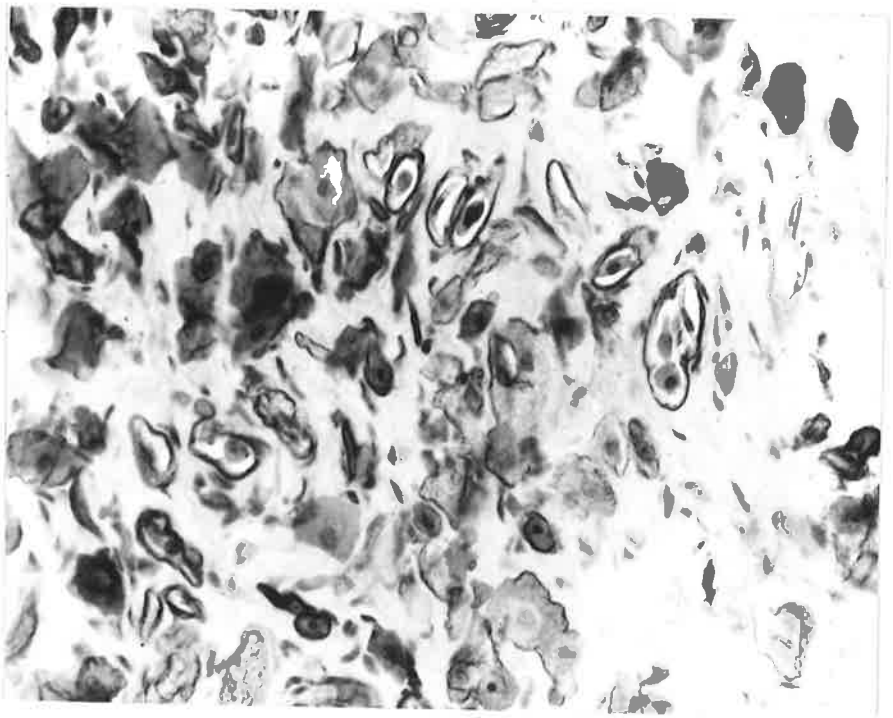


Figure 36.

Fig. 35: Odontogenic Keratocyst.
Globular dystrophic calcifications (arrows) can be seen in the capsular tissues.
H & E. Original magnification x100.

Fig. 36: Odontogenic Keratocyst.
Photomicrograph demonstrating apparently calcified cells in the capsular tissues. This form of calcification was only observed in one specimen.
H & E. Original magnification x250.

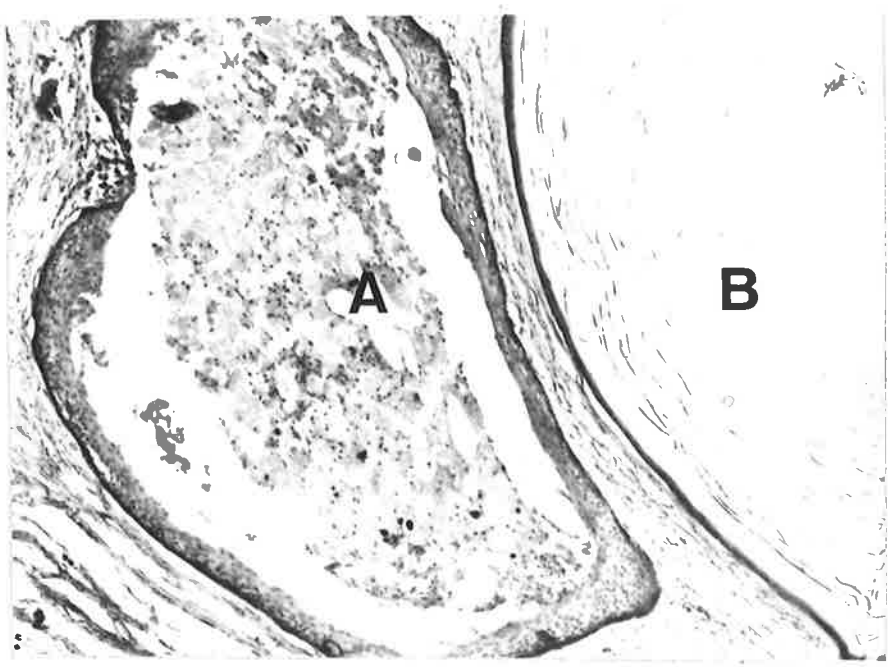


Figure 37.

Fig. 37: Odontogenic Keratocyst.

Portions of two relatively large microcysts (A and B) can be seen. The microcyst on the right is a mature, keratin filled cyst. The microcyst on the left contains degenerate epithelial cell debris and appears to be in a stage of cyst genesis.

H & E. Original magnification x100.

COMPARISON OF SELECTED HISTOLOGIC AND CLINICAL PARAMETERS

In an attempt to determine whether or not certain clinical and histologic features of the three cyst types examined exhibited significant inter-relationships appropriate data from the three groups of lesions was tablulated and analyzed.

The data obtained was originally subjected to chi-square analysis. However, because the frequency of a number of parameters could not be determined for the total samples and because as can be seen in the Tables, some frequency figures were small, it was decided that the chi-square analysis data could be misleading. In addition the percentage frequency figures obtained for some parameters were so obvious as to make chi-square analysis inappropriate. For these reasons and on the basis of statistical advice received it was considered more appropriate for the purposes of this study to tabulate the available comparative data and attempt to determine trends based on an analysis of percentage figures alone rather than chi-square analysis.

The cyst parameters chosen for analysis were selected on the basis of subjective observations made during the histological assessment of the material. The parameters were chosen for comparison because of the current interest which exists in the literature regarding these factors. For example the results of the histologic survey of the odontogenic keratocysts in this study suggested a close association between microcysts and cell rests with regard to their occurrence and association with one another within cyst capsules.

CYST SIZE VERSUS EPITHELIAL REGULARITY (TABLE I)

a. Odontogenic Keratocysts

Regular epithelium was observed in eight (38%) small odontogenic keratocysts while seven (18%) large cysts possessed regular epithelium. Irregular epithelium was observed in 13 (62%) small cysts while 33 (82%) large odontogenic keratocysts exhibited the presence of an irregular epithelium.

b. Epidermoid cysts

Regular epithelium was observed in 22 (65%) of the small epidermoid cysts while four (33%) large epidermoid cysts possessed regular epithelium. Irregular epithelium was observed in 12 (35%) of the small epidermoid cysts while eight (67%) large epidermoid cysts possessed irregular epithelium.

c. Cholesteatomas

Regular epithelium was observed in 15 (75%) of the small cholesteatomas while three (75%) of the large lesions exhibited the presence of a regular epithelium. Irregular epithelium was observed in five (25%) of the small cholesteatomas while one (25%) of the large cholesteatomas possessed an irregular epithelium.

CYST SIZE VERSUS SEPARATION OF EPITHELIUM FROM THE CAPSULE (TABLE II)

a. Odontogenic Keratocysts

Separation of the epithelial cyst lining from the surrounding connective tissue capsule was observed in 13 (65%) small odontogenic keratocysts while 27 (66%) of the large lesions exhibited this phenomenon. Separation was not detected in seven (35%) of the small odontogenic keratocysts or in 14 (34%) of the large lesions.

b. Epidermoid cysts

Separation of the epithelial cyst lining from the surrounding connective tissue was observed in 24 (71%) small epidermoid cysts, while seven (58%) of the large epidermoid cysts exhibited separation. Separation was not detected in 10 (29%) small epidermoid cysts and in five (42%) of the large epidermoid cysts.

c. Cholesteatomas

Separation of the cyst lining epithelium from the surrounding connective tissue was observed in 17 (85%) small cholesteatomas while three (75%) of the large cysts exhibited separation. Separation was not detected in three (15%) of the small cholesteatomas or in one (25%) of the large lesions.

CYST SIZE VERSUS THE PRESENCE OF INFLAMMATORY CELLS IN THE CAPSULE (TABLE III)

a. Odontogenic Keratocysts

Inflammatory cells were observed in 18 (78%) small odontogenic keratocysts while 39 (97%) of the large lesions exhibited the presence of inflammatory cells within the capsule. An absence of inflammatory cells was observed in five (22%) of the small odontogenic keratocysts and in one (3%) of the large lesions.

b. Epidermoid cysts

Inflammatory cells were observed in 13 (38%) small epidermoid cysts and in 10 (83%) of the large epidermoid cysts. An absence of inflammatory cells was noted in 21 (62%) of the small lesions and in two (17%) of the large epidermoid cysts.

c. Cholesteatomas

Inflammatory cells were observed in nine (45%) small cholesteatomas and in three (75%) of the large cysts. An absence of inflammatory cells was observed in 11 (55%) small cholesteatomas and in one (25%) large cholesteatoma.

CYST SIZE VERSUS THE PRESENCE OF MICROCYSTS AND EPITHELIAL CELL RESTS (TABLE IV)

a. Odontogenic Keratocysts

The presence of microcysts and/or epithelial cell rests was observed in nine (45%) small odontogenic keratocysts and in 29 (71%) of the large lesions. Microcysts and epithelial cell rests were not detected in 11 (55%) of the small lesions or in 12 (29%) of the large cysts.

b. Epidermoid Cysts

The presence of microcysts and/or epithelial cell rests was noted in six (19%) small epidermoid cysts and in two (15%) of the large lesions. There was no evidence of microcysts and/or cell rests in 27 (82%) of the small epidermoid cysts or in 11 (85%) of the large lesions.

c. Cholesteatomas

The presence of microcysts and/or epithelial cell rests was noted in one (5%) small cholesteatoma and in two (50%) of the large lesions. There was no evidence of microcyst formation and/or cell rests in 19 (95%) small cholesteatomas or in two (50%) of the large cholesteatomas.

EPITHELIAL REGULARITY VERSUS THE PRESENCE OF INFLAMMATORY CELLS IN THE EPITHELIUM (TABLE V)

a. Odontogenic Keratocysts

The presence of inflammatory cells within the epithelium was noted in seven (33%) of the odontogenic keratocysts possessing a regular cyst lining epithelium. Inflammatory cells were detected in 53 (69%) of the cysts with irregular cyst lining epithelium epithelium. No evidence of inflammatory cell infiltration was found in 14 (67%) of the odontogenic keratocysts with regular epithelium or in 24 (31%) of the lesions with irregular epithelium.

b. Epidermoid cysts

The presence of inflammatory cells within the epithelium was noted in three (12%) of the epidermoid cysts with regular epithelium and in 12 (50%) of the epidermoid cysts with irregular epithelium. No evidence of inflammatory cell infiltration was found in 23 (88%) of the cysts with regular epithelium or in 12 (50%) of the lesions with irregular epithelium.

c. Cholesteatomas

The presence of inflammatory cells was observed in 11 (48%) of the cholesteatomas with regular epithelium and in six (86%) of the cholesteatomas with irregular epithelium. No evidence of inflammatory cell infiltration was found in 12 (52%) of the cholesteatomas with regular epithelium or in one (14%) of the cholesteatomas with an irregular epithelium.

EPITHELIAL REGULARITY VERSUS THE PRESENCE OF INFLAMMATORY CELLS IN THE CAPSULE (TABLE VI)

a. Odontogenic Keratocysts

The presence of an inflammatory cell infiltrate was noted in 12 (67%) of the odontogenic keratocysts with regular epithelium and in 71 (96%) of the cysts with irregular epithelium There was no evidence of an inflammatory infiltrate in six (33%) of the cysts with regular epithelium or in three (4%) of the odontogenic keratocysts with an irregular epithelium.

b. Epidermoid cysts

The presence of inflammatory cells in the capsular tissues was noted in nine (35%) of the epidermoid cysts with regular epithelium and in 16 (67%) of the lesions with an irregular cyst lining epithelium. There was no evidence of inflammatory cell infiltrates in the capsules of 17 (65%) of the epidermoid cysts with regular epithelium or in eight (33%) of the lesions with an irregular epithelium.

c. Cholesteatomas

The presence of inflammatory cells was observed in the capsules of 13 (57%) of the cholesteatomas with an irregular cyst lining epithelium. There was no evidence of inflammatory cells in the capsules of 10 (43%) of the cholesteatomas with regular epithelium or in two (29%) of the cholesteatomas with irregular epithelium.

EPITHELIAL SEPARATION VERSUS THE PRESENCE OF A HOMOGENOUS ZONE (TABLE VII)

a. Odontogenic Keratocysts

Separation of the cyst lining epithelium was observed in 45 (87%) of the cysts in which a homogenous zone was present and in

18 (50%) of cysts exhibiting an absence of a homogeneous zone. No evidence of separation was found in 17 (13%) of odontogenic keratocysts possessing a homogeneous zone or in 18 (50%) of the cysts devoid of a homogeneous zone.

b. Epidermoid cysts.

Cyst lining epithelium separation from the surrounding connective tissue was observed in 29 (91%) of the epidermoid cysts in which a homogeneous zone was present and in 12 (67%) of the cysts with an absence of a homogenous zone. No evidence of separation was found in three (9%) of the epidermoid cysts having a homogenous zone or in six (33%) of the cysts devoid of a homogenous zone.

c. Cholesteatomas.

Separation of the cyst lining epithelium from the connective tissue was observed in 18 (75%) of the cholesteatomas in which a homogeneous zone was present and in two (33%) of the cholesteatomas exhibiting the absence of a homogeneous zone. No evidence of separation was found in six (25%) of the cholesteatomas possessing a homogeneous zone or in four (67%) of the cholesteatomas devoid of a homogeneous zone.

EPITHELIAL BUDDING VERSUS THE PRESENCE OF MICROCYSTS (TABLE VIII)

a. Odontogenic Keratocysts.

Microcysts were found in the surrounding capsules of 12 (75%) of the odontogenic keratocysts in which the epithelium showed evidence of budding and in 28 (34%) of the odontogenic keratocysts exhibiting and absence of budding of the cyst lining epithelium. Microcysts were not found in four (25%) of the odontogenic keratocysts exhibiting

epithelial budding or in 54 (66%) of the cysts in which the epithelium did not show epithelial budding.

This feature was not assessed in relation to epidermoid cysts and cholesteatomas because of the small numbers of microcysts detected in these specimens.

EPITHELIAL BUDDING VERSUS THE PRESENCE OF CELL RESTS (TABLE IX)

a. Odontogenic Keratocysts.

Cell rests were found in the surrounding capsules of 13 (81%) of the cysts in which the epithelium showed evidence of budding and in 37 (44%) of the cysts which exhibited an absence of budding of the cyst lingin epithelium. No cell rests were found in 3 (19%) of the cysts exhibiting epithelial budding or in 45 (56%) of the cysts in which the cyst lining epithelium exhibited an absence of budding.

This feature was not assessed in relation to epidermoid cysts or cholesteatomas because of the small number of cell rests detected in the specimens.

INFLAMMATORY CELLS IN THE EPITHELIUM VERSUS THE PRESENCE OR ABSENCE OF INFLAMMATORY CELLS IN THE CAPSULE (TABLE X)

a. Odontogenic Keratocysts.

Inflammatory cells in the epithelium were observed in 61 (73%) of the odontogenic keratocysts in which inflammatory cells were also detected in the capsule. No specimen exhibited the presence of inflammatory cells in the epithelium without the presence of inflammatory cells in the capsule. In 22 (27%) of the specimens inflammatory cells in the capsule were detected in the absence of an inflammatory

cell infiltrate within the epithelium and in 15 (100%) no evidence of inflammatory cells were found in either the epithelium or capsule.

b. Epidermoid cysts.

Inflammatory cells within the cyst lining epithelium were observed in 13 (50%) of the epidermoid cysts in which inflammatory cells were detected in the capsular tissues. No specimen exhibited the presence of inflammatory cells in the cyst lining epithelium without the associated presence of inflammatory cells in the capsular tissues. In 13 (50%) of specimens inflmmatory cells in the capsule were detected in the absence of inflammatory cells within the epithelium and in 24 (100%) there was no evidence of inflammatory cells in either the epithelium or capsule.

c. Cholesteatomas.

Inflammatory cells in the epithelium were noted in 14 (78%) of the cholesteatomas in which inflammatory cells were also detected in the capsule. No specimens exhibited the presence of inflammatory cells within the epithelium without the presence of inflammatory cells in the capsule. In four specimens (22%) inflammatory cells in the capsule were detected in the absence of inflammatory cells in the epithelium and in 12 (100%) of specimens no evidence of inflammatory cells could be detected in either the epithelium or capsule.

PRESENCE OR ABSENCE OF MICROCYSTS VERSUS THE PRESENCE OR ABSENCE OF EPITHELIAL CELL RESTS (TABLE XI)

a. Odontogenic Keratocysts.

Microcysts were detected in 39 (80%) of the odontogenic keratocysts in which epithelial cell rests were also observed.

Microcysts were found in only one (2%) cyst which exhibited an absence of cell rests. In 10 (29%) of specimens in which epithelial cell rests were detected no microcysts were found. In 48 (98%) specimens epithelial cell rests and microcysts were both absent.

This feature was not assessed in relation to epidermoid cysts and cholesteatomas because of the small numbers of cell rests and microcysts.

TABLE I

Table I: Comparison of cyst size versus epithelial regularity for odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratocysts

Cyst Size	Epithelial Regularity		
	Regular	Irregular	Total
small	8 (38%)	13 (62%)	21
large	7 (18%)	33 (82%)	40
	15	46	61

b. Epidermoid Cysts

	Regular	Irregular	Total
small	22 (65%)	12 (35%)	34
large	4 (33%)	8 (67%)	12
	26	20	46

c. Cholesteatomas

	Regular	Irregular	Total
small	15 (75%)	5 (25%)	20
large	3 (75%)	1 (25%)	4
	18	6	24

TABLE II

Table II: Comparison of cyst size versus epithelial cyst lining separation from capsular tissues for odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratosysts

Cyst Size	Separation		
	Separation	No Separation	Total
small	13 (65%)	7 (35%)	20
large	27 (66%)	14 (34%)	41
	40	21	61

b. Epidermoid Cysts

	Separation	No Separation	Total
small	24 (71%)	10 (29%)	34
large	7 (58%)	5 (42%)	12
	31	15	46

c. Cholesteatomas

	Separation	No Separation	Total
small	17 (85%)	3 (15%)	20
large	3 (75%)	1 (25%)	4
	20	4	24

TABLE III

Table III: Comparison of cyst size versus the presence or absence of inflammatory cells within the capsular tissues of odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratocysts

Cyst Size	Capsular Inflammation		
	Presence	Absence	Total
small	18 (78%)	5 (22%)	23
large	39 (97%)	1 (3%)	40
	57	6	63

b. Epidermoid Cysts

	Presence	Absence	Total
small	13 (38%)	21 (63%)	34
large	10 (83%)	2 (17%)	12
	23	23	46

c. Cholesteatomas

	Presence	Absence	Total
small	9 (45%)	11 (55%)	20
large	3 (75%)	1 (25%)	4
	12	12	24

TABLE IV

Table IV: Comparison of cyst size versus the presence or absence of microcysts and/or cell rests in odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratocysts

Cyst Size	Cell rests and/or Microcysts		
	Presence	Absence	Total
small	9 (45%)	11 (55%)	20
large	29 (71%)	12 (29%)	41
	38	23	61

b. Epidermoid Cysts

	Presence	Absence	Total
small	6 (18%)	27 (82%)	33
large	2 (15%)	11 (85%)	13
	8	38	46

c. Cholesteatomas

	Presence	Absence	Total
small	1 (5%)	19 (95%)	20
large	2 (50%)	2 (50%)	4
	3	21	24

TABLE V

Table V: Comparison of epithelial cyst lining regularity with the presence or absence of inflammatory cells within the epithelium in odontogenic keratocysts, epidermoid cysts,and cholesteatomas.

a. Odontogenic Keratocysts

Epithelial Regularity	Inflammatory Cells		
	Presence	Absence	Total
regular	7 (33%)	14 (67%)	21
irregular	53 (69%)	24 (31%)	77
	60	38	98

b. Epidermoid Cysts

	Presence	Absence	Total
regular	3 (12%)	23 (88%)	26
irregular	12 (50%)	12 (50%)	24
	15	35	50

c. Cholesteatomas

	Presence	Absence	Total
regular	11 (48%)	12 (52%)	23
irregular	6 (86%)	1 (14%)	7
	17	13	30

Table VI: Comparison of epithelial cyst lining regularity with the presence or absence of inflammatory cells in the capsule of odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratocysts

Epithelial Regularity	Capsular Inflammation		
	Presence	Absence	Total
regular	12 (67%)	6 (33%)	18
irregular	71 (96%)	3 (4%)	74
	83	9	92

b. Epidermoid Cysts

	Presence	Absence	Total
regular	9 (35%)	17 (65%)	26
irregular	16 (67%)	8 (33%)	50
	25	25	76

c. Cholesteatomas

	Presence	Absence	Total
regular	13 (57%)	10 (43%)	23
irregular	5 (71%)	2 (29%)	7
	18	12	30

TABLE VII

Table VII: Comparison of epithelial cyst lining separation from capsular tissues with the presence or absence of a homogeneous zone in odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratocysts

Separation	Homogeneous Zone		
	Presence	Absence	Total
Yes	45 (87%)	17 (13%)	62
No	18 (50%)	18 (50%)	36
	63	35	98

b. Epidermoid Cysts

	Presence	Absence	Total
Yes	29 (91%)	3 (9%)	32
No	12 (67%)	6 (33%)	18
	41	9	50

c. Cholesteatomas

	Presence	Absence	Total
Yes	18 (75%)	6 (25%)	24
No	2 (33%)	4 (67%)	6
	20	10	30

TABLE VIII

Table VIII: Comparison of the presence or absence of epithelial budding with the presence or absence of microcysts in the capsular tissues of odontogenic keratocysts.

a. Odontogenic Keratocysts

Epithelial Budding	Microcysts		
	Presence	Absence	Total
presence	12 (75%)	4 (25%)	16
absence	28 (34%)	54 (66%)	82
	40	58	98

TABLE IX

Table IX: Comparison of the presence or absence of epithelial budding with the presence or absence of cell rests in the capsular tissue.

a. Odontogenic Keratocysts

Epithelial Budding	Cell Rests		
	Presence	Absence	Total
presence	13 (81%)	3 (19%)	16
absence	36 (44%)	46 (56%)	82
	49	49	98

TABLE X

Table X: Comparison of the presence or absence of inflammatory cells in the epithelium with the presence or absence of inflammatory cells in the capsular tissue of odontogenic keratocysts, epidermoid cysts and cholesteatomas.

a. Odontogenic Keratocysts

Capsular Inflammation	Inflammatory cells in the epithelium		
	Presence	Absence	Total
presence	61 (73%)	22 (27%)	83
absence	0 (0%)	15 (100%)	15
	61	37	98

b. Epidermoid cysts

	Presence	Absence	Total
presence	13 (50%)	13 (50%)	26
absence	0 (0%)	24 (100%)	24
	13	37	50

c. Cholesteatomas

	Presence	Absence	Total
presence	14 (78%)	4 (22%)	18
absence	0 (0%)	12 (100%)	12
	14	16	30

TABLE XI

Table XI: Comparison of the presence or absence of cell rests with the presence or absence of microcysts in the capsular tissue of odontogenic keratocysts.

a. Odontogenic Keratocysts

Cell Rests	Microcysts		
	Presence	Absence	Total
presence	39 (80%)	10 (20%)	49
absence	1 (2%)	48 (98%)	49
	40	58	98

DISCUSSION

CLINICAL FEATURES

The age and sex distribution and site of occurrence of odontogenic keratocysts analyzed in this study show close agreement with the findings reported by others (Pindborg and Hanson 1963, Soskolne and Shear 1967, Toller 1967, Browne 1973, Radden and Reade 1973b, Brannon 1976).

The present study confirms the widely known site predeliction of the odontogenic keratocyst for the mandible in particular the posterior mandible. Thirty-three percent of all odontogenic keratocysts analyzed in the present study occurred in the mandibular third molar/ramus area, while 77% of the total sample occurred in the mandible. Analysis of the distribution data for the odontogenic keratocysts occurring in sites outside the third molar/ramus area of the mandible did not reveal any particular site distribution pattern a finding similar to that of Radden and Reade (1973b). Although Browne (1970) and Hodgkinson et al (1978) have indicated that odontogenic keratocysts may preferentially occur in the posterior and anterior maxilla respectively it is felt that such findings reflect inherent variables for example, sample size, actual cyst size and method of site distribution analysis rather than a definite trend.

Analysis of the age data available on the cysts examined in the present study shows peaks in the second and third decades similar to that reported by Browne 1871, Payne 1972, Shear 1976). However relatively high peaks were also observed in the fourth and fifth decades. Toller (1967) and Hodgkinson et al (1978) have also reported a higher incidence of odontogenic keratocysts in older range patients. Browne (1970)

considered that the available age distribution data on odontogenic keratocysts supports the hypothesis that these lesions are of developmental origin. Whilst it is accepted that there is no evidence to refute this hypothesis it is felt that odontogenic keratocyst age data is not necessarily an appropriate parameter to employ in support of a developmental origin hypothesis for odontogenic keratocysts. A number of variables for example, the presence or absence of signs or symptoms at the time of diagnosis and access to diagnostic facilities must be factors associated with the initial detection of odontogenic keratocysts. Accordingly age data will reflect these variables.

The age, sex and site distribution of epidermoid cysts and cholesteatomas reported here is similar to that reported by other investigators (Love and Montgomery 1943, Friedmann 1974). Of interest is the finding of similarity between the age and sex distribution data of odontogenic keratocysts, epidermoid cysts and cholesteatomas (Fig.s. 1,2 and 3). The significance of this observation is unknown although it is tempting to postulate that the similarity reflects the pathogenesis of these lesions.

HISTOLOGIC FEATURES

The histologic features of the three cysts types studied in this investigation are essentially similar to those reported by others. Thus the odontogenic keratocysts examined exhibited the general histologic features widely attributed to this cyst type (Shear 1960, Pindborg and Hansen 1963, Browne 1971, Radden and Reade 1973b, Brannon 1977). Similarly the epidermoid cysts and cholesteatomas investigated revealed general histologic characteristics essentially similar to those described by others (McGavran and Binnington 1966, Friedmann 1974).

Detailed analysis of the histologic results reported in this study does however reveal that a number of the parameters usually employed in descriptions of these cyst types in particular the odontogenic keratocyst show considerable variation.

A considerable proportion (68%) of odontogenic keratocysts examined in this study exhibited the presence of an irregular cyst lining epithelium. Previous reports of this lesion have emphasised theregularity of odontogenic keratocyst epithelium (Shear 1960 and 1976, Browne 1971) although it is recognised that the presence of capsular inflammation can result in alteration of odontogenic keratocyst lining epithelium morphology. This alteration is characterised by thickening, rete peg formation and loss of keratinization (Browne 1971, W.H.O. 1971). A comparison of odontogenic keratocyst epithelium regularity with parameters such as size and the presence of capsular inflammation and inflammatory cells within the epithelium carried out in the present investigation revealed data (Tables V & VI) which supports the view that variations in odontogenic keratocyst epithelium regularity are related to features such as the presence or absence of capsular inflammation (Browne 1971). A similar trend is evident for epidermoid cysts and cholesteatomas (Tables V & VI) Lever and Schaumberg-Lever (1975) record the association of inflammation in the epithelial cyst lining proliferation in epidermoid cysts.

Why such a high proportion of the odontogenic keratocysts examined revealed the presence of inflammatory cells particularly in capsular tissues is puzzling. Shear (1960) reports that inflammatory cells are infrequently found in odontogenic keratocysts.

However a number of surveys of this lesion record the finding of inflammation (Browne 1971, Radden and Reade 1973b, Brannon 1977) thus indicating that inflammation in odontogenic keratocysts is not perhaps as infrequent as is generally held. The presence of inflammation in odontogenic keratocyst capsules is generally regarded as being a consequence of infection (Soskolne and Shear 1967, Browne 1971, Radden and Reade 1973b). Analysis of the severity of inflammation and its distribution within the odontogenic keratocyst capsules examined in the present study did not reveal any new information regarding the cause of inflammation found in odontogenic keratocysts. This study does, however, indicate that larger cysts (that is cysts greater than 1cm in diameter) tend to exhibit capsular inflammation more frequently than do small cysts (98% vs. 78% respectively) (Table III). In addition, as mentioned previously the presence of capsular inflammation appears to correlate well with the presence of inflammatory cells within the epithelium (Table X). The latter parameter in turn appears to correlate with the observed irregularities in odontogenic keratocyst lining epithelia (Table V). Similar patterns appeared to be evident for epidermoid cysts and cholesteatomas.

A point of clinical significance which arises as a result of the findings regarding the presence of inflammation in a relatively high proportion of the odontogenic keratocysts examined concerns the question of luminal contents of such cysts. Electrophoretic analysis of odontogenic contents has been proposed as a useful clinical diagnostic tool (Toller 1970a, Browne 1976). Odontogenic keratocysts contents were not analyzed in the present investigation. However on the basis of the findings regarding the relatively high

frequency of inflammatory change in the capsule and adjacent epithelium it can be hypothesised that inflammation in such cysts would alter the electrophoretic pattern obtained from the analysis of cyst fluid thus possibly misleading clinicians and giving rise to erroneous pre-operative diagnosis.

Oedema and vacuolization of the prickle cell layer of the cyst lining epithelium of odontogenic keratocysts has been recorded by Pindborg and Hanson (1963) and Shear (1976) as being a relatively characteristic feature of this lesion. Both of these histologic features were noted in the odontogenic keratocysts, epidermoid cysts and cholesteatomas surveyed in the present study. However, the percentage frequencies in all three cyst types were relatively low. The reasons for the presence of intercellular and intracellular oedema of the prickle cell layer of the epithelium of odontogenic keratocysts is uncertain. Whilst it is not unreasonable to suggest that epithelial oedema is related to the presence or absence of inflammation in the cyst wall the figure obtained in this study indicate that the presence of inflammatory cells in the capsule and the epithelium does not correlate well with the presence of oedema and vacuolisation. While inflammation may be associated with the portion of instances of oedema and vacuolisation of the epithelium other causative factors are possibly involved.

A histologic feature of odontogenic keratocysts which has been stressed by previous investigators concerns the morphology of the basal layer of the cyst lining epithelium. Shear (1960) has pointed out that the basal layer of the epithelium in odontogenic keratocysts is characterised by its regular columnar/cuboidal cell morphology with the nuclei orientated away from the basement membrane. This statement

has been accepted by many investigators. In the present study columnar cells were found in only 5% of the odontogenic keratocysts and the orientation of the nuclei away from the basement membrane was found in only 11% of lesions. These findings suggest that the columnar basal cell having a nucleus orientated away from the basement membrane is not a characteristic feature of odontogenic keratocyst lining epithelium. It is considered that the attention given to this feature in histologic descriptions of odontogenic keratocysts is misleading and confusing. This opinion would appear to be supported in the findings of a recent study by Brannon (1977).

Columnar basal cells with polarized nuclei were also observed in a proportion of epidermoid cysts and cholesteatomas examined in the present study. However, like the odontogenic keratocyst sample the predominant basal cell morphology observed in the epidermoid cysts and cholesteatomas was found to be either cuboidal or mixed in nature.

Keratinization patterns in the epithelium of odontogenic keratocysts are known to vary. Parakeratinization is generally regarded as being the predominant keratin type found in odontogenic keratocysts (Browne 1971, Shear 1976). The results of this study support this general view. In the present study approximately half of the odontogenic keratocysts exhibited parakeratinization of the entire epithelial cyst lining. It is perhaps worth noting however that 44% of cysts exhibited the presence of a mixed orthokeratinization/ parakeratinization pattern.

The predominant keratinization pattern found in epidermoid cysts was that of orthokeratinisation. However, it is interesting to note that a number (32%) of epidermoid cysts did exhibit a predominatly mixed keratinization pattern. In the sample of cholesteatomas studied approximately 62% of the sample demonstrated a mixed keratinization pattern with only 27% of the cysts exhibiting a predominant orthokeratin pattern. Cholesteatomas thus appeared to exhibit a tendency towards a less characteristic single keratin type than do odontogenic keratocysts and epidermoid cysts. Cholesteatomas however do appear to preferentially express an epidermoid rather than a mucosal type of keratinization potential. This potential possibly reflects the presumed histogenesis of the majority of cholesteatomas from what is essentially mature epidermoid type epithelium. The histogenic origins of the three cyst types are possibly also reflected in the data obtained with respect to the presence of keratohyalin granules in the cyst lining epithelia. Keratohyalin granules were noted in 23% of odontogenic keratocysts, 92% of epidermoid cysts and 90% of cholesteatomas.

Discontinuity of the keratin layer was noted in 63% of odontogenic keratocysts, 40% of cholesteatomas and 12% of epidermoid cysts. The exact reason for the discontinuity cannot be explained. Several investigators (Shear 1960, Browne, 1971, Brannon 1977) have related the absence of keratin in odontogenic keratocysts to the presence of capsular and epithelial inflammation. The results of the present study tend to support this view. However analysis of the data in the present investigation also indicates a close correlation between epithelial discontinuities and the presence of intraepithelial inflammatory cells rather than the presence of capsular inflammation alone.

Epithelial budding, similar to that reported by Payne (1972) and Bramley (1974) was found in all three cyst types examined. The incidence of epithelial budding however, was low. The signficance of epithelial budding is unknown (Bramley 1974). It has been suggested (Payne 1972) that epithelial budding may be related to odontogenic keratocyst recurrence and multiplicity. The reason for the formation of epithelial buds in association with the cyst linings of odontogenic keratocysts is likewise unknown. In the present study there did not appear to be any correlation between the presence of epithelial budding and the presence of inflammation thus tending to negate the possibility that basal cell budding represents a proliferative response of the epithelium to inflammatory irritation. Relative frequency figures for the presence of epithelial cell rests and microcysts in the capsules of the odontogenic keratocysts similarly did not appear to correlate well with the figures obtained for epithelial budding. This apparent lack of correlation between these two parameters indicates that epithelial budding is not a likely factor involved in the genesis of epithelial cell rests and microcysts in the capsular tissues.

The presence of epithelial cell rests and microcysts in the capsules of odontogenic keratocysts has been noted by several investigators (Soskolne and Shear 1967, Browne 1971, Brannon 1977). Epithelial cell rests and microcysts were observed in 47% and 43% respectively of the odontogenic keratocysts examined in this investigation. These figures are higher than those reported by Browne (1971) and Brannon (1977). Cell rests and microcysts were also observed in the epidermoid cysts and cholesteatomas but their respective frequencies were very low. Cell rests and microcysts are not generally mentioned in histologic descriptions of epidermoid cysts

and cholesteatomas. The significance of the presence of cell rests and microcysts is thus difficult to comment upon especially in view of their low frequency. In contrast cell rests and microcysts in odontogenic keratocysts, have, as indicated previously, received considerable discussion in the literature. The presence of cell rests and microcysts has been proposed as a factor responsible for odontogenic keratocyst recurrence (Fickling 1965, Shear 1976). The presence of cell rests in the capsular tissues of odontogenic keratocysts has also been construed as evidence that odontogenic keratocysts derive from odontogenic tissues (Soskolne and Shear 1967). Whether these hypotheses have a basis in fact remains to be finally proven.

The genesis of microcysts in the walls of odontogenic keratocysts is generally thought to be due to cystic transformation of epithelial cell rests derived from odontogenic epithelium (Soskolne and Shear 1976) or oral mucosa (Stoelinga 1971, Stoelinga and Peters 1973). Payne (1972) has also suggested that microcysts could derive from epithelial cell rests formed as a result of budding of the cyst lining epithelium itself. Microcysts and epithelial cell rests were found with approximately equal frequency (43% and 47% respectively) in the odontogenic keratocysts examined. With the exception of one case both entities occurred together in the same specimen thus supporting the view that microcysts originate from epithelial cell rests. No new information regarding the origin of the epithelial cell rests themselves was obtained in the present study. However in a proportion of cases examined both microcysts and cell rests were found close to oral mucosal epithelium thus lending support to the views of Stoelinga (1971) and Stoelinga and Peters (1973) regarding the oral mucosal origin of some epithelial cell rests and microcysts

found in association with the jaws. Aside from the biologic implications that such cell rests derived from the oral mucosa may proliferate and give rise to primary or recurrent odontogenic keratocysts there is also the clinical implication that overlying mucosa should be excised when removing odontogenic keratocysts particularly in the third molar and ramus areas of the mandible (Stoelinga 1971, Bramley 1974).

Separation of odontogenic keratocyst lining epithelium from the subjacent capsular tissues has been recorded by several investigators (Browne 1971, Donoff et al 1972a, Wilson 1978). The finding of epithelial separation in 61% of odontogenic keratocysts examined confirms the observation made by others. An interesting finding arising from the present study is however, that similar frequency figures were recorded for this phenomenon in relation to epidermoid cysts (62%) and cholesteatomas (87%), thus indicating that separation of cyst lining epithelium is not a unique or characteristic feature of the odontogenic keratocyst alone. Separation of the epithelial lining of epidermoid cysts and cholesteatomas from the capsular tissues is not recorded in the relevant literature.

At a clinical level separation of odontogenic keratocyst lining epithelium from the capsular tissues has been related to the phenomenon of cyst recurrence (Fickling 1965). The mechanisms of cyst lining epithelial separation however, remain unknown (Wilson 1978) although Browne (1971) has suggested that an inherently defective basement membrane may be responsible for the separation and Donoff et al (1972a) have suggested possible mechanisms of separation related to enzymatic activity. In the present study the phenomen of epithelial separation

was compared with parameters such as cyst size and the presence of absence of a homogeneous zone. The results of this comparison (Table II and Table VII) did not demonstrate an unequivocal relationship between these various parameters in any of the cyst types studied. Further studies aimed at a more detailed comparative investigation of the phenomenon of cyst lining epithelium separation in the three cyst types would be of interest and perhaps provide further data regarding the phenomenon of separation and perhaps also further insight into the biologic and histologic similarity between the three apparently distinct lesions.

It has been stated (Toller 1967) that odontogenic keratocysts may be more likely than other odontogenic cysts to undergo malignant transformation. As pointed out by Browne and Gough (1972), however, there is little evidence to support this view. These investigators suggest instead that malignant transformation of odontogenic cyst lining epithelia is more likely to occur in association with keratin metaplasia occurring in normally non-keratinizing cysts. In the present study moderate to severe epithelial atypia was reported in one odontogenic keratocyst. The atypia was confined to a small localised area of the cyst lining epithelium. Epithelial atypia was not observed in the epidermoid cysts and cholesteatomas examined. Although neoplastic transformation and atypia of odontogenic keratocyst lining epithelia has been recorded (Byrd et al 1973, Radden and Reade 1973b, Shear 1976, Brannon 1977, Hodgkinson et al 1978) the small number of cases reported, do not support the view that odontogenic keratocyst lining epithelia have a greater tendency towards dysplastic change or true neoplastic transformation.

Previous histologic surveys of odontogenic keratocysts (Browne 1971, Brannon 1977) have recorded the presence of metaplastic epithelial cells associated with this cyst lining epithelia. Metaplasia of odontogenic keratocyst lining epithelium was not observed in any of the 98 cysts examined in the present investigation. Neither was it observed in the epidermoid cyst and cholesteatoma samples. Browne (1971) observed the phenomenon of mucous metaplasia in 3.7% of a sample of 136 odontogenic keratocysts. Browne (1971) further noted that this phenomenon was expressed to only a very insignificant degree in that only a few cells within the total epithelial cyst lining were of a mucous type. Given the apparent rarity of this phenomenon it is felt that little signficance can be attached to the presence of mucous metaplasia in the epithelium of odontogenic keratocysts.

Melanocytes were observed in 6% of the odontogenic keratocysts studied in the present investigation. Comparative figures for the epidermoid cyst and cholesteatoma samples were 38% and 7% respectively. The reported cases of melanocytes within odontogenic keratocyst lining epithelia (Browne 1971, Brannon 1977) have all occurred in cysts obtained from patients of Negro or West Indian descent. Race data was not available for the odontogenic keratocyst examined in the present study. The reported melanocyte incidence of 6% is higher than that reported by Browne (1971) and Brannon (1977). Whilst the figure of 6% could reflect an unknown race bias present in the sample of odontogenic keratocysts studied in this investigation it might also indicate that melanocytic pigmentation is not necessarily confined to lesions obtained from patients of non-Caucasian origin. In the case of epidermoid cysts melanocytic pigmentation of the epithelium

is reportedly more common in those cysts obtained from patients of Negroid origin (McGavaren and Binnington 1966). Once again the data relating to race was not obtainable with respect to the epidermoid cyst samples studied, however the finding that 38% of epidermoid cysts exhibited this phenomenon indicates that it is perhaps not necessarily a race related phenomenon. Interestingly only 7% of cholesteatomas exhibited the presence of melanocytic pigmentation and in this regard these lesions closely approximated the odontogenic keratocyst.

Calcified material of a non-osseous type was observed in 2% of the odontogenic keratocysts examined in the present investigation. The calcifications were confined to the capsular tissues. Morphologically the predominant type of material found was calcification of a dystrophic type. In one instance apparently calcified cellular tissue within the capsule was observed. The incidence of calcifications reported here is much lower than that reported by Browne (1971) and Brannon (1977). The reason for this discrepancy cannot be explained although it could be due in part to differences in methods of cyst sampling. The material in the present study was not consistently serially sectioned.

A most interesting finding arising from the present study is the apparent histologic similarity between odontogenic keratocysts, epidermoid cysts and cholesteatomas. This similarity is particularly evident with regard to certain parameters such as the overall morphology of the cyst lining epithelium, keratinization patterns and phenomena such as separation of the cyst lining epithelium. Considering the fact that each of these cyst types is a keratinizing cyst found in a

different anatomical sites it is felt that the apparent similarity warrants some discussion.

First the observed histologic similarity between odontogenic keratocysts, epidermoid cysts and cholesteatomas raises questions concerning the currently held view regarding the uniqueness of odontogenic keratocysts. Odontogenic keratocysts are histologically unique when compared to other forms of odontogenic cyst. However the results of the present study indicate that several of the basic histologic criteria normally applied to odontogenic keratocysts are not pathonogmonic of this lesion alone. Some epidermoid cysts especially those with mixed keratinization of the epithelial cyst lining may be similar histologically to a proportion of odontogenic keratocysts. Similarly cholesteatomas may resemble odontogenic keratocysts. This similarity is particularly apparent when cholesteatomas and odontogenic keratocysts having a mixed keratinization of the cyst lining epithelium and an epithelium 6-10 cells thick are compared. It is considered that without a clinical history related to the site of origin of some of the lesions examined in the present study distinction at the histologic level between the three cyst types is extremely difficult and in some cases impossible. The recognition and acceptance of the view that odontogenic keratocysts are perhaps not histologically unique could pave the way for further studies.

A second point arising from the apparent similarity between the three cyst types concerns the supposed pathogenesis of the various lesions. Current theory concerning the nature of odontogenic keratocysts is that they are developmental lesions which histogenically derive from dental lamina tissues in either a preformative tooth stage or a postformative tooth development stage (Soskolne and Shear 1967,

Toller 1967, Browne 1975). It is also held (Stoelinga and Peters 1973) that some odontogenic keratocysts may derive from cell rests originating from mature oral mucosal epithelium. Although there is some support for the suggestion that some epidermoid cysts (Ettinger and Manderson 1973) and cholesteatomas (Friedmann 1974) are of developmental origin, the majority of opinion is that these lesions derive from mature epidermoid type epithelium which proliferates in response to a variety of aetiologic stimuli particularly inflammation and trauma. Although the present study was primarily a histologic one the observed similarity between odontogenic keratocysts, cholesteatomas and to a lesser extent epidermoid cysts raises questions concerning our concept regarding the pathogenesis of these lesions and indicates a need for further comparative study.

SUMMARY

The clinical and histological features of 98 odontogenic keratocysts from the Department of Oral Pathology and Oral Surgery, the University of Adelaide, 50 epidermoid cysts and 30 cholesteatomas from the Institute of Medical and Veterinary Science of South Australia, were investigated in this study.

The results of the study, in general, support the findings of other investigators regarding the clinical and histologic features of the three cyst types studied. However, considerable variation particularly with regard to the regularity and thickness of odontogenic keratocyst lining epithelium, the morphology of basal epithelial cells and the presence of inflammation was observed. Similar histological variations were also noted in relation to epidermoid cysts and cholesteatomas. The significance of these features are discussed.

An interesting finding resulting from this investigation is the histological similarity between odontogenic keratocysts, epidermoid cysts and cholesteatomas. These histological similarities indicate a need for further comparative studies of these lesions.

HAEMATOXYLIN AND EOSIN

METHOD:

1) Sections to water,

2) Hillie/Mayer Haematoxylin, 5 mins.,

3) Blue in running water, 5 mins.,

4) Differentiate in 1% Hydrochloric acid in 70% Alcohol,

5) Blue in running water,

6) Eosin, 30 seconds,

7) Rinse in water,

8) Dehydrate, clear and mount.

RESULTS:

The various elements stain as follows:

Nuclei - blue

Keratin - red,

Collagen - rose/pink,

Other elements - various shades of red.

MODIFICATION OF MALLORY (Ayoub-Shklar)

METHOD:

1) Sections to distilled water,
2) Acid fuchsin solution, 3 mins.,
3) Direct to Aniline Blue - Orange G solution - 45 mins.,
4) 95% alcohol - 3 changes,
5) Dehydrate, clear and mount.

RESULTS:

Keratin - brilliant red.

Stratified squamous epithelium - grey.

Stratum spinosum - orange.

Connective tissue - deep blue.

Erythrocytes - deep red.

HAEMATOXYLIN - PHOLOXINE - ALCIAN BLUE - ORANGE G. DIFFERENTIAL.

Specific stain for prekeratin keratin and mucin.

METHOD:

1) Sections to water,
2) Mayer's Haemalum, 10 mins.,
3) Blue in running tap water,
4) Wash in distilled water,
5) 1% Phloxine B 3 mins. (or 0.5% phloxine in 0.5% calcium chloride for 5 mins.),
6) Wash in running tap water, distilled water,
7) 0.5% aqueous Alcian Blue, 5 mins. (Alcian blue in 0.5% Acetic Acid-Lison),
8) Wash in distilled water,
9) 0.5% Orange G in 2% Phosphotungstic Acid, 13 mins.,
10) Dehydrate quickly in 2 changes 95% alcohol (5 dips in each),
11) Dehydrate quickly in 2 changes Absolute alcohol (15 dips to differentiate),
12) Clear and mount.

RESULTS:

Collagen etc. (connective tissue) - turquoise,

Acid Mucopolysaccharides - turquoise blue,

Pre-keratin to keratin - orange to red,

Nuclei - orange to pale brown.

MASSON METHOD Foot Modification

TRICHROME STAIN

METHOD:

1) Sections to water,
2) Solution 1 freshly mixed before use, 6 mins.,
3) Differentiate in acid alcohol,
4) Wash well in running tap water,
5) Solution 2, 5 mins., rinse in water, acid pH
6) Solution 3, 1½ - 2 mins., rinse in water,
7) Solution 4, 5 mins., rinse in water,
8) Dehydrate, clear and mount.

RESULTS:

Nuclei and calcareous matter - blue black

Bone, cartilage, collagen, mucus - green,

Elastic fibres - port wine to red,

Myelin sheaths - golden yellow,

Keratinized epithelium, erythrocytes, fibrin - vermillion to orange,

Mature collagen - orange,

Neuroglia fibrils - pink,

Muscle - red,

Cytoplasm - rose red,

Zymogen granules - brilliant vermillion.

FLUORESCENT TECHNIQUE

METHOD:

1) Section to water,
2) 1:1.00 Rhodamine B - 3 mins.,
3) Dehydrate, clear and mount.

RESULTS:

Cytoplasm of epidermis and appendages - blue,

Nuclei of epithelial cells, appendages and leucocytes - pink,

Collagen - purple,

Keratin - bright orange - yellow,

Keratin in the lining of the selected primordial cyst appeared pink and desquamated keratin appeared blue. Sections were examined for fluorescence using Leitz equipment, with U.V. excitation filter and 510 barrier or secondary filter.

THE KREYBERG STAIN.

METHOD:

1) Take the sections to water,
2) Nucleic staining: Celestin Blue (filtered), 5 mins.,
   Rinse in H_2O,
   Mayer's Haemalum (filtered), 5 mins.,
   Rinse in H_2O,
3) Differentiate in acid alcohol,
4) Wash well in tap water,
5) Stain in 1% aqueous solution Erythrosin (filtered), 5 mins.,
6) Rinse quickly in water,
7) Differentiate quickly in 95% alcohol,
8) Rinse quickly in water,
9) Stain with Alcian Green for 30 mins. (filtered,
10) Rinse in water (pink colour),
11) Dehydrate quickly in 95% alcohol,
12) Stain with Ethanolic Saffron for a few seconds (MQ 5 mins.),
13) Rinse in 2 changes absolute alcohol,
14) Clear and mount.

Blue Kreyberg: Substitute Alcian Blue for Alcian Green (Lison) Stain, 5 mins.

RESULTS:

Nuclei - Deep blue,

Acid mucopolysaccharides - turquoise blue or green,

Connective tissue - yellow to orange,

Keratin - deep red,

Other elements - various shades of red.

MODIFICATION OF THE KREYBERG STAIN.

Staining method for keratin and mucin like substances

METHOD:

1) Bring the sections to water,
2) 1% Alcian Green in 1% acetic acid, 5 mins.,
3) Haematoxylin, 2 mins.,
4) Differentiate, and blue in running water,
5) 1% aqueous phloxine, 5 mins.,
6) Rinse in water,
7) Differentiate in 95% alcohol until no more colour washes out,
8) Rinse in water,
9) Counterstain with lissamine yellow, 30 seconds,
10) Dehydrate, clear and mount.

RESULT:

The various elements stain as follows:

Nuclei - Deep Blue,

Acid mucopolysaccharides - Green,

Connective tissue - Yellow to Lime,

Keratin - Bright Red,

Other elements - Various shades of red.

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