Cysts of the Oral and Maxillofacial Regions

Fourth edition

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This book is dedicated to the memory of Dr Robert J. (Bob) Gorlin

'Felix qui potuit rerum cognoscere causas'

Vergil, Georgics II, 490

Contents

Foreword

Cysts of the jaws and maxillofacial regions are not new lesions. There is evidence of cystic lesions in the jaws of humans and other animals in the distant past. Lesions of the jaws interpreted as cysts have been found in mummified specimens from the predynastic era (*c.*4500 BC) and from the 5th dynasty (*c.*2800 BC) in Egypt. Early descriptions of cystic lesions of the jaws were written by Aulus Cornelius Celsus (early part of 1st century), Pierre Fauchard (1690–1762) and John Hunter (1729–1793), among others.

From about 1850, papers on the nature and treatment of jaw cysts became more frequent. Attempts to understand the relationship between various morphological types of cyst led to classifications such as Paul Broca's classification of odontomas (1866) which included odontogenic tumours, cysts and malformations.

During the 20th century, a number of recognized treatises on cysts of the jaws were published, including the first three editions of the present book, and the first (1971) and second (1992) editions of *Histologic Typing of Odontogenic Tumours* issued by WHO, which included classification, definitions and histological descriptions of cysts of the jaws. However, since 1992 no updated classification or monographs on jaw cysts have been published. In the WHO classification of *Head and Neck Tumours* (1995), cysts were excluded, as they have been in all WHO classifications of tumours published since 2000.

For some years oral pathologists in particular have been looking forward to an updated book on the subject, so the appearance of the fourth edition of Professor Mervyn Shear's book on which Professor Paul Speight has become joint author is therefore highly appreciated. The book will be of particular interest to postgraduates and specialists in oral and maxillofacial pathology, general pathologists, oral and maxillofacial surgeons and radiologists, and undergraduate students of dentistry.

Both authors have worldwide reputations and are highly esteemed oral pathologists. Professor Shear has for many years been one of the foremost experts on the subject. He has been a member of all three expert groups established by WHO to classify odontogenic tumours and cysts. Professor J.J. Pindborg, who was head of the corresponding WHO International Reference Centre, often referred to Professor Shear as 'The Cyst Man'.

Professor Speight is a diagnostic histopathologist with special expertise in odontogenic and bone tumours of the jaws, salivary gland tumours and mucosal pathology. His main research interests are in the field of oral cancer with emphasis on mechanisms of infiltration and progression of oral carcinomas using, among other methods, immunocytochemistry, DNA transfection techniques, genetic markers and DNA ploidy analysis.

If you are looking for a comprehensive, detailed and updated presentation of our knowledge in the field of cysts of the oral and maxillofacial regions you could not find a better book.

Finn Prætorius

Preface to the Fourth Edition

There have been many changes to the fourth edition of this book, the first of which was published in 1976, 30 years ago. Professor Paul Speight, Head of the Department of Oral Pathology in the University of Sheffield, has joined Professor Mervyn Shear as a joint author. The book has a new publisher, Blackwell Publishing, Oxford, who have taken over responsibility for the title from Wright and Butterworth Heinemann. The title of the book has been modified to 'Cysts of the Oral and Maxillofacial Regions', which reflects its scope more accurately.

The format of the book has changed and the clinical photographs and photomicrographs are now in colour. The text of this edition has been lengthened considerably in line with the proliferation of new publications in this field, particularly the odontogenic keratocyst. This will be reflected in the current list of references, which has increased significantly. We have tried to keep this text as up-to-date as possible by including articles that have appeared well into 2006.

We have however, omitted the chapters on 'history' and on 'treatment'. The latter chapter by Professor Gordon Seward was well-received by reviewers of the 3rd edition, but the authors and publishers felt that this topic was now very well covered in specialist publications on oral surgery. We have instead added paragraphs on general principles of treatment at the end of each of the chapters.

As in the past, we have attempted to produce a text that will be useful to a range of professionals and also to undergraduate and postgraduate students as well as anyone doing research in this field. The clinical features, radiology, pathogenesis and histopathology of each of the cysts, are set out at the beginning of each chapter, and we believe that undergraduate and postgraduate students will find these useful in their studies and in their preparation for examinations.

This edition has been dedicated to the memory of Dr RJ (Bob) Gorlin who died on 29 August 2006. His contributions to oral pathology, particularly in human genetics, have been extraordinary. In the field of jaw cysts, his name is linked to the calcifying odontogenic cyst, eponymously known as the Gorlin cyst; for his work associating the odontogenic keratocyst with the naevoid basal cell carcinoma syndrome, often referred to as the Gorlin syndrome; and for his studies on the genetics of the syndrome.

Mervyn Shear
Cape Town
Paul Speight
Sheffield
October 2006

Preface to the Third Edition

Over the past 8 years since publication of the second edition of this book, the subject of jaw cysts and cysts of the soft tissues in and around the mouth has continued to evoke considerable interest among clinicians, pathologists and basic scientists, and numerous papers have been published on these topics. Advances in immunocytochemistry have provided the opportunity for studies on the epithelium of cyst linings in an attempt to clarify the pathogenesis of the many varieties and to improve the accuracy of microscopic diagnosis; while further immunological investigations have been undertaken to identify the changes which initiate the formation of radicular cysts in periapical granulomas, and into other aspects of cyst pathology. Basic research has also led to progress in the understanding of the mechanisms involved in the enlargement of cysts. A few new entities have been identified such as the mandibular infected buccal cyst, the glandular odontogenic cyst and AIDS-related bilateral lymphoepithelial cysts of the parotid glands; while our understanding of lesions such as the unicystic ameloblastoma, the botryoid odontogenic cyst and the postoperative maxillary cyst has been enhanced by careful clinicopathological research.

In order to do justice to all this recent work and to bring it to the attention of others in the field, I have added references to about 250 new papers. In preparing the book I have tried to make the work useful to undergraduate and postgraduate students, dentists, oral and general surgeons, radiologists, oral and general pathologists, and anyone doing research in the field. I trust that readers will not find it difficult to gain access to the information they seek.

In consultation with the publishers, Butterworth-Heinemann, it was decided to take the book out of the *Dental Practitioner Handbook* series, and to produce it in a new format. We have also invited the collaboration of Professor Gordon Seward, who kindly agreed to write a chapter on the treatment of cysts. His expert input will undoubtedly enhance the value of the book to those who treat these lesions.

As with past editions, I have received invaluable assistance from a number of people. I am greatly indebted to Professor Mario Altini, Head of the Department of Oral Pathology of the University of the Witwatersrand, for allowing me access to the material in the department, and to him and other members of his staff who were generous in assisting me with the preparation of material. Likewise, Dr Jos Hille, Head of the Department of Oral Pathology of the University of the Western Cape, was most helpful. Many other colleagues were also extremely kind in lending me good sections and good illustrations, and these have been acknowledged in the text.

M.S.
Johannesburg

Preface to the Second Edition

In the period since the first edition of this book, there have been many publications in the field. This has given me the opportunity of doing an extensive revision of the text by introducing the newer concepts and reassessing the older. Some 160 references have been added, not all of them published since the first edition. The numbers of jaw cysts from my own department which have been used in this edition, particularly for the clinical analyses, have been increased from 750 to 1345. Most of the diagrams have therefore been redrawn and the tables revised to include the new data. These additional cases were extracted from the departmental archives by Dr A. Rudick in preparation for his research dissertation leading to the degree of MSc (Dent), and it is a pleasure to acknowledge his contribution in this regard.

The classification used in the first edition has been modified slightly as a result of my experience using it in teaching undergraduate and postgraduate students.

The number of figures used has been increased by 24 and many of the original illustrations have been replaced. Colleagues have been most generous in allowing me to

use their clinical photographs and radiographs and this is greatly appreciated.

Members of staff and students in my Department have been extremely helpful in many ways and I should like to record my indebtedness to Mario Altini, Simon Bender, Mark Cohen, David Fleming, Chris Rachanis, Stevan Thompson, Archibald Scott, Christine Stewart and Lenah Free. Miss Ann Line typed the manuscript and checked the reference list with great skill and I am very grateful to her. Mrs Marlies Jansen of the Photographic Division of our School was of considerable assistance in reproducing illustrations.

M.S.
Johannesburg

Preface to the First Edition

Cysts of the jaws and mouth have been recognized as clinical problems for a long time. During the past few years, however, there have been a large number of publications on the subject, reflecting a great increase in interest in the causes, pathogenesis, behaviour, diagnosis and treatment of the various types of cyst.

This book was written in an attempt to record, in one volume, current views on these cysts. Clinical data, primarily from my own records, radiological features, discussion on pathogenesis, descriptions of the pathology and brief comments on treatment have been included for each variety. It is hoped that the work will be helpful to undergraduate and postgraduate students, general dental practitioners, surgeons, radiologists and pathologists.

A considerable proportion of this book was written during a sabbatical leave spent in the Department of Oral Pathology, Royal Dental College, Copenhagen, Denmark, and I am extremely grateful to Professor Jens Pindborg, Head of this Department, for so kindly allowing me access to his material and for letting me use some of it for this book. I should also like to record my gratitude to Denmark's National Bank for generously inviting my family and me to live in one of their flats in Nyhavn 18 during our stay in Copenhagen.

In the preparation of this book, I have been very greatly helped by colleagues who have kindly lent me clinical photographs and radiographs of their cases. I am particularly indebted to Professor John Lemmer for allowing me access to the records of the Division of Radiology in his Department of our School of Dentistry. It is a pleasure to acknowledge the very considerable assistance which I have received from members of my Department, especially Mario Altini, Archibald Scott, Janice Croft, Renee Goldstein, Lenah Free, Miriam Nadel and Barbara Marcus, as well as from Marlies Jansen in the Photographic Division of our School.

M.S.
Johannesburg

Acknowledgements

Caroline Connolly was the Commissioning Editor for Blackwell Publishing, Oxford, who took us through the discussions leading to the offer of a contract to publish the book. Her negotiating skills and sensitivity to the wishes of the authors as well as the requirements of the publishers were greatly appreciated. After her transfer to another position, her place was taken by Katrina Chandler, who has seen us through to publication. Our main contact with the publisher has been Amy Brown, senior editorial assistant, who has provided invaluable support, guidance and advice in the preparation of the manuscript and the accompanying illustrations. We are greatly indebted to her. Kate Gardner, the Production Editor, and Mirjana Misina, were responsible for all aspects of production of the book: copy editing, typesetting, proof reading and dealing with all the artwork. The authors are indebted to them for their meticulous attention to detail. An academic work of this kind is dependent on a close and harmonious relationship between authors and production staff, and it is a pleasure to recognise the partnership that we have enjoyed.

Our respected colleague and friend, Dr Finn Prætorius, very kindly agreed to write a foreword to the book and we are immensely grateful to him for doing so.

Professor Mario Altini, head of the Department of Oral Pathology in the University of the Witwatersrand, Johannesburg, has been supportive and encouraging, and has generously provided the authors with updated data on the material accessioned in his department since the previous edition in 1992. Likewise, Professor Jos Hille, Head of the Department of Oral Pathology in the University of the Western Cape, has been accommodating in many ways. We should like to thank both of them for their contribution to this edition.

Our colleagues in the Department of Oral Pathology, University of Sheffield have been very helpful in allowing us access to their files and photographs, especially Professor Chris Franklin and Dr Adam Jones who have provided data from their analyses of lesion incidence and Dr Geoffrey Craig for useful discussions on the paradental cysts and for giving free access to his archival material.

Other colleagues have responded generously to requests for use of clinical photographs and radiographs, and they have been acknowledged by name in the legends to the relevant figures. We very much appreciate their kind contributions.

Professor Finn Prætorius of the University of Copenhagen has been extremely obliging in discussions with him on the classification of odontogenic ghost cell lesions, a very complex and controversial subject, and we acknowledge with gratitude his generosity in allowing us to use his most recent classification of this group, as illustrated in Table 8.1.

We are indebted to Elsevier Publishers and Professor Crispian Scully, the editor of *Oral Oncology* for permission to reuse text material from Shear M. 'The aggressive nature of the odontogenic keratocyst. Is it a benign neoplasm?' Parts 2 and 3 in *Oral Oncology*, vol. 38, 323–31 and 407–15.

We should like to acknowledge with sincere thanks the assistance of Renee Reagon, Information Librarian, Clive Sargeant, Dental Faculty Librarian, University of the Western Cape and Lew Fryer of Blackwell Publishing who have been exceptionally helpful in accessing journal articles.

1

Classification and Frequency of Cysts of the Oral and Maxillofacial Tissues

Kramer (1974) has defined a cyst as 'a pathological cavity having fluid, semifluid or gaseous contents and which is not created by the accumulation of pus'. Most cysts, but not all, are lined by epithelium. Cysts of the oral and maxillofacial tissues that are not lined by epithelium are the mucous extravasation cyst of the salivary glands, the aneurysmal bone cyst and the solitary bone cyst. Despite these examples, most pathologists prefer to describe those pathological cavities not lined by epithelium as 'pseudocysts'. Reichart and Philipsen (2004) prefer to describe these as 'cavities' rather than cysts; hence, for example, 'aneurysmal bone cavity'. The classification proposed in this book divides the cysts of the oral regions into those lined by epithelium, and those that are not. Epithelial-lined cystic odontogenic neoplasms, such as the unicystic ameloblastoma, are not included in this edition.

Cysts historically named globulomaxillary, median palatine and median mandibular cysts have been convincingly shown by numbers of studies to be other odontogenic or developmental cysts. This terminology is no longer used in diagnostic oral pathology departments in most parts of the world and the authors of this edition have decided to exclude it from the classification.

This is **a** classification of jaw cysts, not **the** classification. Many other classifications have been published and may well be perfectly satisfactory and readers are encouraged to use any classification they find valuable as an aid to memory and understanding.

In this edition of the book, the cysts are classified under three main headings:

I Cysts of the jaws
II Cysts associated with the maxillary antrum
III Cysts of the soft tissues of the mouth, face, neck and salivary glands

The cysts of the jaws are divided into those that are:

A Epithelial lined
B Not epithelial lined

The epithelial-lined cysts may be either of:

1 Developmental origin
2 Inflammatory origin

Cysts of developmental origin may be either:

(a) Odontogenic, meaning arising from odontogenic tissues
(b) Non-odontogenic, meaning cysts arising from ectoderm involved in the development of the facial tissues

Classification

I Cysts of the jaws

A Epithelial-lined cysts

1 Developmental origin
  (a) Odontogenic
    i Gingival cyst of infants
    ii Odontogenic keratocyst
    iii Dentigerous cyst
    iv Eruption cyst
    v Gingival cyst of adults
    vi Developmental lateral periodontal cyst
    vii Botryoid odontogenic cyst
    viii Glandular odontogenic cyst
    ix Calcifying odontogenic cyst
  (b) Non-odontogenic
    i Midpalatal raphé cyst of infants
    ii Nasopalatine duct cyst
    iii Nasolabial cyst
2 Inflammatory origin
  i Radicular cyst, apical and lateral
  ii Residual cyst
  iii Paradental cyst and juvenile paradental cyst
  iv Inflammatory collateral cyst

B Non-epithelial-lined cysts

1 Solitary bone cyst
2 Aneurysmal bone cyst

II Cysts associated with the maxillary antrum

1 Mucocele
2 Retention cyst
3 Pseudocyst
4 Postoperative maxillary cyst

III Cysts of the soft tissues of the mouth, face and neck

1 Dermoid and epidermoid cysts
2 Lymphoepithelial (branchial) cyst
3 Thyroglossal duct cyst
4 Anterior median lingual cyst (intralingual cyst of foregut origin)
5 Oral cysts with gastric or intestinal epithelium (oral alimentary tract cyst)
6 Cystic hygroma
7 Nasopharyngeal cyst
8 Thymic cyst
9 Cysts of the salivary glands: mucous extravasation cyst; mucous retention cyst; ranula; polycystic (dysgenetic) disease of the parotid
10 Parasitic cysts: hydatid cyst; *Cysticercus cellulosae*; trichinosis

Frequency of cysts of the oral regions

Frequency statistics differ from incidence studies in that they are not standardised against known population data, such as age, gender and ethnicity. For data to be comparable between populations and internationally, age standardised incidence rates per 100 000 for each lesion, compared with a standard world population, are a requirement for all national cancer registries.

Age-standardised incidence rates for odontogenic keratocysts and for dentigerous cysts in a defined area (the Witwatersrand) of South Africa have been reported by Shear and Singh (1978) and Rachanis and Shear (1978). The resulting data for these two cysts are discussed in the relevant chapters.

Frequency studies, based either on hospital or on departmental archival records, are the method used most often in clinical investigations. These may have been based on very few cases, particularly in rare conditions, or large numbers of cases in departments with considerable patient turnover recorded over many years. While these provide useful data on the behaviour and treatment of different diseases, they are of limited use in international comparative studies. However, the larger the sample, the more accurate will be the age, gender and race distributions. In the course of this book, published data on the relatively rare cysts have been pooled in order to improve their accuracy.

Table 1.1 Distribution of 3498 jaw cysts according to diagnosis.

Cysts	Number	%
Radicular/residual cyst	1825	52.2
Dentigerous (follicular) cyst	599	17.1
Odontogenic keratocyst (including orthokeratinised)	355	10.2
Nasopalatine duct cyst	404	11.6
Paradental cyst (including juvenile type)	94	2.7
Solitary bone cyst	35	1.0
Calcifying cystic odontogenic tumour	28	0.8
Eruption cyst	27	0.8
Developmental lateral periodontal cyst	24	0.7
Nasolabial cyst	21	0.6
Gingival cyst of adults	21	0.6
So-called 'globulomaxillary' cysts	18	0.5
Inflammatory collateral cyst	15	0.4
Aneurysmal bone cyst	15	0.4
Glandular odontogenic cyst (since 1992)	6	0.2
Postoperative maxillary cyst	5	0.1
Mucosal cyst of maxillary antrum	4	0.1
Total	3498	100.00

Table 1.2 Distribution of 7121 odontogenic cysts according to diagnosis. From Jones *et al.* (2006), Sheffield.

Cysts	Number	%
Radicular cyst	3724	52.3
Dentigerous cyst	1292	18.1
Odontogenic keratocyst (including orthokeratinised)	828	11.6
Residual cyst	573	8.0
Paradental cyst	402	5.6
Unclassified odontogenic cysts	210	2.9
Lateral periodontal cyst	28	0.4
Calcifying odontogenic cyst	21	0.3
Gingival cyst	16	0.2
Eruption cyst	15	0.2
Glandular odontogenic cyst	11	0.2
Epstein pearl	1	0.0
Total	7121	100.00

The relative frequency of cysts of the jaws documented in the Department of Oral Pathology of the University of the Witwatersrand in Johannesburg is shown in Table 1.1.

A very extensive demographic study of odontogenic cysts has recently been published by Jones *et al.* (2006) based on a sample of 7121 cases from the Oral Pathology Department of the University of Sheffield, diagnosed over a 30-year period. While percentages for the three most frequently occurring cysts appear to be similar, their data, shown in Table 1.2, are not strictly comparable as they have been selected from a more restricted cohort of jaw cysts.

The Sheffield authors have also given a more detailed demographic analysis of their data, showing a breakdown of the numbers of odontogenic cysts in paediatric populations and adult populations.

Further demographic data are shown and discussed in the following chapters.

2

Gingival Cyst and Midpalatal Raphé Cyst of Infants

The gingival and the midpalatal raphé cysts of infants are conveniently discussed together because of clinical features that they share, although the first is of odontogenic origin and the latter of developmental origin. In view of their different histogeneses, they are separated in the classification.

Frequency and clinical features

The lesions are small and white or cream coloured (Fig. 2.1). The frequency of gingival cysts is high in newborn infants but they are rarely seen after 3 months of age. It is apparent that most of them undergo involution and disappear, or rupture through the surface epithelium and exfoliate, as very few are submitted for pathological examination. Monteleone and McLellan (1964) and Fromm (1967) have carried out extensive clinical surveys of newborn infants to look for nodules in the mouth, frequently referred to as Bohn's nodules or Epstein's pearls. There is some confusion about the two eponyms and their relation to gingival cysts in neonates. It would appear that Epstein's pearls are those that occur along the midpalatine raphé and are not of odontogenic origin, whereas Bohn's nodules are found on the buccal or lingual aspects of the dental ridges. Fromm (1967) pointed out moreover that Bohn was writing about remnants of mucous glands and had called them 'mucous gland cysts'. Gingival cysts, according to Fromm, were found only on the crests of the maxillary and mandibular dental ridges. For all this, the three terms are frequently used synonymously.

Their absence from the soft palate was explained by Burdi (1968) whose embryological studies indicated that consolidation of the soft palate and uvula took place not by fusion but by subepithelial mesenchymal merging of bilateral primordia without direct apposition and breakdown of epithelium.

Ikemura *et al*. (1983) reported a frequency of 89% in 541 Japanese neonates examined in the the first 8 days after birth. Another high frequency was found in a Taiwanese study in which the mouths of 420 neonates were examined within 3 days of birth. Oral cysts, palatal or gingival, were found in 94% of the infants (Liu and Huang, 2004). There was no association between the frequency of the cysts and gender, body weight or gestation age. In a review article intended for physicians, Dilley *et al*. (1991) pointed out that congenital lesions such as palatal and alveolar cysts occurred in almost 50% of newborns.

Common as they are in infants, gingival cysts are extremely rare over 3 months of age. However, Saunders (1972) has reported a case in a 3 month old child and some occur in adults although these are of a different nature (see Chapter 6).

Pathogenesis

There is general agreement that gingival cysts in infants arise from the dental lamina. Stout *et al*. (1968) studied epithelial remnants in fetal, infant and adult material. In human fetuses aged between 10 and 12 weeks there was evidence of small amounts of keratin formation in fragmented portions of dental lamina. By late in the 12th week the dental laminae were fragmented and many fragments showed keratin cyst formation (Fig. 2.2). They found epithelial remnants or gingival cysts in the maxillae of 109 infants ranging in age from birth to 4 years who were examined at autopsy. In their adult material, only 1 of 266 subjects had a cyst although epithelial rests were demonstrated in 90.

The epithelial remnants of the dental lamina, the so-called glands of Serres, have the capacity, from as early a stage in development as 10 weeks *in utero*, to proliferate, keratinise and form small cysts. Moskow and Bloom (1983) noted in human fetal material that as tooth development progressed, but prior to separation of the tooth germ from the oral epithelium, a proliferative tendency was often noted in the dental lamina with the formation of multiple areas of distinct microcyst formation and keratin production. In the morphodifferentiation (late bell) stage of tooth development, according to Moskow and Bloom, disintegration of the dental lamina occurred and numerous islands and strands of odontogenic

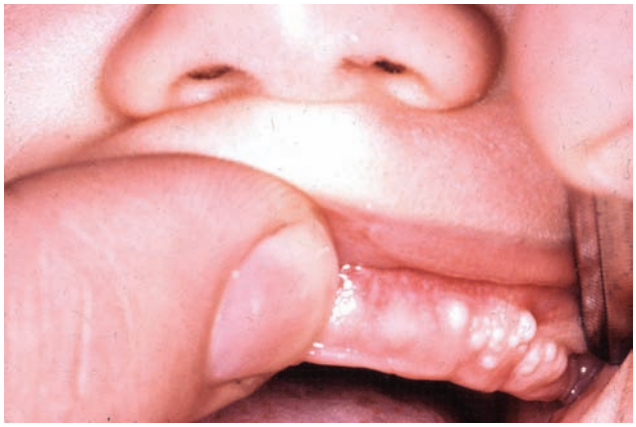


Fig. 2.1 Gingival cysts in an infant. (Courtesy of the Department of Oral Medicine and Oral Pathology, University of Copenhagen.)

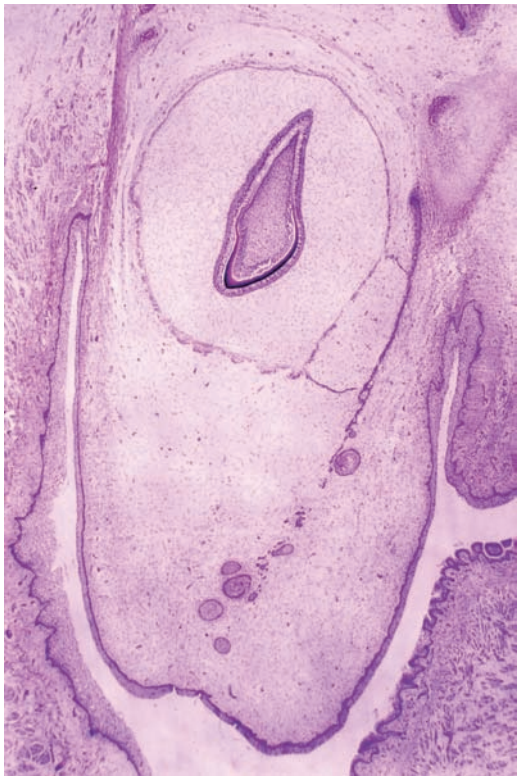


Fig. 2.2 Rests of Serres in the developing alveolus of a human fetus. (Section by courtesy of the late Professor C.W. van Wyk.)

epithelium are seen in the corium between the tooth germ and the oral epithelium, remote from the developing alveolar process. Those dental lamina remnants, which had already evolved into small cysts, expanded rapidly at this stage (15–20 week embryos) and there was thinning of the overlying oral epithelium.

Some of the gingival cysts probably open onto the surface leaving clefts (Fig. 2.3); others may be involved by

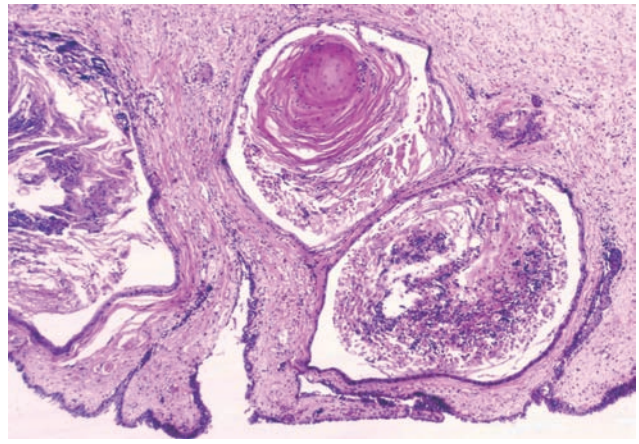


Fig. 2.3 Gingival cysts in an infant. (Section by courtesy of the late Dr W.G. Shafer.)

developing teeth. Some degenerate and disappear, the keratin and debris being digested by giant cells. Saunders (1972) reported that when he incised the mucosa over one of these cysts the contents were ejected, suggesting that they might be under pressure. Very few, as previously mentioned, become clinical problems.

After birth the epithelial inclusions usually atrophy and become resorbed. However, some may produce keratin-containing microcysts (Fig. 2.3), which extend to the surface and rupture during the first few months after birth. Burke *et al.* (1966) confirmed the presence of frequent palatine raphé cysts but suggested the possibility that they may represent abortive glandular differentiation leading to cyst formation.

In a meticulous study on serial sections of 32 human heads, approximately 8–22 weeks of fetal age, Moreillon and Schroeder (1982) showed that keratinising microcysts developing from the dental lamina increase in number from the 12th to the 22nd week, with a maximum of 190 cysts per fetus. Not more than 20 midpalatal raphé cysts were found in any fetus by week 14 and they did not increase in frequency with time. These authors' observations suggested that as the cysts developed, their epithelium differentiated, fused with the oral epithelium, and their contents were discharged.

It is of importance to note that the ability of the dental lamina to proliferate in the course of development of the gingival cyst of infants must be of limited potential, quite unlike that of the odontogenic keratocyst. The latter cyst has a different etiology and pathogenesis, as discussed in detail in Chapter 3, and despite their common origin its behaviour is decidedly different.

The cysts along the midpalatal raphé have a different origin. They arise from epithelial inclusions at the line of fusion of the palatine shelves and the nasal processes

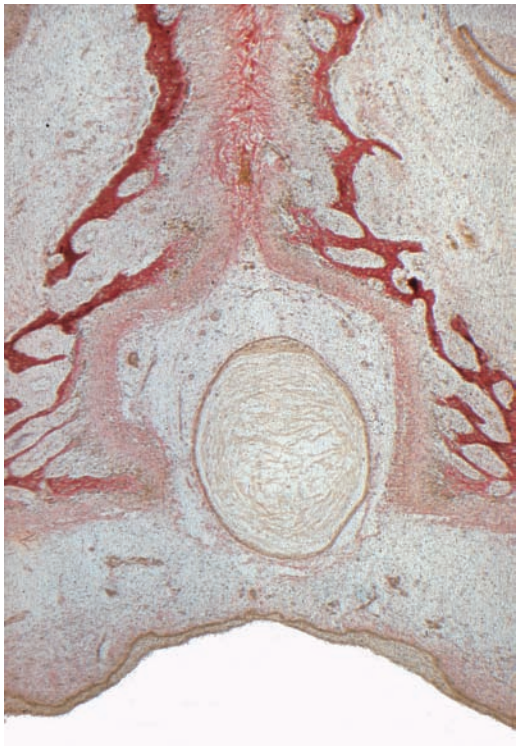


Fig. 2.4 Midpalatal raphé cyst in a human fetus. Van Gieson stain.

(Fig. 2.4). This is normally completed by the 10th week (Sadler, 1995).

Pathology

The cysts are round or ovoid and may have a smooth or an undulating outline in histological sections. There is a thin lining of stratified squamous epithelium with a parakeratotic surface and keratin fills the cyst cavity, usually in concentric laminations containing flattened cell nuclei. The basal cells are flat, unlike those in the keratocyst. Epithelial-lined clefts may develop between the cyst and the surface oral epithelium. As a result of pressure from the cyst, the oral epithelium may be atrophic (Fig. 2.3). Midpalatine raphé cysts have a similar histological appearance (Fig. 2.4).

Garlick *et al.* (1989) have described a congenital gingival cyst 1 cm in diameter, with the histological features of a gingival cyst of adults, but this is exceptionally rare.

Treatment

There is no indication for any treatment of gingival cysts or of midpalatal raphé cysts in infants. Once their contents are expelled, they atrophy and disappear.

3
Odontogenic Keratocyst

There has been a great deal of interest in the odontogenic keratocyst (OKC) since it became apparent that it may grow to a large size before it manifests clinically and that, unlike other jaw cysts, it has a particular tendency to recur following surgical treatment. Later in this chapter there is a discussion on the evidence that has accumulated over the years, that the OKC may be a benign cystic neoplasm. Arising from this, there has been much discussion recently on a change in terminology. In an invited lecture in 2003, Shear provocatively used the term 'keratocystoma' in the title. Other suggestions have been 'keratocystic odontogenic tumour' (Philipsen, 2005), and 'keratinising cystic odontogenic tumour' (Reichart and Philipsen, 2004). There is as yet no international consensus, either on the question of the cyst's neoplastic nature, or on a name change. As the term 'odontogenic keratocyst', or 'keratocyst', is so widely used by clinicians and pathologists, a good case can be made for retaining this term even if it is agreed that the cyst is indeed neoplastic. There is precedent for using terms for other neoplasms without the suffix–oma such as 'plasma cell tumour', although these are usually eponyms such as 'Kaposi's', or 'Ewing's tumour'. Pending any consensus on a name change, the term 'odontogenic keratocyst', abbreviated OKC, will continue to be used in this book.[1]

In the earlier literature, the OKC was described as a cholesteatoma (Hauer, 1926; Kostecka, 1929). In his detailed study of the cyst, Forssell (1980) concluded that the first account of this lesion was that of Mikulicz who, in 1876, described it as a dermoid cyst. Further historical details have been documented by Pogrel (2003a).

The term 'odontogenic keratocyst' was introduced by Philipsen (1956). In this and in a subsequent paper (Pindborg *et al.*, 1962), and in a paper by Pindborg and Hansen (1963), the designation 'keratocyst' was used to describe any jaw cyst in which keratin was formed to a large extent. Some dentigerous, radicular and residual cysts were therefore included in the category of odontogenic keratocyst. Moreover, OKCs may give an erroneous radiographical impression that they are dentigerous, lateral periodontal, residual, or even so-called fissural cysts, thus giving rise to the view that these latter entities are lined by keratinised epithelium (Forssell, 1980).

Although a few radicular and residual cyst linings may become keratinised by metaplasia (Fig. 3.1), these linings are distinctly different from the characteristic lining epithelium of the OKC (Browne, 1971a; Forssell and Sainio, 1979). However, there are other histological features that distinguish them and it is these that are responsible for their biological behaviour, rather than the presence of keratin. Lucas (1972) has made the point that the emphasis that has been placed on keratinisation is to some extent misleading, in that there is the implication that cysts of widely differing types may all keratinise and that if they do they are then liable to recur. There is now a great deal of evidence that the cyst under discussion here is a distinct entity, probably genetically determined, arising from primordial odontogenic epithelium. It was this belief in the origin of the cyst from primordial odontogenic epithelium that led for some time to the use of the term 'primordial cyst' (Shear, 1960a; Shear and Altini, 1976; Pindborg *et al.*, 1971). The term 'primordial cyst' has now fallen into disuse.

In early studies of this lesion, Browne (1969, 1972) showed that keratinising cysts had a significantly ($P < 0.01$) different age distribution (mean age 32.1 years; peak in second and third decades) from dentigerous (mean age 36.6 years; peak in fifth decade) and radicular cysts (mean age 40.2 years; peak from third to sixth decades). He concluded from this that the three types of

[1] At the recent meeting of the International Association of Oral Pathologists in June 2006, these questions were debated. There was consensus among those present that the term 'odontogenic keratocyst' should be retained. However, with regard to the question of the neoplastic nature of the lesion, there was no consensus, although when a popular vote was taken after hearing arguments both in favour and against, the majority favoured the view that as yet the molecular findings were not sufficiently definitive to support the thesis that the lesion was a benign neoplasm.

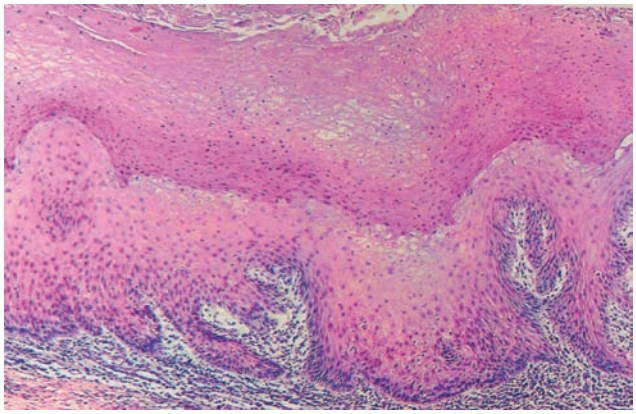


Fig. 3.1 Parakeratinised stratified squamous epithelium lining a cyst of the jaws. This is not an odontogenic keratocyst. (From *Histological Typing of Odontogenic Tumours, Jaw Cysts, and Allied Lesions* by Pindborg, J.J. and Kramer, I.R.H., World Health Organization Geneva, 1971, with permission.)

cyst arose from different populations and that the OKC was therefore a distinct lesion in its own right. The fact that it occured at a younger age than the others made it unlikely that it had arisen in long-standing dentigerous or radicular cysts.

Browne (1969) and Hjørting-Hansen *et al*. (1969) have demonstrated, moreover, that the site distribution of keratinising cysts differed significantly ($P < 0.01$) from that of non-keratinised cysts; a fact that was confirmed by Rud and Pindborg (1969), who believed that this supported the assumption that OKCs were a distinct entity of developmental origin. Forssell and Sainio (1979), who at that time also had a preference for the term 'primordial cyst', showed that in these lesions ('genuine keratocysts') the epithelium was distinctly parakeratotic with cuboidal or columnar palisaded basal cells, and occasionally orthokeratotic. They postulated that cysts showing local orthokeratinisation in otherwise non-keratinised epithelium; cysts with epithelium similar to that seen in parakeratotic oral mucosa; and cysts with scanty areas of thin parakeratinisation, should not be regarded as 'primordial cysts'. None of these varieties, moreover, had accentuated basal cells.

Despite agreeing that these cysts were distinct entities, Browne (1969) argued that they could not be primordial cysts because he defined a primordial cyst, according to the original description of Robinson (1945), as one which arose by breakdown of the stellate reticulum of the enamel organ before any mineralised tissue was formed. Hence it developed in place of a tooth which might have been one of the normal series or a supernumerary. Despite an extensive literature on the subject of primordial cysts and odontogenic OKCs over the 45 years since Robinson published his paper, there has been no convincing evidence to support the theory that he postulated. Later in this chapter, we present the evidence supporting origin of the OKC from primordial odontogenic epithelium, i.e. dental lamina or its remnants (Soskolne and Shear, 1967; Toller, 1967), or odontogenic basal cell hamartias (Stoelinga, 1971a, 1973; Voorsmit, 1984).

Clinical features[2]

Frequency

Over the past 46 years, 355 OKCs (10.2%) were registered in the archives of the Department of Oral Pathology, University of the Witwatersrand, among a total of 3498 cysts of the jaws (see Table 1.1). The 355 cases occurred in 318 patients.

This number included both parakeratinised and orthokeratinised cases. In a study carried out on 87 cases (Cohen and Shear, 1980), 72 (82.8%) were parakeratinised, 6 (6.9%) orthokeratinised, and in 9 (10.3%), both para- and orthokeratinised areas were observed.

The frequency in other studies, recorded over a period of 26 years, is shown in Table 3.1. The varying frequencies in different reported series probably reflect, to a large extent, the range of material seen in these departments and are not reliable indicators of their incidence. As Table 3.1 shows, some investigators have recorded numbers of OKCs in relation to all odontogenic cysts, others to epithelial jaw cysts and others, as in the present study, to all jaw cysts. In an epidemiological study performed in 1978, age-standardised incidence rates, which are the most reliable indicators for regional, race and gender variations, are shown for OKCs (Table 3.2) standardised against a World Standard population, per million per year. The incidence at the time of the study was 0.61, 0, 4.86 and 3.50 for black males and females, and white males and females, respectively, in the Witwatersrand region of South Africa, with Johannesburg as its centre (Rachanis and Shear, 1978; Shear, 2003a). There is reason to believe that if a similar epidemiological survey were to be carried out now, the incidence rates would be likely to be different, with a substantially higher number in black patients. The reasons for this belief are discussed later in the section on gender and race.

Age

OKCs occur over a wide age range and cases have been recorded as early as the first decade (Meara *et al*., 1996)

[2] The authors would have preferred to use the gender designations of 'men' and 'women' but as many cysts are found also in 'boys' and 'girls' we decided that it would be less cumbersome to retain 'males' and 'females'.

Table 3.1 Frequency of keratocysts in different series over 26 years, separated by denominator and frequency.

Author(s)	Material	Denominator	%
Reff-Eberwein *et al*., 1985	82 of 3328	Odontogenic cysts	2.5
Magnusson, 1978	52 of 1420	Odontogenic cysts	3.2
Pindborg *et al*., 1962	26 of 791	Odontogenic cysts	3.3
Daley *et al*., 1994	334 of 6847	Odontogenic cysts	4.9
Browne, 1970	41 of 537	Odontogenic cysts	7.6
Payne, 1972	103 of 1313	Odontogenic cysts	7.8
Craig, 1976	85 of 1051	Odontogenic cysts	8.1
Hjørting-Hansen *et al*., 1969	56 of 502	Odontogenic cysts	11.2
Radden and Reade, 1973	64 of 368	Odontogenic cysts	17.4
Djamshidi, 1976	91 of 417	Odontogenic cysts	21.8
Main, 1970a	12 of 289	Epithelial jaw cysts	4.2
Hoffmeister and Härle, 1985	51 of 3353	Jaw cysts	1.5
Killey *et al*., 1977	25 of 746	Jaw cysts	3.3
Ahlfors *et al*., 1984	319 of 5914	Jaw cysts	5.4
Köndell and Wiberg, 1988	29 of 531	Jaw cysts	5.4
Hodgkinson *et al*., 1978	79 of 1100	Jaw cysts	7.2
Shear, present study	355 of 3498	Jaw cysts	10.2
Stoelinga, 1971a	54 of 486	Jaw cysts	11.1
Brannon, 1976	312 of 2972	Oral cysts	10.5
Toller, 1967	33 of 300	Cysts all types	11.0

Table 3.2 Age-standardised incidence rates of keratocysts in the Witwatersrand area of South Africa, 1965–1974, standardised against standard European, World and African populations. (From Rachanis and Shear, 1978.)

	Per million per year		
	European	World	African
Black males	0.67	0.61	0.63
Black females	0	0	0
White males	5.37	4.86	4.78
White females	3.64	3.50	3.54

and as late as the ninth. In most series there has been a pronounced peak frequency in the second and third decades, with figures ranging from 40% to 60% of patients being in this age group. The ages at diagnosis of 162 OKCs from the Johannesburg material are shown in Fig. 3.2. Very few cysts were found in patients in the first decade, but there is a sharp increase in the second decade.

Many workers have demonstrated a bimodal age distribution with a second peak in the fifth decade or later (Toller, 1967; Magnusson, 1978; Vedtofte and Prætorius, 1979; Forssell, 1980; Ahlfors *et al*., 1984; Voorsmit, 1984; Donath, 1985; Partridge and Towers, 1987; Woolgar *et al*., 1987b; Rippin and Woolgar, 1991; Jones *et al*., 2006). The study on age-specific morbidity rates carried out at the University of the Witwatersrand department confirmed this bimodal trend (Rachanis and Shear, 1978). It showed, moreover, that the incidence was highest in the older age groups (Table 3.3; Fig. 3.3). The data also showed that the peak age incidence at the time of that survey was approximately a decade younger in females than in males, a factor also discussed in a study of 430 cases of OKC in the Northwestern USA (Oda *et al*., 2000). In the hospital sample of 256 cases in South Korea, however, this gender difference was not found and illustrated the importance of acknowledging regional and institutional differences (Myoung *et al*., 2001).

To address the question of whether two different types of OKC might exist, one in younger and one in older age groups, we reviewed the clinical features and histopathology of a series of OKCs from patients in the age groups 10–29 and 50–64 years and the data were analysed statistically (Rachanis *et al*., 1979). No significant differences were observed between the two groups. We concluded therefore that it was unlikely that these were different varieties of OKC and subscribed to the view of Browne (1975) that the cysts in older age groups have probably been present but undiagnosed for many years. This is in keeping with the observation made elsewhere in this chapter, that OKCs may involve the body and ascending ramus of the mandible extensively, with little or no bony expansion. However, in view of recent genetic studies on the OKC, dealt with later in this chapter, it is

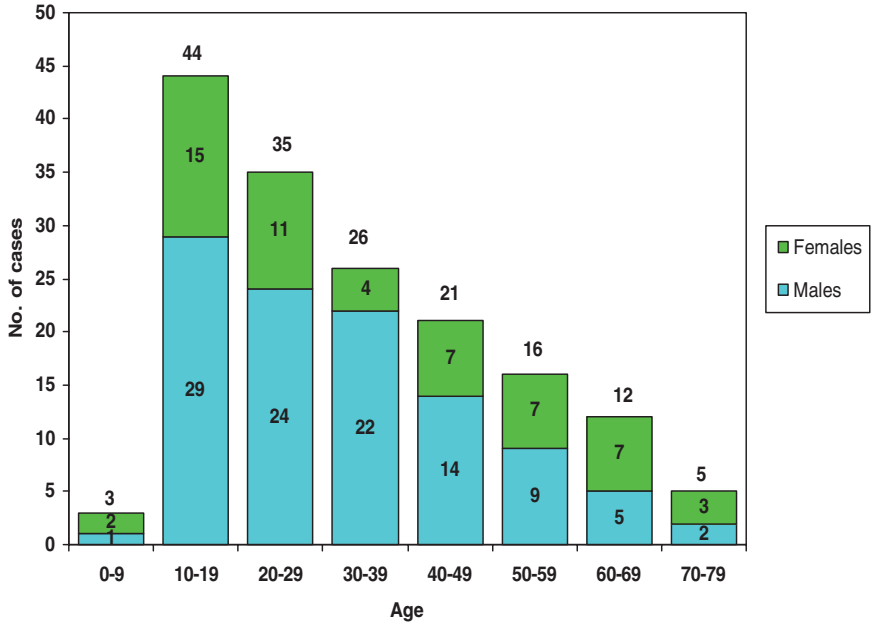


Fig. 3.2 Age distribution of 162 patients with odontogenic keratocysts.

Table 3.3 Average annual incidence rates for keratocysts on the Witwatersrand, South Africa, 1965–1974.

	Average annual incidence per million by age group (years)							
	0–9	10–19	20–29	30–39	40–49	50–64	65–74	75+
Black males	0	0.65	0.44	1.24	0.85	1.28	0	0
Black females	0	0	0	0	0	0	0	0
White males	0.94	4.56	5.73	7.00	1.81	11.58	6.84	0
White females	0	6.02	5.88	1.49	5.47	1.62	4.97	8.90

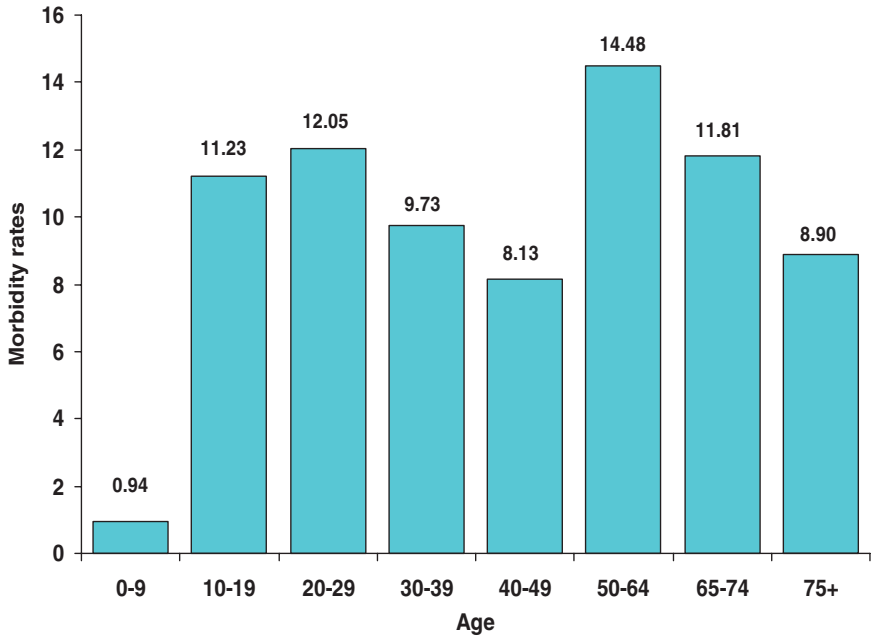


Fig. 3.3 Age-specific morbidity rates for odontogenic keratocysts on the Witwatersrand, South Africa, 1965–1974, shown as cases per million population per year.

possible to speculate that older individuals may be prone to the two independent mutational events required in the somatic cell for the development of a sporadic OKC.

A series of publications by Woolgar *et al*. (1987a–c) compared the ages of patients with sporadic OKCs with those occuring in the naevoid basal cell carcinoma syndrome (NBCCS) and found that the mean ages were significantly different between the groups (P <0.001). In the group without the syndrome, the mean age at removal of the cysts was 40.4 years (SD±19.2), with a bimodal distribution, the first peak at 15–45 years and the second smaller peak at 55–65 years. In patients with the syndrome, there was a single peak at 10–30 years and a mean of 26.2 years (SD±17.3). Log linear modelling of the variables showed that in their sample there were significantly more syndrome than non-syndrome patients before the age of 36 years and that in both groups, females were more likely to be seen in the younger ages. In a later article, Rippin and Woolgar (1991) compared the age distribution, at removal, of a sample of 379 non-syndrome patients with the ages, at removal, of first OKC in 60 patients with the NBCCS. They demonstrated that it was the patients with sporadic cysts who accounted predominantly for the second peak.

A 19-year retrospective institutional review of OKCs in a paediatric population identified 11 children with this histologically confirmed lesion (Meara *et al*., 1996). Their ages ranged from 8 to 18 years. Most cases were treated by enucleation and followed for 1–8 years. Recurrences or second primary lesions occurred in four patients, all of whom had a family history of NBCCS or multiple cysts suggestive of this diagnosis.

Gender and race

OKCs generally are found more frequently in males than in females and this gender predilection was also found in the South African sample. In the present sample of 176 patients for whom data were available, 110 (63%) were males and 66 (37%) were females (1.7:1). Of these, 58 were white males and 43 white females (1.3:1); 52 were black males and 23 were black females (2.3:1) (Table 3.4). These ratios for race and gender are substantially different from those reported in the previous 1992 edition of this book when the archival data indicated a much lower prevalence among black patients, and particularly black females, than the cases registered in the years since then. Altini (personal communication, 2005) has pointed out that the biopsy material now received in his Johannesburg department is predominantly from black patients. This must reflect the ready access to the Johannesburg Academic Hospital previously denied to black patients during the apartheid years.

Table 3.4 Gender distribution of 176 black and white patients with keratocysts.

	Men	Women	Row total	M:F ratio
Black	52	23	75 (43%)	2.3:1
White	58	43	101 (57%)	1.3:1
Column total	110 (63%)	66 (37%)	176	1.7:1
W:B ratio	1.1:1	1.9:1	1.4:1	

In another series (Woolgar *et al*., 1987a,b), the gender distribution of patients with solitary OKCs in which there was a preponderance of males (62% males and 38% females; n=377) was significantly different (P <0.025) from the syndrome sample in which females were more frequently affected (45% males and 55% females; n=60).

A more accurate assessment of the gender and race distribution of patients with specific diseases is usually determined from standardised incidence studies. The age-standardised incidence rates for histologically confirmed OKCs among black and white males and females were determined by an extensive survey carried out in 1978 of the records of all the pathology departments in hospitals and private practices on the Witwatersrand (Rachanis and Shear, 1978). The results are shown in Table 3.2 and the age-specific morbidity rates for these four groups in Table 3.3. These figures confirmed the observation that the incidence of OKCs was higher in males than in females. They also indicated that they were considerably more common in whites than in blacks and that they were particularly rare in black females – so rare that they translated to a zero average annual incidence in all age decades. The most recent figures from the same source indicated that the race data found in the biopsy diagnoses used in the 1978 study may well have been skewed, and that a repeat epidemiological study may produce a different result.

In the study of Vedtofte and Prætorius (1979) an equal gender distribution was observed, and in a selected sample of 20 patients with multiple OKCs, of whom 10 had the NBCCS, Brannon (1976) observed a female preponderance of 17:1. In the recent Sheffield study (Jones *et al*., 2006) the male:female ratio was 1.27:1).

Site

The mandible is involved far more frequently than the maxilla. In our own material, 149 of 193 cysts (77%) for which data were available have occurred in the mandible. The high frequency of mandibular involvement, borne out in other series, is 77% (Hansen, 1967); 83% (Browne, 1970); 65% (Brannon, 1976); 72% (Hodgkinson *et al*., 1978); 71% (Vedtofte and Prætorius, 1979); 78% (Forssell, 1980); 75% (Ahlfors *et al*., 1984); 69% (Voorsmit, 1984); 69% (Chow Hsun-Tau, 1998); 62% (Lam and Chan, 2000); 73% (Morgan *et al*., 2005);

and 71% (Jones *et al*., 2006). About half of all OKCs occur at the angle of the mandible extending for varying distances into the ascending ramus and forward into the body. As to the site distribution of the other cases, reports of a number of studies indicated that they can occur anywhere in the jaws, including the midline of the mandible and maxilla and the previously designated 'globulomaxillary area' in the maxilla (Soskolne and Shear, 1967; Browne, 1971a; Brannon, 1976; Vedtofte and Prætorius, 1979; Forssell, 1980; Chow Hsun-Tau, 1998; Jones *et al*., 2006). Some cases have been reported in which both jaws have been involved, not necessarily confined to patients with the NBCCS (Chow Hsun-Tau, 1998). Woolgar *et al*. (1987c) have shown that OKCs occur with much greater frequency in the maxilla after the age of 50 years.

With regard to location within the jaws, Woolgar *et al*. (1987a, c) reported a higher frequency in the mandibular molar-ramus area (60%) of cysts unassociated with the syndrome than those with (44%); whereas more syndrome (21%) than non-syndrome cysts (11%) occurred in the maxillary molar region. Eighteen patients with the syndrome initially had only one cyst. In all except three, further cysts developed subsequently. Of 24 syndrome patients with cysts in two quadrants, 13 had bilateral mandibular cysts related to third molar teeth. Five patients had cysts in three quadrants and 13 patients had cysts in all four quadrants. The time interval at which subsequent cysts were diagnosed varied from 1 to 23 years.

These authors emphasised that the term 'multiple', when applied to cysts occurring in patients with the syndrome, referred to the lifetime history of the patient and not that more than one cyst was present at any one time. They also made the important point that any patient with more than one OKC other than a recurrence will show some other features of the syndrome, albeit only minor anomalies which may be revealed only on full examination.

Clinical presentation

Patients with OKCs complain of pain, swelling or discharge. Occasionally, they experience paraesthesia of the lower lip or teeth. Some are unaware of the lesions until they develop pathological fractures. Other cysts have been discovered fortuitously during dental examination when radiographs were taken. In many instances, patients are remarkably free of symptoms until the cysts have reached a large size, involving the maxillary sinus and the entire ascending ramus, including the condylar and coronoid processes. This occurs because the OKC tends to extend in the medullary cavity and clinically observable expansion of the bone occurs late.

Although the cysts vary considerably in size, Forssell (1980) has shown that about half of his cases were 40 mm or more in diameter and that this was particularly the case with cysts of the ascending ramus and angle of the mandible compared with cysts of the maxilla or body of the mandible. He suggested that the maxillary cysts were more likely than those in the mandible to become infected even when small, and would probably therefore be diagnosed at an earlier stage in their development. As with other intraosseous jaw lesions, the enlarging cyst may lead to displacement of the teeth; Voorsmit (1984) and Lund (1985) have described the occurrence of large OKCs involving the maxillary sinus that led to displacement and destruction of the floor of the orbit and proptosis of the eyeballs. Vencio *et al*. (2006) also reported a case that had extended into the maxillary antrum, destroying the floor. Other authors have reported on aggressive behaviour of OKCs to the extent that they penetrated cortical bone and involved surrounding soft tissues (Emerson *et al*., 1972; Partridge and Towers, 1987). Another reported case extended from the maxilla and eventually involved the base of the skull, 'behaving rather like a low-grade squamous cell carcinoma' (Jackson *et al*., 1993); whereas others extended from the maxilla into the orbit and infratemporal fossa (Chuong *et al*., 1982), or into the infratemporal fossa (Worrall, 1992). Neurological symptoms are occasionally seen (Browne, 1970; Brannon, 1976).

Importantly, it has been shown in some studies that the orthokeratinised OKCs have a substantially lower recurrence rate than those that were parakeratinised (Wright, 1981; Siar and Ng, 1988; Crowley *et al*., 1992) and later molecular studies showed significant differences between the two varieties (High *et al*., 1993; Li *et al*., 1998; Da Silva *et al*., 2002). Unfortunately, there is not yet clarity on the behaviour of OKCs that show both ortho- and parakeratotic areas histologically.

Dayan *et al*. (1988) have described the occurrence of a lesion entirely within the gingiva, which had the clinical features of a gingival cyst of adults but the histological characteristics of a typical OKC. They have suggested the term 'peripheral odontogenic keratocyst' for this rare presentation of the lesion; a useful distinction in view of its apparently unaggressive nature. Two similar cases have been reported, where no recurrence was noted after simple enucleation (Ide *et al*., 2002). The latter authors suggested that the peripheral OKC should be included under the histological spectrum of gingival cyst in the adult, which is probably not a good idea. It may well be that their peripheral location leads to early diagnosis of OKC and ease of complete surgical removal, a view also held by Ide and Saito (2003) who pointed out that only one of nine well-documented cases of peripheral OKC had recurred after simple excision. Chi *et al*. (2005) have also reported two cases and supported the view that these should be regarded as peripheral OKCs and not as gingival cysts of the adult.

Yih *et al*. (2000) demonstrated substantial immunohistochemical differences between a sample of six gingival

cysts of the adult and three peripheral OKCs. They showed moderately positive staining for p53 and strongly positive staining for Ki-67 in the basal and parabasal cells of the epithelial linings of the peripheral OKCs, whereas the six gingival cyst epithelial linings were all completely negative for Ki-67 and negative for p53 in five of the six. The expression of bcl-2 was strongly positive in the basal and parabasal cells of the three peripheral OKCs, but was only weakly positive in some of the gingival cysts. The authors concluded that this supported the view that the two lesions were distinct entities.

An analysis of the location and frequency of bony expansion has been made by Browne (1970). In his study, expansion of bone occurred in about 60% of cases. One-third of maxillary cysts caused buccal expansion, but palatal expansion was very rarely seen. About half of the mandibular lesions produced buccal expansion and one-third produced lingual expansion. The great majority of the latter group were in the third molar or ascending ramus regions. Forssell (1980) observed expansion of bone in 53% of his material and this occurred significantly more frequently in the angle or ascending ramus of the mandible than in the maxilla or in the body of the mandible. Perforation of bone, as observed in orthopantomograms, occurred in 39% of his cases. Brannon (1976), however, reported only a 25% frequency of bony expansion or perforation.

Multiple OKCs are found in some patients. Among a group of 122 patients in our series, 113 had single cysts and nine (7%) had more than one. In three of the latter, the cysts were part of the NBCCS. Of these patients, one has had six cysts, another has had five and one has had two. However, Rippin and Woolgar (1991) have argued that all patients with multiple OKCs have other syndrome features. Their figures indicated that approximately 12.5% of patients with OKCs had multiple cysts and other features of the syndrome, whereas another 1% had the syndrome with only single cysts at the time of diagnosis. Clinicians need to be aware of the probability that if a patient has more than one OKC, other features of the syndrome should be investigated. Moreover, if a patient has a single obvious OKC, careful scrutiny of appropriate radiographs should be performed to exclude the possibility of other cysts.

The naevoid basal cell carcinoma syndrome

Binkley and Johnson (1951) reported the case of a 30-year-old woman with multiple 'dental follicular cysts' involving both sides of the mandible. She also had numerous hard papules situated over various parts of the body which histological examination showed were 'basal cell naevi'. A radiograph of the chest revealed an anteriorly bifid sixth rib. Gorlin and Goltz (1960) established the association of multiple basal cell epitheliomas, jaw cysts (which they described as 'true cysts, having a typical stratified squamous epithelium') and bifid ribs, a combination that is frequently referred to as the 'Gorlin–Goltz syndrome', the 'Gorlin syndrome' or the naevoid basal cell carcinoma syndrome (NBCCS). Gorlin *et al.* (1963) and Meerkotter and Shear (1964) identified the jaw cysts as OKCs, and numerous clinical and molecular studies have been, and continue to be, undertaken on the OKCs occurring in patients with the syndrome. The syndrome is inherited as a set of autosomal dominant characteristics with strong penetrance. It has variable expressivity, including multiple naevoid basal cell carcinomas, OKCs, other congenital skeletal defects, ectopic calcifications, plantar and palmar pits, central nervous system and ocular lesions, and fairly typical facial features with frontal bossing and ocular hypertelorism (Fig. 3.4). OKCs are among one of the most consistent features of the syndrome, occurring in 65–75% of cases and skeletal anomalies are also common.

Guidelines for diagnosis include a family history, oral and skin examinations, chest and skull radiographs, panoramic radiographs of the jaws, magnetic resonance imaging (MRI) of the brain, and pelvic ultrasonography in women (Bitar *et al.*, 2002).

Later genetic studies showed that the NBCCS gene mapped to chromosome 9q22.3 and probably functioned as a tumour suppressor by deletion of this region in many of the neoplasms related to the syndrome. Cloning of the NBCCS gene showed it to be the human homologue of the *Drosophila* segment polarity gene *Patched (PTCH)*. The *PTCH* gene encodes a transmembranous protein that acts in opposition to the *Hedgehog* signalling protein (shh), controlling cell fates, patterning, and growth in numerous tissues, including tooth (Barretto *et al.*, 2000).

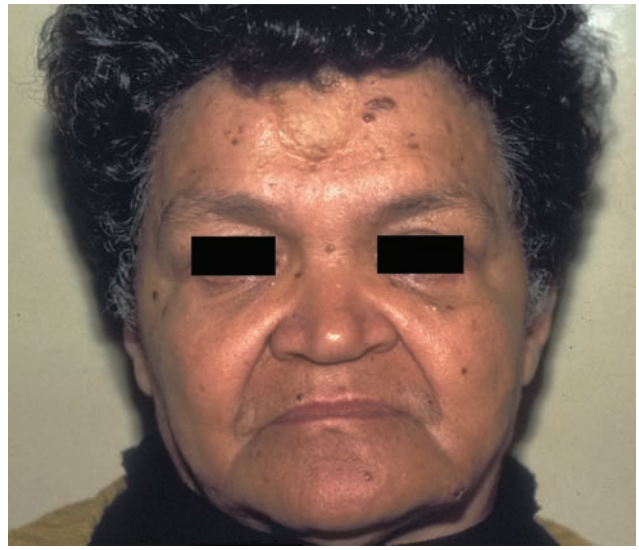


Fig. 3.4 Facial features of a patient with the naevoid basal cell carcinoma syndrome.

A detailed account of *PTCH* and *Hedgehog* has been published by Cohen (1999). Molecular studies on solitary (sporadic) and syndrome-related OKCs are discussed later in this chapter.

Recurrences

It has been known for many years that the OKC has a particular tendency to recur after surgical treatment, and many groups of investigators have documented their results (Table 3.5). The first to point out this peculiarly aggressive behaviour were Pindborg and Hansen (1963). They observed no correlation between the size or location of the cyst and its tendency to recur; nor was there any difference in recurrence rate between cases that were treated by 'extirpation' and those treated by 'fenestration'. A few years later, Hansen (1967) reported a recurrence rate of 52% in a series of 52 cases followed for a period of at least 6 months, and in the same year Toller (1967) confirmed this propensity when he reported a recurrence rate of 51% in a series of 55 cases. Browne (1970) reported a 25% recurrence rate in 85 cysts followed for 6 months or longer. He found that most recurrences occurred in the first 5 years after surgery but one of his cases recurred 20 years after operation. Bramley (1971) reported a case with a recurrence 40 years after surgical treatment. Browne (1970) could find no statistically significant correlation between the frequency of recurrence and the age of the patient, location of the cyst, the method of treatment (enucleation or marsupialisation), the nature of the cyst lining, and the presence of cortical perforation. In a later paper (Browne, 1971a), he

Table 3.5 Recurrences of keratocysts in various series.

Authors	No. of cases followed	% Recurrence rate
Pindborg and Hansen, 1963	16	62
Hansen, 1967	52	52
Toller, 1967	55	51
Cernéa *et al.*, 1969	28	18
Rud and Pindborg, 1969	21	33
Panders and Hadders, 1969	22	14
Browne, 1970	85	25
Ebling *et al.*, 1971	24	38
Stoelinga, 1971a	54	10
Klammt, 1972	32	22
Machtens *et al.*, 1972	44	59
McIvor, 1972	43	5
Payne, 1972	20	45
Borg *et al.*, 1974	25	24
Butz (personal communication, 1975)	38	11
Eversole *et al.*, 1975	35	20
Brannon, 1976	283	12
Hodgkinson *et al.*, 1978	74	39
Vedtofte and Prætorius, 1979	57	51
Forssell, 1980	121	40
Voorsmit *et al.*, 1981 (Group 1, early cases)	52	14
(Group 2, later cases)	40	3
Anniko *et al.*, 1981	21	50
Ahlfors *et al.*, 1984	255	27
Reff-Eberwein *et al.*, 1985	82	56
Niemeyer *et al.*, 1985	64	36
Zachariades *et al.*, 1985	16	25
Partridge and Towers, 1987	45	27
Forssell *et al.*, 1988	75	43
(Group 1, treated before 1975)		50
(Group 2, treated 1975–1980)		22
Köndell and Wiberg, 1988	29	24
Stoelinga and Bronkhorst, 1988	27	10
Myoung *et al.*, 2001	256	58
Stoelinga, 2001 (enucleation only)	33	18
(enucleation plus excision overlying mucosa and Carnoy's of defect)	49	6

showed that there was a very similar rate of recurrence following removal of OKCs with satellite cysts (23.7%) and those without satellite cysts (24.4%). There was a higher frequency of recurrence of cysts without epithelial residues (28.1%) than with (8.3%), but the difference was not statistically significant. These observations were confirmed by Vedtofte and Prætorius (1979).

Toller (1971) summarised the findings of a number of different groups of workers. In a total of 195 patients there were 85 first recurrences (44%). Butz (personal communication, 1975) followed 38 patients for between 8 months and 17 years. There were two definite recurrences, proved at operation and histologically, and a further two probable cases on the basis of radiological evidence, a recurrence rate of 11%. Of the definite recurrences, one was discovered 2½ years and the other 1 year after the original operation. Lower recurrence rates (10–14%) than occurred in most other studies were reported by Panders and Hadders (1969); Stoelinga (1971a); Stoelinga and Bronkhorst (1988); Brannon (1976); Voorsmit *et al.* (1981); and Stoelinga (2001) (Table 3.5). A higher recurrence rate of cysts located in the angle or ascending ramus of the mandible was reported in one study, but the size of the cyst did not appear to have an influence (Forssell, 1980).

Thirty-three patients were followed for at least 6 years in a series of 62 patients with OKCs and recurrences were found to be related to the operative procedure employed. The highest frequency of recurrences occurred in the patients treated by cystostomy (Niemeyer *et al.*, 1985).

A more recent detailed South Korean review of 256 patients showed significantly higher recurrence rates ($P = 0.005$) for the 14 of 17 patients in the 41–50 year age group; in 30 of 40 patients with cysts in the mandibular molar region ($P = 0.001$); and in 27 of 37 patients whose cysts had associated daughter cysts ($P = 0.03$) (Myoung *et al.*, 2001). Their overall recurrence rate was 58.3% in an average follow-up period of 29 months. Ninety-nine per cent of the cysts were treated by surgical enucleation, 8.6% of them after marsupialisation. A total of 11.7% of patients with recurrences had multiple recurrences.

When 24 patients with orthokeratinised OKCs were followed for periods of 6 months to 8 years, only one recurrence was found and it occurred 6½ years postoperatively (Wright, 1981). This was the first indication that the orthokeratinised cysts may be less aggressive than the more common parakeratinised type, a contention that has been reinforced in other studies, and will be referred to later.

The considerable variation in recurrence rate reported by different workers may be ascribed partly to the variability in the follow-up period. Vedtofte and Prætorius (1979), Forssell (1980) and Forssell *et al.* (1988) have shown quite clearly that in their own material the recurrence rate increased with extension of the follow-up period to 5 years or more. The latter authors found that of 75 cases in 63 patients followed for periods ranging from 5 to 17 years (mean 8.3), 32 (43%) recurred. The cumulative recurrence rate of 67 of these cysts in patients examined annually increased from 3% after the first year to 37% after the third year. Thereafter no new recurrences were noted. They observed that recurrences were more frequent (63%) with cysts in patients with the NBCCS than with cysts in patients without the syndrome (37%). OKCs enucleated in one piece recurred significantly less often ($P < 0.01$) than cysts enucleated in several pieces, and the recurrence rate in cases with a clinically observable infection, a fistula or with a perforated bony wall was higher than when these features were not present. The size of the cyst did not seem to influence its prognosis after surgery, but those whose radiographic appearance was multilocular had a higher recurrence rate than those with a unilocular appearance.

There are many possible reasons for the wide range of variation in recurrence rates shown in Table 3.5. Some of these are discussed in the following paragraph, and there is further discussion on this subject in the section on treatment, dealt with later in this chapter.

Possible reasons for recurrences

There are several possible reasons why OKCs recur so frequently and require meticulous surgical planning and execution. The first of these is related to their tendency to multiplicity in some patients, including the occurrence of satellite cysts which may be retained during an enucleation procedure. If enucleation procedures are incomplete, some instances of recurrence may be new cysts arising from retained satellite microcysts or retained mural cell islands. Second, OKC linings are very thin and fragile, particularly when the cysts are large, and are therefore more difficult to enucleate than cysts with thick walls. Portions of the lining may be left behind (Kramer, 1963; Fickling, 1965) and constitute the origin of a recurrence. In a series of studies over a period of years, Forssell and co-workers (1974, 1980, 1988) showed that recurrences were extremely infrequent if the cyst was enucleated in one piece but occurred in over half of cases when the cyst was removed in several pieces. An attempt to save vital adjacent teeth or nerves during the operation may lead to incomplete eradication and hence to recurrence. Likewise, enucleation in one piece may be more difficult with cysts that have scalloped margins and this may explain the higher recurrence rates than with those with a smoother contour. A relationship between perforation of the lingual plate of the mandible and recurrence after treatment was observed by Borg *et al.* (1974).

A further possible reason for an apparently unsuccessful treatment has been provided by evidence derived from patients with the NBCCS. It was shown by Soskolne and Shear (1967) that these patients have a particular

predisposition to form OKCs from the dental lamina or its remnants and they suggested that OKCs in patients without the syndrome were also likely to arise from the dental lamina. If these individuals also have an innate tendency to develop such cysts, then any remnants of dental lamina may form the target for new OKC formation (Fig. 3.5).

In the same year, Toller (1967) suggested that the epithelial linings of OKCs had intrinsic growth potential and he was the first to suggest that there was some basis for regarding them as benign neoplasms. Later, Ahlfors *et al*. (1984) also proposed that the OKC should be regarded as a benign cystic neoplasm. Since then, evidence has accumulated to support the neoplastic nature of the OKC and this has been reviewed elsewhere (Shear 2002a–c, 2003a,b).

Yet another source of the recurrences has been proposed by Stoelinga (1971a, 2001, 2003a) and Stoelinga and Peters (1973). In numbers of publications they have demonstrated convincingly that OKCs may also arise from proliferations of the basal cells of the oral mucosa, often referred to as basal cell hamartias, particularly in the third molar region and ascending ramus of the mandible. They have referred to the frequent observation of perforation of the overlying bone and firm adhesion of the cysts to the overlying mucosa and recommended that when the cysts were surgically removed, the overlying mucosa should be excised with them in an attempt to prevent possible recurrence or the formation of new cysts from residual basal cell proliferations. In these publications, credible evidence has been provided in support of this mode of origin, and an example from another source is shown in Fig. 3.6. The two theories of origin are not incompatible, as both dental lamina and basal cell hamartias have common parentage, the stomadeal ectoderm, and both are influenced by ectomesenchyme or residual ectomesenchymal inductive influences (Shear and Altini, 1976). This being the case, it seems reasonable to speculate that mucosal basal cells could be targeted by the same genetic influences as dental lamina.

Voorsmit *et al*. (1981) believed that a recurrent OKC may develop in three different ways: by incomplete removal of the original cyst lining; by the retention of daughter cysts, from microcysts or epithelial islands in the wall of the original cyst; or by the development of new OKCs from epithelial off-shoots of the basal layer of the oral epithelium. In the latter respect, the authors supported the hypothesis of Shear and Altini (1976) that there may be residual ectomesenchymal inductive influence on the overlying epithelium to initiate this process.

In one series, basal cell budding was observed in as many as 52.6% of cases with one or more daughter cysts (Myoung *et al*., 2001) and in a well-documented follow-up study on a series of 82 OKCs, a histological study was made of 44 cases in which the overlying mucosa was excised (Stoelinga, 2001). In 23 of these cases there were clusters of epithelial islands, and in 11 cases microcysts were observed in the area in which the cyst lay deep to the overlying mucosa. Working on the hypothesis that many OKCs arose from the basal cells of the overlying epithelium, the treatment protocol in this investigation had aimed at avoiding postoperative recurrences by including excision of the overlying attached mucosa and treatment of the bony defect with Carnoy's solution.

Reference has already been made to publications that have reported on behaviour of OKCs so aggressive that they have penetrated cortical bone and involved surrounding soft tissues (Emerson *et al*., 1972; Partridge and Towers, 1987). Another reported OKC extended from the maxilla and eventually involved the base of the skull,

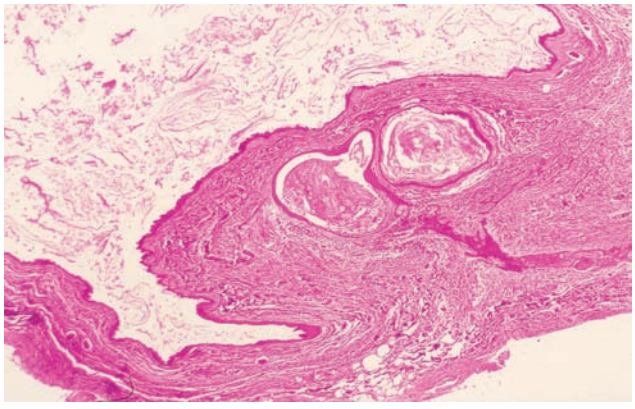


Fig. 3.5 Satellite microcysts in the wall of an odontogenic keratocyst that appear to be arising directly from an active dental lamina.

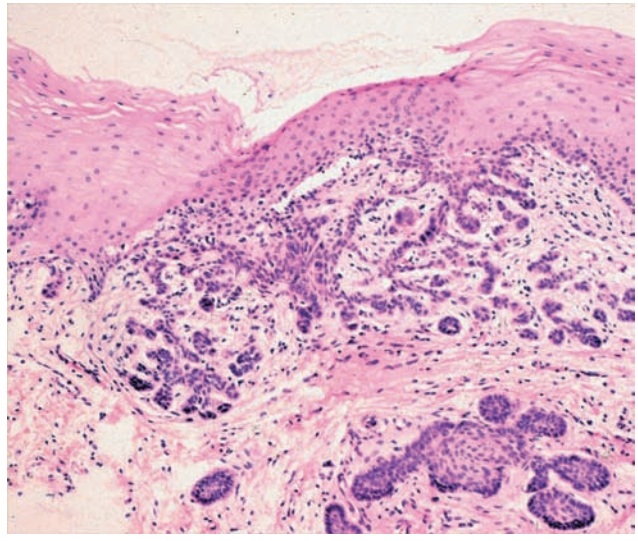


Fig. 3.6 Basal cell hamartias extending from the basal layer of the oral mucosa overlying an odontogenic keratocyst. (Courtesy of Dr Adalberto Mosqueda.)

'behaving rather like a low-grade squamous cell carcinoma' (Jackson *et al.*, 1993); whereas others extended from the maxilla into the orbit and infratemporal fossa (Chuong *et al.*, 1982), or into the infratemporal fossa (Worrall, 1992). DeGould and Goldberg (1991) described the recurrence of an OKC in a bone graft after partial mandibulectomy, and the source of this may well have been the mucosa.

Many studies have been carried out on patients with multiple OKCs and in patients with the NBCCS in an attempt to find explanations for the recurrences. Payne (1972) compared the histological features of recurrent OKCs with non-recurrent specimens and those from patients with the syndrome. The presence of inflammation and the type of keratin produced did not seem to be significant. He found bud-like proliferations of the basal cell layer in five of 11 recurrent cysts (45%) and four of nine cysts from patients with the syndrome (44%). By comparison, only six of 72 non-recurrent OKCs (8%) showed this feature. Satellite microcysts were observed in the cyst walls of 78% of cysts from patients with the syndrome, 18% of the recurrent cysts and 4% of the non-recurrent cysts. Donatsky *et al.* (1976) found only five of 55 cysts (9%) in patients with the syndrome to have bud-like proliferations of the basal layer of epithelium. There was, however, a significantly higher (P <0.01) occurrence of epithelial islands and/or microcysts in the walls of the syndrome cysts (51%) and solitary recurring cysts (53%) than in the solitary non-recurring cysts (17%).

Woolgar *et al.* (1987a,b) compared the clinical presentation and histological features of single OKCs and those occurring in the NBCCS. The gender distribution of their sample without the syndrome (62% males and 38% females; n=377) was significantly different (P <0.025) from the sample with the syndrome (45% males and 55% females; n=60). The mean ages were significantly different between the groups (P <0.001). In the group without the syndrome, the mean age at removal of the cyst was 40.4 years (SD±19.2) with a bimodal distribution, the first peak at 15–45 years and the second smaller peak at 55–65 years. In patients with the syndrome, there was a single peak at 10–30 years and a mean of 26.2 years (SD ±17.3). Log linear modelling of the variables showed that in their sample there were significantly more syndrome than non-syndrome patients before the age of 36 years and that in both groups of patients females were more likely to be seen in the younger age group. Their findings indicated that females with OKCs who are younger than 36 years are the group most likely to have the syndrome. With regard to site, there was a higher frequency in the mandibular molar-ramus area (60%) of cysts unassociated with the syndrome than those with (44%); whereas more syndrome cysts (21%) than non-syndrome cysts (11%) occurred in the maxillary molar region. Eighteen patients with the syndrome initially had only one cyst. In all except three, further cysts have developed subsequently. Of 24 syndrome patients with cysts in two quadrants, 13 had bilateral mandibular cysts related to third molar teeth. Five patients had cysts in three quadrants and 13 patients had cysts in all four quadrants. The time interval at which subsequent cysts were diagnosed varied from 1 to 23 years.

In a third paper, Woolgar *et al.* (1987c) were able to identify no significant differences in age, gender or site between a sample of patients with single, non-recurrent OKCs followed for 5 years or more and another sample of patients with OKCs that had recurred in the same sites as their original lesions. In a histological comparison of material from both samples, the only significant difference was that the recurrences were less inflamed than the primary cysts or the controls.

In their histological study, Woolgar *et al.* (1987a) compared 164 OKCs from 60 patients having the NBCCS with a similar number of OKCs from patients without the syndrome, matched for age and size. Significantly higher numbers of satellite cysts (P <0.001), solid islands of epithelial proliferation (P <0.001), odontogenic rests within the capsule (P <0.01), and in the numbers of mitotic figures in the epithelium lining the parent cyst cavity (P <0.001), were found in the syndrome group. The authors derived an index of activity by grading the solid proliferations, satellite cysts, ameloblastomatoid proliferations and the mitotic rate, and found that this was significantly higher in the syndrome group (P <0.001). Epithelial rests were strikingly more prevalent in the capsules of cysts from the younger age group and in the mandibular molar region. They found no association to support the theory that satellite cysts arose by basal budding of epithelium lining the parent cyst. Their results did, however, support the view that satellite cysts are formed when islands of proliferating epithelial cells derived from small epithelial rests reach a size where cystic breakdown occurs. They found no evidence that the ameloblastomatoid proliferations develop into true ameloblastomas. They suggested that there was some inherent genetic potential for proliferation of odontogenic epithelium in the syndrome patients.

Dominguez and Keszler (1988) compared solitary and syndrome-associated OKCs histologically and histometrically. Satellite cysts and/or epithelial islands were present in 36% of the syndrome-associated cysts and in only 6% of the solitary group (P <0.005). Histometric analysis showed that total nuclear numbers and numbers of basal nuclei were significantly higher (P <0.001) in solitary OKCs. Solitary cysts also had a significantly greater epithelial height (P <0.01). They suggested that the solitary and the syndrome-associated OKCs could be two distinct populations.

Numbers of authors have referred to the occurrence of multiple OKCs in patients without obvious signs of other

features of the syndrome, or of a familial trend. Brannon (1976) reported a frequency of 3% with multiple cysts in his sample, Vedtofte and Prætorius (1979) 4%, Ahlfors *et al.* (1984) 6%, Voorsmit (1984) 2% and Stoelinga and Bronkhorst (1988) 4.5%.

As oral surgeons have become increasingly aware of the need to treat OKCs more aggressively than other jaw cysts, or by the use of special protocols, it is likely that future studies will show a declining frequency of recurrences. It is difficult to ignore the possibility that the variability in reported recurrence rates may at least partly be attributable to differences in the surgical techniques used and in the experience of the surgeons. This view is borne out by the experience of Voorsmit *et al.* (1981) who reported the results of a follow-up study of two groups of patients treated for OKCs. In the first group of 52 cases treated between 1959 and 1980, the cysts were treated conservatively by careful enucleation of the entire wall. In the second group of 40 cases treated between 1970 and 1980, the cysts were removed by enucleation along with excision of the mucosa overlying a perforation of the cortical bone which was determined at operation. Before removal, all cysts in this group were treated with Carnoy's solution (Table 3.5). The recurrence rate in their first group was 13.5% in a 1–21 year follow-up while the recurrence rate in their second group was 2.5% in a 1–10 year follow-up. Similarly, Forssell *et al.* (1988) have pointed out that in their series of OKCs treated before 1975, the recurrence rate was 50%, whereas in the group treated during the period 1975–1980, the recurrence rate had dropped to 22%.

Enlargement

Rate of growth

It has been pointed out in a number of studies that inflammatory exudate had a negligible role in the enlargement of OKCs (Toller, 1970b; Browne, 1976; Smith *et al.*, 1983). Reference has already been made to Toller's rather tentative view that OKCs might possibly be regarded as benign neoplasms, and this whole question is dealt with in some detail elsewhere in this chapter. However, at that time there was not much information about their rate of growth. As they tended to extend along the cancellous component of the mandible without producing noteworthy expansion of the cortical plates, they frequently reached a large size before they were diagnosed. Although Browne (1971a) was of the opinion that these cysts grew more rapidly than other jaw cysts, Toller's view (1967) was that they grew at a similar rate to other epithelial cysts of the jaws. He suggested that the majority of OKCs would take about 6 years to recur to a clinically significant size of more than 1 cm diameter but with a wide time range, varying from 1 to 25 years.

Forssell (1980) estimated that the rate of growth of OKCs varied from 2 to 14 mm a year, with an average of about 7 mm; and that the rate was slow in patients over 50 years of age. The relevant point was that although the rate of enlargement of OKCs may not be greater than that of other jaw cysts, its growth was more unremitting (Main, 1970b). The reason for this unremitting growth was investigated by both Main (1970a) and Toller (1971). Main showed that the mitotic value of OKC linings ranged from 0 to 19 with a mean of 8.0. This figure was similar to that in the ameloblastoma and in dental lamina, and higher than that found in non-odontogenic cysts which had a mean mitotic value of 2.3, and in radicular cysts with a mean mitotic value of 4.5.

Toller (1971) estimated mitotic activity in an autoradiographic study following the *in vitro* incubation of cyst linings with tritiated thymidine in tissue culture medium. His results showed mean labelling indices of 13.0% for a series of six OKCs compared with 1.7% for five non-OKC cysts and 7.0% for human buccal mucous membrane.

Nuclear morphometric variables of the epithelium of 20 OKCs, compared with those of dentigerous (10) and radicular (10) cysts (Gunhan *et al.*, 2003) showed that the number of cells in the basal layer was higher in the OKCs than in the others. The mean nuclear area of the basal cells of the OKCs was smaller than that of the intermediate cells of all three cyst types (P <0.001). The basal cells of the OKC nuclei were more ovoid than those of the other cysts (P <0.001) and more variable in size. Nuclear densitometric findings showed that the DNA indices of all the OKCs were close to 1.0 and the cells were considered diploid.

A study of the proliferation patterns of the epithelium and connective tissue of an OKC and a radicular cyst found that the epithelium of the OKC, mainly in the basal and suprabasal cells as marked with H_3-thymidine, showed a higher rate of proliferation than the radicular cyst with a mean value of 4.5 proliferating cells per mm^2 compared with a mean value of 0.51 proliferating cells per mm^2 in the radicular cyst (Scharffetter *et al.*, 1989). The mean marking index (percentage of marked cells out of a total of 770 cells counted per representative area) was also substantially higher in the OKC than in the radicular.

Slowly and rapidly proliferating areas were identified in different parts and in different planes of section of the epithelium and connective tissue walls of both cysts, but their respective mean marking indices were substantially higher in the OKC. Microscopically, the autoradiographic sections showed that proliferation of the epithelium and the connective tissue of the OKC was irregular and in clusters, not homogeneous, but that there were areas where epithelium and connective tissue had proliferated simultaneously as well as areas where they had not (Scharffetter *et al.*, 1989).

They concluded that exclusively passive expansion of the cyst connective tissue as a reaction to the growth of the OKC was unlikely and that active growth of the connective tissue wall contributed to the invasive growth of this cyst.

A later and alternative view, based on a larger sample of material, was that there had been an over-interpretation of published figures for mitotic indices and tritiated thymidine labelling indices; that mitotic activity could not be equated with the numbers of mitotic figures in a field, and that neither could labelling indices unless cycle time, growth fraction and duration of DNA synthesis were known (Hume *et al*., 1990). This group studied the growth *in vitro* of explants and/or cell suspensions of 23 OKCs, 28 dentigerous cysts, 30 apical radicular cysts and 12 residual cysts. They found little evidence of differences in explant growth of OKCs (87%) and dentigerous cysts (75%), but less successful growth of the inflammatory cysts (57%). Dentigerous cysts were found to have grown more successfully from suspensions (91%) compared with OKCs (58%).

Having ruled out patient age as a factor, they took issue with the conclusions drawn from a similar study in which explants of three OKCs, three dentigerous cysts and one ameloblastoma had been grown *in vitro* and growth had been observed in the OKCs and ameloblastoma, but not in the dentigerous cyst (Stenman *et al*., 1986). On this basis it had been postulated that the OKCs had a similar growth potential to the ameloblastoma. The Hume group, however, argued that 'from these types of experiments' there was no evidence to support a conclusion as to the neoplastic potential of the OKC (Hume *et al*., 1990).

Role of osmolality in growth of the cysts

Toller (1970b) considered the part played by the osmolality of the cyst fluid in enlargement of OKCs. He showed that there was a statistically significant difference ($P < 0.01$) between the mean osmolality of the OKCs (296 ± 15.6 mOsm; $n = 11$) compared with the mean serum osmolality (282 ± 14.75 mOsm). In view of the low total soluble protein level in OKCs (Toller, 1970a), he suggested that osmotic differences between sera and cyst fluids were not directly related to proteins in cyst fluids and may be the result of the liberation of the products of cell lysis which may not be proteins. He believed strongly that the raised osmolalities have an important, even if not the sole, role in the expansive growth in the size of the OKC as well as other jaw cysts.

Main (1970b), on the other hand, felt that mural growth in the form of epithelial proliferation was the essential process involved in the enlargement of OKCs and that the evidence for osmotic diffusion was inconclusive. This view was supported by Browne (1970, 1975) and Kramer (1974). They believed that the multilocular and loculated outlines exhibited by some OKCs were difficult to interpret on the basis of unicentric hydrostatic expansion alone. This form of cyst outline suggested a multicentric pattern of cyst growth brought about by the proliferation of local groups of epithelial cells against the semi-solid cyst contents.

Ahlfors *et al*. (1984) also believed that the OKC should be regarded as a benign neoplasm. They drew attention to the infolding of the epithelial lining into the capsule and suggested that this was the result of active epithelial proliferation accompanied by collagenolytic activity within the fibrous capsule and resorption of bone.

Role of inflammatory exudate in growth of the cysts

Inflammatory exudate has a negligible role in OKC enlargement. Its cavity fluid contains low quantities of soluble protein, composed predominantly of albumin and only relatively small quantities of immunoglobulins (Toller, 1970a; Browne, 1976). Moreover, the cyst walls are usually free of inflammatory cell infiltrate except for occasional foci, and the more or less continuous lining of OKC epithelium is not a barrier readily penetrable by proteins. Smith *et al*. (1983) confirmed that OKC fluids contained smaller amounts of protein and that few high molecular weight proteins were present, compared with radicular and dentigerous cysts. This supported the hypothesis that the epithelial wall of the OKC was less permeable than that of other odontogenic cysts and that an exclusion barrier exists to higher molecular weight molecules (greater than approximately 68 000).

Role of glycosaminoglycans in growth of the cysts

Smith *et al*. (1984, 1988a,b) reported a series of three studies on the presence and role of glycosaminoglycans in odontogenic cysts, including OKCs. In the first of these studies, on cyst fluids, hyaluronic acid showed the highest frequency and abundance in all three cyst types. Appreciable amounts of chondroitin-4-sulphate were also observed, particularly in the radicular cysts, and heparin sulphate showed a higher frequency and abundance in the OKC than the other cysts. A considerable proportion of the glycosaminoglycans appeared to be complexed with protein and was released only after proteolytic digestion. The authors were uncertain about the origin of these macromolecules but concluded that they were probably derived from both the connective tissue and the epithelium of the cyst wall.

In their histochemical investigation of odontogenic cyst connective tissue, they demonstrated appreciable amounts of extracellular glycosaminoglycans and proteoglycans in the connective tissue capsules of all three cyst types, predominantly hyaluronic acid, with lesser amounts of sulphated glycosaminoglycans. They observed a subepithelial band of alcianophilia in all cyst types, predominantly in the dentigerous cyst, which was strongest adjacent to the epithelium and extended through the thickness of the

epithelium with diminishing intensity. This appeared to represent the presence of heparin sulphate. Mast cells were widespread in the connective tissue of all cyst types, particularly adjacent to the epithelium, and were probably the source of the heparin. They concluded that the major source of the glycosaminoglycans and proteoglycans in cyst fluids is from the ground substance of the connective tissue capsule, released as a result of normal metabolic turnover and inflammatory degradation. Degranulating mast cells released heparin and hydrolytic enzymes and the latter facilitated the breakdown of the glycosaminoglycans and proteoglycans. The epithelial contribution was mainly from goblet cells (Shear, 1960b; Browne, 1972; Slabbert *et al*., 1995). The authors suggested that the variation between individual cysts depended on the amount of inflammation, the epithelial permeability and the extent of mucous metaplasia.

In their third study, Smith *et al*. (1988b) extracted glycosaminoglycans from fresh connective tissue capsules of OKCs, dentigerous and radicular cysts. In all cyst types, hyaluronic acid was the predominant glycosaminoglycan present, as it was in the cyst fluids. Heparin and chondroitin-4-sulphate were present in substantial amounts. Epithelial permeability, the authors suggested, would probably allow passage of smaller glycosaminoglycan chains into the luminal fluid. The larger chains would probably pass through epithelial discontinuities and through intra-epithelial channels (Cohen, 1979). Meurman and Ylipaavalniemi (1982) asserted that these channels were not observed in OKCs, the epithelium of which was relatively impermeable to high molecular weight substances.

Passage of glycosaminoglycans into OKC fluid would therefore be, in the view of Smith *et al*., through areas overlying foci of inflammation, where the normal epithelial structure is replaced by a non-keratinised stratified squamous epithelium. They concluded from their series of studies that the release of these molecules into the luminal fluid could be expected to contribute significantly to its osmotic and hydrostatic pressures and hence to the expansile growth of odontogenic cysts.

Bone resorption and OKC growth

Role of collagenolytic activity in growth of the cysts

Donoff *et al*. (1972) demonstrated the presence of collagenolytic activity on skin collagen in explant and tissue cultures of OKCs – but only when both epithelium and fibrous wall were present in the media. No similar activity was demonstrable in dentigerous cysts and it was tentatively proposed that enzymatic mechanisms may be important in the growth of OKCs.

Uitto and Ylipaavalniemi (1977) also demonstrated collagenolytic activity in homogenates of OKC and radicular cyst walls. This activity was inhibited by the fluids of both cysts but that from the OKC to a lesser extent than that from the radicular cyst. It seemed probable that the activity of collagenase in tissues was controlled by a complex regulatory system which, in cyst tissues, might exert effects on collagenase activity, and thus influence the expansion of cysts within bone.

In a later study from the same laboratory, Sorsa *et al*. (1988) showed that human OKC collagenase degraded types I and II collagens at almost equal rates, but during the same time period no significant degradation of type III collagen occurred, a feature that also characterised human polymorphonuclear (PMN) type collagenase. The authors related this PMN collagenase and/or interstitial collagenase with 'PMN-like' characteristics, to connective tissue destruction associated with the growth of OKCs. The mechanism by which PMN collagenase may contribute to connective tissue destruction in the absence of circulating inflammatory cells in the OKC wall is explained by the authors as possibly the result of degranulation of subcellular compartments of PMNs stimulated by specific OKC antigen-induced immunocomplexes and/or by direct contact with the connective tissue being destroyed.

A different approach to investigating the character of the collagen fibres of the OKC compared with other jaw cysts, and the role these might have in their expansion, involved staining of sections of cysts with picrosirius red and assessing the colour reactions with polarising microscopy (Hirshberg *et al*., 1999). The sample comprised 15 specimens each of OKC, dentigerous and radicular cysts. It was found that although the thin fibres (0.8 µm or less) of all three cyst types were of similar amounts, mostly greenish-yellow (86–89%), there were statistically significant differences between the OKC and the dentigerous (P <0.00001) and radicular (P <0.0001) cysts in the distribution of the thick fibres (1.6–2.4 µm) which were yellow-orange. In the OKCs the green to greenish-yellow colour of both the thin and thick fibres suggested that the collagen of the wall was loosely packed and might be composed of procollagens, intermediates or pathologic collagens rather than the tightly packed fibres in the other cyst types. As this pattern had also been demonstrated in odontogenic tumours, the authors speculated that the stroma of the OKC could possibly be regarded not just as structural support, but also as playing a part in their neoplastic behaviour (Hirschberg *et al*., 1999).

Interleukins, tumour necrosis factor, matrix metalloproteins, tenascin, fibronectin and collagen IV, myofibroblasts, parathyroid hormone related protein

Interleukin-1 (IL-1) and tumour necrosis factor (TNF), cytokines that are particularly associated with chronic inflammatory lesions, had been shown to account for much of the bone-resorbing activity attributed to

osteoclast activating factor produced by mononuclear leucocytes. Studies on radicular and dentigerous cysts were originally undertaken to investigate the possibility that IL-1 might be produced by odontogenic cysts and might account for the raised levels of prostaglandin and collagenase synthesis that had been demonstrated in cyst capsules (Meghji *et al*., 1989).

In a follow-up paper by these authors on OKCs, it was pointed out that while in the radicular cysts the stimulus for the production of IL-1 was presumed to be bacterial products, this was unlikely to be a factor in OKCs (Meghji *et al*., 1992). Considering that keratinocytes had been shown to synthesise IL-1 and IL-6 and that these cytokines and TNF had potent bone-resorbing properties, it was postulated that these might account for raised levels of prostaglandin and collagenase synthesis by the uninflamed OKC capsule. Fresh fragments of six OKCs were maintained in explant culture and the media were assayed for IL-1, IL-6 and tumour growth factor (TGF) and for their ability to stimulate bone resorption.

All six cysts released IL-1 and IL-6 bioactivity, but not TNF. Dialysed cyst media stimulated bone resorption which could be completely inhibited by a monospecific antibody that neutralised IL-1α and IL-1β. The media supporting control gingival specimens showed no osteolytic activity. Immunohistochemical staining of cryostat sections of OKCs showed a strong reaction for IL-1α and IL-6 in the cyst epithelial cells but not in other cells, and control gingiva and buccal mucosa were also negative. Sections did not react with antibodies to IL-1β or TNF. They proposed therefore that IL-1α was the principal osteolytic cytokine produced by OKCs leading to bone resorption but that the role of IL-6 was less clear. It might, they suggested, contribute to OKC growth by promoting epithelial proliferation through an autocrine feedback mechanism (Meghji *et al*., 1992).

In a more recent study undertaken to investigate changes in the retained epithelium of OKCs treated by marsupialisation, Ninomiya *et al*. (2000) also demonstrated that the signal intensities for IL-1α mRNA were correlated with the proliferating activities of the epithelial cells, and both the expression of IL-1α mRNA and the epithelial cell-proliferating activities were reduced proportionally by marsupialisation, strongly suggesting a close association between positive intracystic pressure, IL-1α expression and epithelial cell proliferation in OKCs. They showed that a considerable amount of IL-1α was present in the intracystic fluids of OKCs, whereas the levels of other inflammatory cytokines such as IL-6 and TNF-α were very low. The levels of IL-1α were significantly higher than those of dentigerous cysts. The staining intensity for IL-1α in the epithelial linings was stronger than that of the endothelial cells and fibroblasts in the subepithelial layers, suggesting that IL-1α was predominantly produced by the epithelial cells of the OKCs. This suggestion was confirmed by *in situ* hybridisation which showed that the strong signal for IL-1α mRNA was particularly detected in the epithelial cells all through the epithelial layers.

Kubota *et al*. (2004) reasoned that as their group had shown that IL-1α mRNA and protein were expressed intensively in the epithelial cells of OKCs, and that the expression of IL-1α was inhibited after decompression, increased intracystic pressure might, therefore, play a crucial part in the growth of odontogenic jaw cysts. However, they believed that intracystic pressure may change as the cyst progresses, because intracystic fluid pressure is regulated by various factors such as the osmotic tension of the fluid, the elasticity of the cyst wall, the permeability and the blood pressure of the capillaries in the cystic wall, and the lymphatic drainage and venous return from the cavity. They therefore investigated the relation between the size of odontogenic cysts and the intracystic fluid pressure.

Their sample comprised nine OKCs, 16 dentigerous cysts and 10 radicular cysts. The cysts, which had no buccal expansion, were located at the molar regions of the mandible, and completely surrounded by bone. Neither acute infection of the cyst nor communication between oral cavity and cyst were obvious clinically before the intracystic fluid pressure was measured. After the intracystic fluid pressure had been measured, a surgical window was made in the cavity, and the intracystic fluid was completely washed out. The volumes of 25 cysts were then measured by filling each cavity with sterile physiological saline using a fine needle. The volume of the cyst was measured three times, and the mean value was taken as its volume. It was impossible to measure the volume in 10 of 35 cysts because of local bleeding. To measure the radiolucent area of the odontogenic jaw cyst, panoramic radiographs were taken during the first visit to the hospital. After tracing the outlines of the radiolucent areas of the cysts, the areas were measured by a computer system using a scanner (CanoScan FB1200S, Canon Inc., Tokyo, Japan), and calculated by using the software NIH Image version 1.62.

They found that there was a positive correlation between the radiolucent area of an odontogenic jaw cyst and its volume. They also found that when odontogenic jaw cysts were located at the molar regions of the mandible, there was a linear relationship between the radiolucent areas of the cysts on panoramic radiographs and the volume of intracystic cavities as a result of limitation of bucco-lingual growth by the thick cortices. The size of an odontogenic jaw cyst at the mandibular molar region could, therefore, be estimated by panoramic radiographs.

A later study by this group (Oka *et al*., 2005) investigated the effects of positive pressure on the expression of IL-1α matrix metalloproteins (MMPs) and prostaglandin E_2 (PGE_2) in OKCs to determine whether this pressure

stimulates inflammatory cytokine production and signalling of osteoclastogenic events. They found that positive pressure enhanced the expression of IL-1α mRNA and protein in the epithelial cells of the OKC, and increased the secretion of MMP-1, MMP-2, MMP-3 and PGE_2 in a co-culture of OKC fibroblasts and the epithelial cells. The pressure-induced secretions were inhibited by an IL-1 receptor antagonist. They concluded that positive pressure may have a crucial role in OKC growth by stimulating the expression of IL-1α in the epithelial cells.

In the English abstract of an article in Chinese, Gao and Li (2005) reported an investigation on the effects of bone resorption, *in vitro*, by various odontogenic cysts and ameloblastomas. Fragments of 14 OKCs, six inflamed OKCs, five dentigerous cysts and seven ameloblastomas were incubated *in vitro* for 24 h. The supernatant was then removed into the culture system of SD rat calvaria. After incubation for 48 h, the calcium contents of the media were measured by an atom spectrophotometer. The supernatant of odontogenic cysts and ameloblastomas was measured for the bone resorption related factors IL-6, TNF-α, PGE_2, bone Gla-containing protein (BGP) and calcitonin by a radioimmunoassay system.

The calcium released in the calvaria culture media by all the odontogenic lesions was significantly higher than that in the blank controls (P <0.01). The inflamed OKC group had a significantly higher calcium concentration than the uninflamed OKC and ameloblastoma groups (P <0.05). In addition, the concentrations of IL-6, TNF-α, PGE_2 and calcitonin in the culture media of all odontogenic lesions were significantly higher than that of the blank controls (P <0.05). IL-6 concentration in the inflamed and non-inflamed OKC groups were significantly higher than that of the ameloblastoma group (P <0.05). The calcitonin concentration in the inflamed OKCs was significantly higher than those of the OKC and dentigerous cyst groups (P <0.05). Correlation and regression analysis showed that IL-6 was significantly correlated with the calcium content (P <0.01). The authors concluded that the odontogenic lesions could promote bone resorption *in vitro* and it was likely to be related to some of the cytokines secreted by the lesions.

A series of four papers by Teronen *et al.* (1995a,b, 1996; Teronen, 1998) reported the presence and activities, as well as the activation/inhibition profiles, of MMPs in jaw cysts to determine their possible role among the complexity of molecular mechanisms associated with cyst enlargement. MMPs were defined as a superfamily of 17 genetically distinct but structurally related neutral proteinases participating both in physiological tissue remodelling and in pathological tissue destruction associated with diseases such as periodontitis, rheumatoid arthritis, tumour invasion and metastasis. They found that gelatinases MMP-1 and MMP-9 were present in jaw cyst tissue extracts in both latent and activated forms. MMP-2 and MMP-8 were also present, but to a lesser extent (Teronen, 1998). Mast cell tryptase (MCT) was also detected. No significant differences in the MMPs were found between cyst types, but the trypsin-like activities per milligram of soluble protein were higher in radicular and dentigerous cysts than in OKCs.

They suggested that the presence of active forms of MMP-1 and MMP-8 in cyst extracts, as shown by Western blotting, and their activation by both proteolytic and thiol-group reactive activating agents, as well as immunohistochemical work showing MMP-1 in radicular cysts, indicated that MMP-1 should be regarded as a significant mediator of tissue destruction in these cysts. Moreover, they proposed that the presence of both MMP-2 and MMP-9 in cyst tissue extracts, especially the proteolytically activated forms of MMP-2, demonstrated strongly the proteolytic activity of cyst tissue and its active role in the expansion of the cysts at multiple levels of proteolytic cascades (Teronen, 1998).

Following on earlier studies (Meghji *et al.*, 1989), it was shown that levels of IL-1α were significantly higher in the fluids of OKCs than in dentigerous or radicular fluids (Meghji *et al.*, 1992). In this work there was focus on the effects IL-1α on both the secretion and activation of MMP-9 in odontogenic jaw cysts. Total gelatinolytic activity of MMP-9 (92 kDa and 83 kD MMP-9) of cyst fluids was not significantly different between the OKCs and the other cyst types, but the activity ratio of 83 kDa MMP-9 gelatinolytic activities to total MMP-9 gelatinolytic activity (92 kDa and 83 kDa MMP-9) in OKC fluids was significantly higher than in the fluids of the other cysts fluids (Kubota *et al.*, 2000).

OKC fragments in explant culture secreted considerably larger amounts of IL-1α than the other two cyst types and spontaneously secreted both proMMP-9 and an active form of MMP-9. Fragments of dentigerous and radicular cysts, however, secreted a small amount of proMMP-9 but no active form of MMP-9. The epithelial cells isolated from the OKCs secreted IL-1α and proMMP-9 without stimulation. Under cultivation on a fibronectin-coated dish, rhIL-1α increased the secretion of proMMP-9 from the epithelial cells in a dose-dependent manner. It also increased the secretion of proMMP-3 and plasminogen activator urokinase (u-PA) from the epithelial cells and converted the secreted proMMP-3 to the active form in the presence of plasminogen. The secreted proMMP-9 was also activated in the presence of IL-1α and plasminogen fluids (Kubota *et al.*, 2000).

The results suggested that IL-1α may up-regulate not only proMMP-9 secretion but also proMMP-9 activation by inducing proMMP-3 and u-PA production in the epithelial cells by autocrine/paracrine regulatory mechanisms fluids.

Amorim *et al.* (2004) reported differences detected in the immunohistochemical expression of tenascin,

fibronectin and collagen IV, between solitary and syndrome-related OKCs. Tenascin was present in a continuous pattern at the epithelial–connective tissue interface in all five syndrome OKCs, but in only five of the 10 sporadic cases. Expression of this glycoprotein is believed to correlate with cell proliferation and migration, such as in wound epithelialisation and connective tissue invasion. The authors have suggested that the more significant presence of tenascin at the epithelial–connective tissue interface of the cysts associated with the NBCCS can be related not only to an enhanced ability to infiltrate contiguous tissues but also to a higher proliferative activity of the epithelial lining. Tenascin was also present in the interstial matrix of both groups of OKC, and the authors have referred to other work in which tenascin has been thought to have an important role in the stroma of many tumours.

Fibronectin comprises a group of glycoproteins that are present in connective tissues and are thought to have an important role in embryonic development by mediating cell adhesion and migration. This protein was present as a discontinuous line in the basement membrane in syndrome-related OKCs and the authors speculated that this finding might be related to a higher proliferative potential in the cystic structure of the NBCCS cases compared with the non-syndrome cases on the basis that the discontinuity could facilitate epithelial–mesenchymal signalising relations.

Collagen IV was not present in the majority of the syndrome-related cysts, while negative areas for laminin predominated in the basement membranes of both groups, and the authors have speculated similarly on the significance of their respective distributions. They have concluded that these differences might indicate a more aggressive biological behaviour of the NBCCS-related cysts (Amorim *et al*., 2004).

A series of 10 non-syndrome related OKCs, 10 dentigerous cysts and 10 radicular cysts were analysed immunohistochemically to verify the expression of tenascin and fibronectin (de Oliveira *et al*., 2004). Tenascin immunostaining was expressed in OKCs as a thick reticular and/or fibrillar positive band deep to the epithelial–mesenchymal interface and an intense reactivity in half of the cases. The radicular cysts reacted similarly and in these lesions the reaction was usually associated with inflammation. In the dentigerous cysts there was a thin positive tenascin band along the epithelial–mesenchymal interface, where the majority showed only weak expression. With regard to fibronectin, the OKCs demonstrated a fibrillar compacted arrangement and reticular pattern of fibronectin expression of moderate intensity. Fibronectin was visualised as a continuous line in six cases, and discontinuous in four. The authors concluded that the higher tenascin and fibronectin expression in the capsules of the OKCs suggested instability in the structure of the cysts and speculated that this might contribute to its aggressive behaviour.

On the basis of evidence that the presence of myofibroblasts (MF) at the invasion front of a neoplasm is not part of the host defence mechanism against its capacity to infiltrate, but actually promotes it, Vered *et al*. (2005) undertook a study to assess immunohistochemically, the frequency of stromal MF in different odontogenic cysts and tumours and to correlate these findings with their respective known degrees of aggressive biological behaviour. Their material comprised seven cases of dentigerous cyst, eight cases of OKC from non-syndromic patients, nine cases of orthokeratinised OKC, 11 cases of ameloblastic fibroma/fibro-odontoma, six cases of unicystic ameloblastoma and seven cases of solid ameloblastoma. Five cases of oral squamous cell carcinoma served as controls (see p. 34 for further discussion of the orthokeratinised OKC). Alpha smooth muscle actin (αSMA) mouse anti-human antibody was used for the immunohistochemical reaction. The reactions in the different lesions were assessed quantitatively.

Of the odontogenic cysts, the OKC had the highest mean number of αSMA-positive cells per field (25.7± 11.4), while the dentigerous cysts had the lowest (8.7± 11.6). These differences were statistically significant (P = 0.024). Spindle cells showing fine αSMA-positivity were located beneath and parallel to the basement membrane of the odontogenic epithelium of the cystic lesions. Additional small aggregates and short, delicate bundles of similar cells were found within the fibrous wall. The reaction in the OKC was intense.

Among the odontogenic tumours, the mean number of αSMA-positive cells per field in the solid ameloblastomas (29±7) was significantly higher than that in unicystic ameloblastomas (14.9±4.9) (P <0.001). The ameloblastic fibroma/ameloblastic fibro-odontoma group had the lowest mean number of positive cells (5.6±7.5), and this differed significantly from that of the other tumours (P <0.001). Islands of odontogenic epithelium particularly in the solid ameloblastomas were surrounded by layers of αSMA-positive cells. The mean number of αSMA-positive cells per field in the squamous cell carcinomas (21.3±5.3) was not significantly different from that of the solid ameloblastomas and the OKCs (P >0.05). The mean number of αSMA-positive cells per field in the OKCs was significantly higher than that in the ameloblastic fibroma/ameloblastic fibro-odontoma group (P <0.001). Control sections of the squamous cell carcinomas showed that malignant islands were surrounded by abundant αSMA-positive stromal cells (Vered *et al*., 2005).

The authors concluded that their quantitative study provided persuasive evidence that the stroma of these lesions harbour myofibroblasts as reflected by αSMA-positive cells. Furthermore, that it had been shown that the mean number of myofibroblasts in the OKCs and

solid ameloblastomas, lesions that tended to behave aggressively, was high and did not differ significantly from that in the squamous cell carcinomas. In contrast, the lesions that do not tend to behave aggressively showed significantly lower counts. They suggested therefore that a positive link could be identified between the occurrence of large numbers of myofibroblasts in the stroma, and a more aggressive behaviour of the OKC. Odontogenic epithelium, mainly in the solid ameloblastomas and OKCs, they suggested, could act and modulate stromal myofibroblasts in a manner similar to squamous cell carcinomas (Vered *et al*., 2005).

The immunocytochemical expression of parathyroid hormone-related protein (PTHrP) has been studied in odontogenic jaw cysts (Li *et al*., 1997). The authors described this protein as the putative cause of the humoral hypercalcaemia of malignancy, which has potent parathormone-like activity and is a local factor which regulates cell growth and differentiation. It is widely found in carcinomas and it has been shown that PTHrP expression is associated with invasion of the mandible by oral squamous cell carcinoma.

The authors investigated the immunocytochemical expression of PTHrP in odontogenic cysts because of evidence that OKCs have less bone resorbing capacity than the dentigerous and radicular cysts. Using paraffin sections and two antibodies to PTHrP, they found that all the OKCs ($n=10$), 9 of 10 dentigerous and 8 of 10 radicular cysts showed reactivity for PTHrP localised mainly to the basal and suprabasal cells. However, measuring the intensity of PTHrP by TV image analysis, the OKC linings expressed significantly higher levels than those of the dentigerous ($P<0.003$) and the radicular ($P<0.003$) cysts. No differences were detected between sporadic, recurrent and syndrome-related OKCs. The fibrous walls of all three varieties of cyst were reactive for PTHrP, with the OKC showing a higher intensity of staining. They believed that the high level of PTHrP immunoreactivity in the well-differentiated parakeratinised linings of the OKCs was probably the result of local production (Li *et al*., 1997).

These authors speculated that PTHrP might modulate growth and bone resorption in odontogenic cysts and might act synergistically with IL-1 to increase bone resorption or stimulate osteoblasts and inhibit osteoclasts, resulting in reduced resorption, through its TGFβ-like activity.

Radiological features

OKCs may appear radiologically as small, round or ovoid, radiolucent areas. Frequently, however, the lesions are more extensive. They may be well demarcated with distinct sclerotic margins as might be expected from slowly enlarging lesions, but part of the border may be diffuse. Many are unilocular radiolucencies, and these have a smooth periphery (Fig. 3.7).

Some of the unilocular lesions have scalloped margins (Figs 3.8 and 3.9) and these may be misinterpreted as multilocular lesions. Most of them are found in the mandible. The scalloped margins suggest that unequal growth activity may be taking place in different parts of the cyst lining and this may be observed in occasional gross specimens that are removed intact (Fig. 3.9). Voorsmit (1984) described this group of OKCs as multilobular. True multilocular lesions are not uncommon. Browne (1970) found 19 of 83 cysts (23%) to be of this type, all in the mandible, and Forssell (1980) observed a frequency of 25% in a series of 135, also all in the mandible. In the series of Voorsmit (1984), 13 of 103 OKCs were found to be multilocular at operation. Only one of these was in

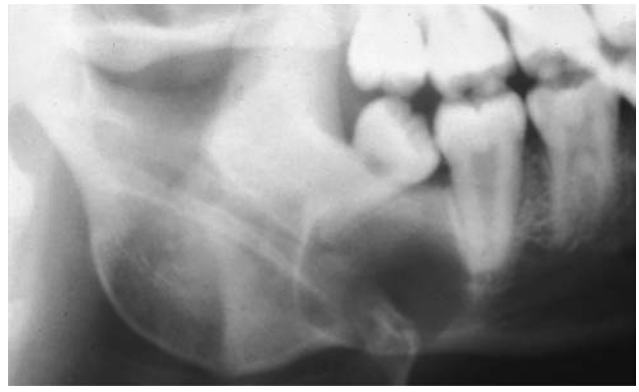


Fig. 3.7 Radiograph of a small odontogenic keratocyst.

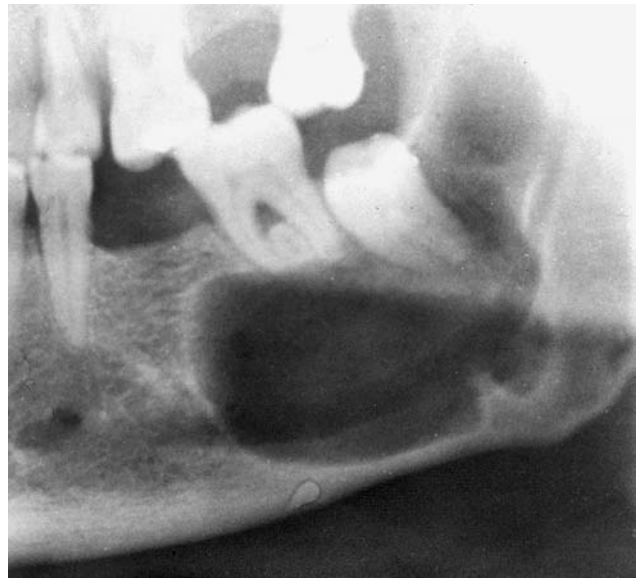


Fig. 3.8 Radiograph of an odontogenic keratocyst with scalloped margins.

the maxilla. Forssell has shown that unilocular cysts with a scalloped contour or multilocular cysts are significantly larger than unilocular cysts with a smooth margin.

The multilocular variety is particularly liable to be misdiagnosed as ameloblastoma (Fig. 3.10). The unilocular and multilocular lesions may involve the body and ascending ramus of the mandible extensively. There may be no expansion of bone at all, but in a substantial proportion of cases, particularly at the angle or in the ramus, expansion may occur (Browne, 1970; McIvor, 1972; Smith and Shear, 1978; Forssell, 1980). Expansion is usually slight but may be considerable in children. Both buccal and lingual expansion occur (Browne, 1970; McIvor, 1972).

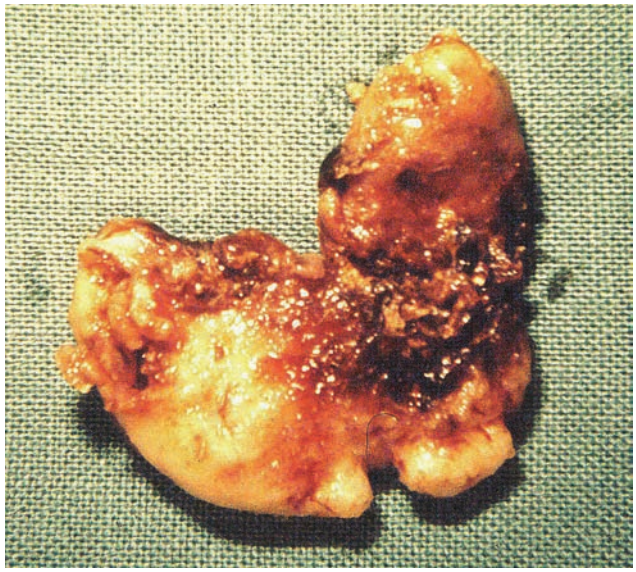


Fig. 3.9 Gross specimen of the odontogenic keratocyst shown in Fig. 3.8 shows the irregular growth responsible for the scalloped margins.

Downward displacement of the inferior alveolar canal and resorption of the lower cortical plate of the mandible may be seen as well as perforation of bone (Smith and Shear, 1978; Forssell, 1980; Voorsmit, 1984), and pathological fractures may occasionally occur (Voorsmit, 1984). There may be extensive involvement of the body and ascending ramus of the mandible, with little or no bony expansion. Spitzer and Steinhäuser (1985) suggested that unilocular or multilocular radiolucencies distal to the third molar in the ascending ramus were very probably OKCs.

OKCs may occur in the periapical region of vital standing teeth, giving the appearance of a radicular cyst (Wright *et al*., 1983). They may impede the eruption of related teeth, resulting in a 'dentigerous' appearance radiologically (Fig. 3.11). Forssell (1980) observed a relationship between the cyst and the crown of a tooth in 41% of a series of 135 cases. This association was more frequent in the maxilla. McIvor (1972), however, demonstrated this relationship exclusively in the mandible. Such lesions are frequently misdiagnosed as dentigerous cysts and this has given rise to two misconceptions (Fig. 3.12). One is that many dentigerous cysts have keratinised epithelial linings similar to those found in OKCs; and the second is that dentigerous cysts may have an extrafollicular origin (Gillette and Weinmann, 1958).

For all this, the point should be made that, very occasionally, the lining of a cyst in a true dentigerous relationship may be identical to that of an OKC. It was suggested by Browne (1969) that this occurred when an enlarging OKC involved the follicle of an unerupted tooth and fused with the reduced enamel epithelium. He

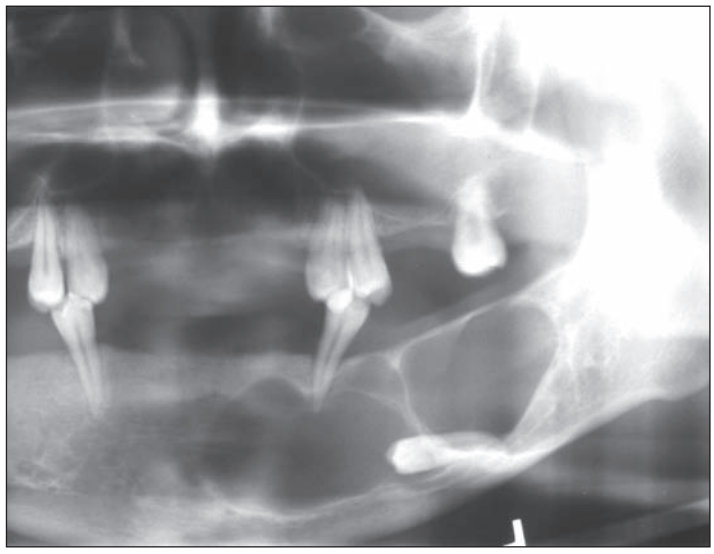


Fig. 3.10 Radiograph of a multilocular odontogenic keratocyst. (Courtesy of Professor C. Nortjé.)

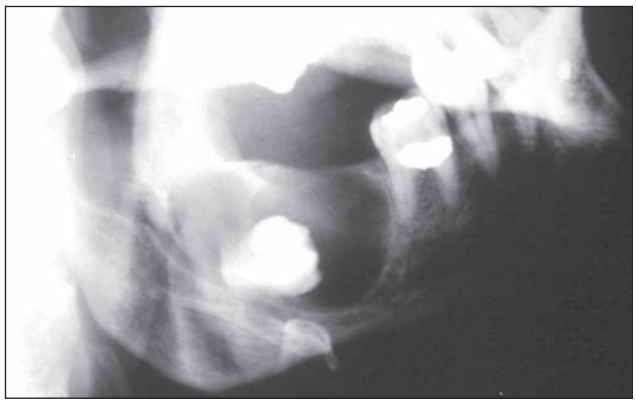


Fig. 3.11 Radiograph of an odontogenic keratocyst that has enveloped an unerupted tooth to produce a 'dentigerous' appearance.

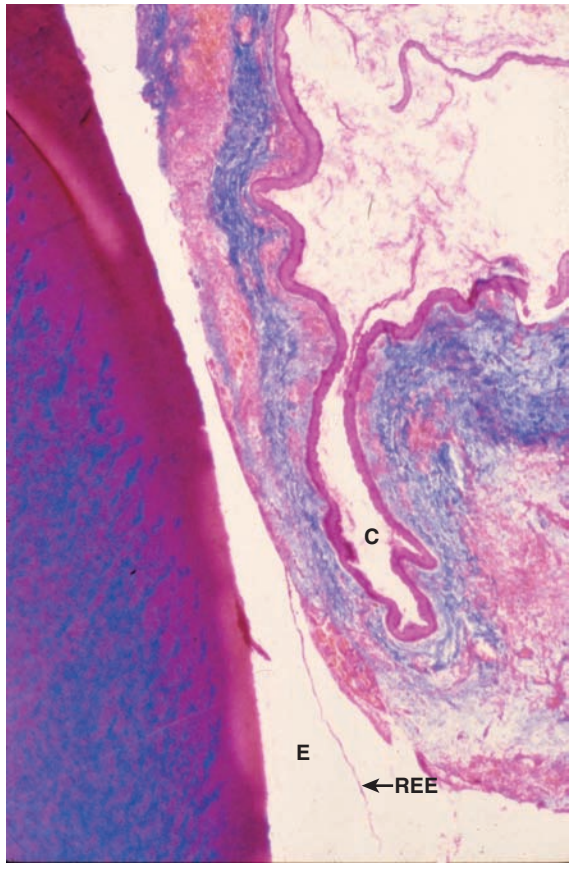


Fig. 3.12 An odontogenic keratocyst (C) that has enveloped an unerupted tooth. The cyst lies external to the enamel space (E) and the reduced enamel epithelium (arrowed). Picromallory stain.

pointed out that in such cysts the epithelium immediately around the neck of the tooth was not keratinised and showed inflammatory changes in the underlying capsule.

This concept has been developed by Altini and Cohen (1980, 1982) who have introduced the term 'follicular primordial cyst' (follicular keratocyst) for this group of lesions. They studied 17 cases in which the cyst lining was typically OKC on histological examination but which on macroscopic examination had completely surrounded the crown of the tooth and had been firmly attached to the neck. Eight of their cases occurred in the mandible and nine in the maxilla. Five of the latter were associated with canine teeth, one mandibular case with an unerupted premolar and all the others with third molars. Altini and Cohen postulated that follicular OKCs might arise following eruption of a tooth into a pre-existing OKC cavity in the same way as a tooth erupted into the oral cavity. Histological study of their series of follicular OKCs showed that the epithelium that lined that part of the cyst closest to the neck of the tooth was typically reduced enamel epithelium. This epithelium formed an attachment to the neck of the tooth and extended for a short but variable distance. Between this and the typical OKC epithelium that lined the remainder of the wall, and fusing with both, was a short segment of non-keratinised, stratified squamous epithelium.

In a later study, they were able to support their hypothesis in a series of animal experiments (Altini and Cohen, 1987). Four weeks after extracting deciduous teeth from both the maxilla and mandible of young vervet monkeys, recipient sites were prepared by drilling holes in the alveolar bone and small pieces of autogenous palatal mucosa were placed in them. Of 33 implants, cyst formation occurred in 11. These cysts were filled with keratin and lined partly by a thick keratinising epithelium and partly by a thin non-keratinising epithelium only a few cell layers thick. In one of the animals killed after 52 weeks, the follicle of of an erupting premolar tooth had collided with one of the cysts, the lining of which became incorporated into the follicle, partly replacing the follicular reduced enamel epithelium and forming an integral part of the follicle of the erupting tooth. In some serial sections the implanted epithelium accounted for up to 30% of the epithelial lining of the follicle.

Main (1970a) has referred to the variety of OKC that embraces an adjacent unerupted tooth as 'envelopmental'. Those cysts that formed in the place of a normal tooth of the series, he called the 'replacement' variety; and those in the ascending ramus away from the teeth he referred to as 'extraneous'. Main proposed the use of the term 'collateral' for those OKCs adjacent to the roots of teeth, usually in the mandibular premolar region, which were indistinguishable radiologically from the lateral periodontal. In Forssell's (1980) series the 'replacement' variety occurred in 7% of 135 cases, and the 'collateral'

type in 19%. There is little support currently for the view that OKCs might develop in the place of a normal tooth of the series and the descriptive term 'replacement variety' is outmoded.

Occasional cases may occur in the anterior midline of the maxilla and simulate a nasopalatine duct cyst (Brannon, 1976; Woo *et al*., 1987).

OKCs may, as they enlarge, produce deflection of roots of teeth. In Voorsmit's (1984) study, there was a displacement of unerupted teeth in 33 cases, mostly in the region of the angle of the mandible towards the inferior border of the mandible and occasionally in the ascending ramus and towards the orbital floor. In our own material, root resorption has rarely occurred (Struthers and Shear, 1976), but Forssell (1980) has observed varying degrees of root resorption in 24% of a series of 90 OKCs associated with roots of adjacent teeth. Forssell pointed out, however, that a large proportion of these showed only a slight degree of resorption. McIvor (1972) noted root resorption in four of a series of 47 cases (8.5%), while Partridge and Towers (1987) observed this in nine of their sample of 82 cases (11%). In a radiological study of 103 OKCs, Voorsmit (1984) found associated root resorption in only three cases (3.4%).

Postoperative radiological examination is important in the diagnosis of recurrences which depends on the presence of a corticated radiolucency which increases in size on a series of radiographs taken over a period of time (McIvor, 1972). McIvor pointed out that a diagnosis cannot be made with confidence on a single film as the bony defect following surgical removal of the cyst may be indistinguishable from a recurrence.

OKCs may present radiologically in the globulomaxillary and median mandibular regions. The question as to whether globulomaxillary and median mandibular cysts in fact exist has been controversial and there is now a widely accepted view that they do not.

Computerised tomography and magnetic resonance imaging

Voorsmit (1984) was probably the first to report on the use of computerised tomography (CT) in the assessment and follow-up of OKCs. He described two cases in which this technique was used 'to obtain accurate measurement of the extent of the lesion, exact localization of areas of perforation through the cortex and, particularly, assessment of soft tissue involvement'. He considered that the reliability and accuracy of CT scans in the diagnosis of large mandibular OKCs was striking and that the technique may be helpful for tumours and cysts of the maxilla, particularly where extension of the lesion to the cranial base is suspected. He described the important features of the technique as lack of image superimposition, preservation of soft tissue detail, selective enlargement of areas of interest, a high degree of accuracy and the possibility of three-dimensional interpretation. On the other hand, he thought, resolution of fine detail was poorer than with conventional or xerotomography. The high expense of the procedure was referred to, but not the hazards of the radiation exposure.

MacKenzie *et al*. (1985) reported the use of CT in the diagnosis of an OKC and emphasised the considerably higher absorbed doses of radiation, particularly to the lens of the eye. In general, these authors stated, the absorbed radiation from CT studies was about 1000 times higher than those associated with a panoramic study. They believed that the associated risks, the cost of the examination and the limits of the CT scan must be weighed against the additional information that could be obtained from the procedure before it was used on an individual patient. Swartz *et al*. (1985) found CT valuable in preoperative diagnosis and surgical management of odontogenic lesions including cysts but made no reference to the higher absorbed doses of radiation. Lehrmann *et al*. (1991) also referred to the value of high-resolution CT in determining the extent of the OKCs and in pinpointing areas of cortical breakthrough and involvement of teeth.

Yoshiura *et al*. (1994) found that a helpful feature in the diagnosis of OKCs was the presence of areas of increased attentuation in CT scans, and that these areas resulted from the presence of keratin in their cavities.

The use of MRI to differentiate OKCs from ameloblastomas and other cysts was the basis of a study by Minami *et al*. (1996). Their sample included 19 OKCs, 11 ameloblastomas and 13 other jaw cysts. Contrast-enhanced MRI was performed on all cases. Various imaging parameters were determined: locularity, solid or cystic pattern, thickness and contrast enhancement of the walls, and homogeneity and signal intensities of the fluids. T2 relaxation times of cystic components were calculated in 31 lesions. They found that MRI of the ameloblastomas differed from the OKC in displaying a mixed solid and cystic pattern and irregularly thick walls in all 11 cases, papillary projections in seven, and strong enhancement of solid components in nine. T2 relaxation times of the cyst components were significantly shorter in the OKCs than in the ameloblastomas. All other cysts showed a unilocular, purely cystic pattern with homogeneous fluids, although T2 relaxation times of four lesions overlapped those of the OKCs. They drew the important conclusion that OKCs could be differentiated from ameloblastomas in all their cases through the use of MRI, but that some other cysts showed similar findings to the OKCs.

A comprehensive review of MRI and CT imaging of 21 cases of OKC has been reported by Van Rensburg *et al*. (2003) and Van Rensburg (2004). On panoramic

radiographs, solitary cases appeared unilocular, lobulated or multilocular. In the mandible, a surprisingly large proportion (6 of 13) of the sporadic cysts appeared multilocular. The unilocular lesions displayed a well-defined sclerotic border, whereas the lobulated and multilocular lesions were irregularly corticated with thinning or scalloping of the cortex. 'Internal spiculation' or incomplete septum was present in two cases.

'Conventional CT and reformatted helical CT images at bone window settings' showed features additional to those visualised in panoramic views. These included 'the extent of the lesions within the mandibular ramus, coronoid process, palate, extension into the maxillary and ethmoid sinuses and the nasal fossa, floor of the orbit, scalloping of the margins, internal spiculation, and small crevices involving the peripheral cortex of the lesions. . . . On soft tissue window settings, OKCs appeared hypodense to isodense to muscle' (Van Rensburg *et al*., 2003).

On what are termed T1-weighted images, OKCs imparted hypointense to isointense signals to muscle. Epithelial linings with increased signal intensity on T1-weighted images proved to be infected cysts. On T2-weighted images, small crevices could be visualised, as could small daughter cysts.

Van Rensburg *et al*. (2003) argued that while panoramic radiographs depicted the location and expansile nature of most lesions, they did not help in determining the locularity or extent of some lesions within the jaws and the state of the surrounding soft tissue. CT images, on the other hand, revealed features such as areas of thinning, perforation and cortical loculation. A lesion that might appear on panoramic views to be multilocular may show no internal septation on a CT image. In differential diagnosis from the OKC, the authors were confident about excluding most cases of ameloblastoma and other cystic lesions not containing keratin, such as dentigerous and radicular cysts.

In another publication, Hisatomi *et al*. (2003) also reported on the use of MRI and contrast-enhanced imaging to distinguish different jaw cysts from one another, and concluded that they were able to obtain more information from these images than from conventional radiographic findings.

It seems important to refer here to a report by a joint working party of the National Radiological Protection Board and the Royal College of Radiologists. While stressing the benefits of X-rays in diagnosing disease, the report commented nevertheless that the avoidable dose of radiation from medicine 'outweighs the combined contribution of all other man-made sources of population radiation exposure by a factor of three' (Brown, 1990). Data obtained by the Board indicated that CT scans, at the time of their study, accounted for at least 20% of the total effective dose of diagnostic radiation to the population, and the working party suggested that radiologists should be informed of the 'high-dose implications' of CT scans. Wherever possible, it was suggested, doctors should use the alternatives to X-ray, mainly ultrasound and MRI.

Ferreira *et al*. (2004) suggested an interesting technique to distinguish OKCs from solitary bone cysts (SBC) of the mandible by identifying their contour and pixel grey levels in digitised panoramic radiographs of 32 SBCs and 20 OKCs. These were digitised and analysed by six examiners. The contours of the images were classified as indistinct, distinct without a sclerotic border, and distinct with a sclerotic border. The presence or absence of scalloping and the pixel grey levels of the radiolucent part of the images were also determined. They found that the sclerotic border was more frequent in the OKC, especially in the posterior segment ($P=0.03$) while scalloping was more frequent in the superior segment of the SBC ($P=0.03$). The pixel values were higher in the OKC than in the SBC images ($P=0.001$).

Figure 3.13 is an axial CT scan of an OKC in the left mandible showing expansion of the buccal and lingual cortical plates of bone, and a perforation of the lingual plate. Figure 3.14 is a CT scan of the mandible showing buccal and lingual expansion, with thinning and perforation of the lingual plate. Figure 3.15 is a CT scan showing

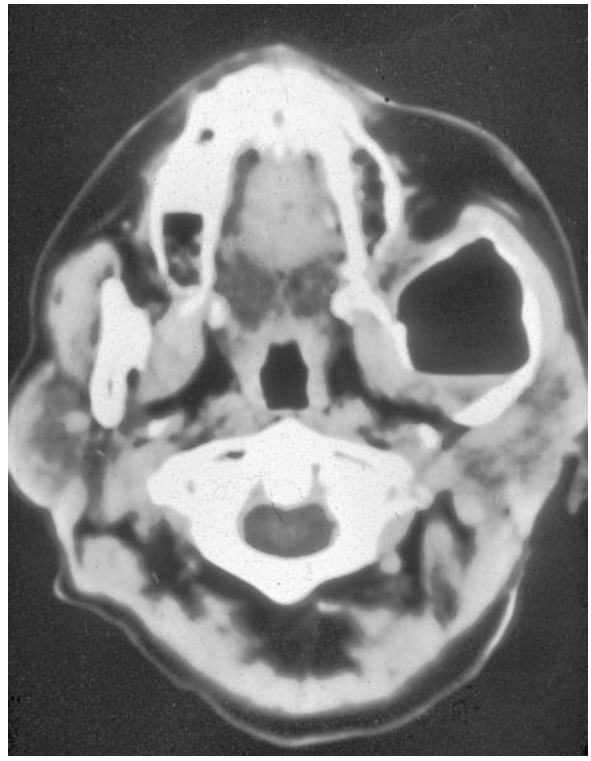


Fig. 3.13 Axial CT scan showing an odontogenic keratocyst in the left ascending ramus of the mandible. There is buccal and lingual expansion and thinning of the cortical plate which is breached on the lingual aspect. (Courtesy of Professor J. Lownie.)

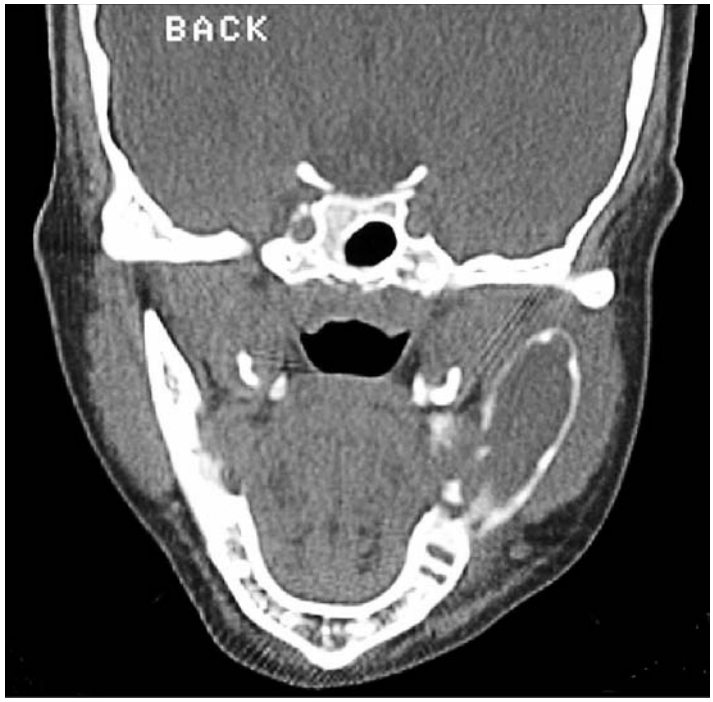


Fig. 3.14 CT scan of the mandible showing buccal and lingual expansion on the left side, with thinning and perforation of the lingual plate. (Courtesy of Dr R. Hendricks.)

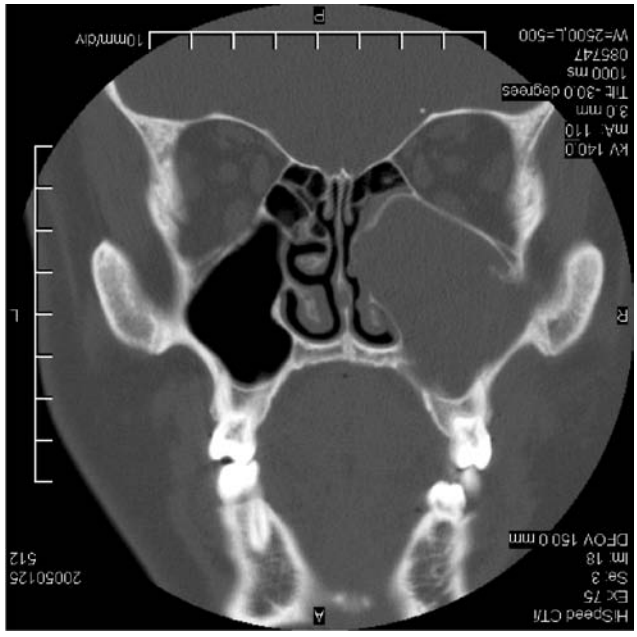


Fig. 3.15 CT scan showing infiltration into, and expansion of, the left maxillary sinus by an odontogenic keratocyst.

infiltration into, and expansion of, the left maxillary sinus by an OKC. The solid image indicates that the cyst is filled with keratin. Figure 3.16 is a coronal MR image showing infiltrative lobularity of an OKC in the left maxilla.

Pathogenesis

It is generally agreed that the OKC is an abnormality arising from odontogenic epithelium. Most of the available evidence points to two main sources of the epithelium from which the cyst is derived:

- the dental lamina or its remnants (Soskolne and Shear, 1967; Toller, 1967; Browne, 1975; Harris and Toller, 1975; Brannon, 1977; Gardner *et al*., 1978; Browne and Smith, 1991) and
- extensions of basal cells from the overlying oral epithelium (Stoelinga, 1971a, 1973, 1976, 2001, 2003a; Stoelinga and Peters, 1973; Stoelinga *et al*., 1975; Ackermann, 1976; Voorsmit *et al*., 1981)

Shear (2003b) accepted that the two theories of origin were not mutually exclusive.

The term 'primordial cyst' was first used by Robinson (1945) to describe a cyst of the jaw that he suggested was derived from the enamel organ in its early stages of development by degeneration of the stellate reticulum before any calcified structures had been laid down. He stated that primordial cysts may occur in single or multiple form arising either from an enamel organ of a single tooth of the regular series or from numerous aberrant dental anlage which become cystic. No histological description of the cyst was given in this paper.

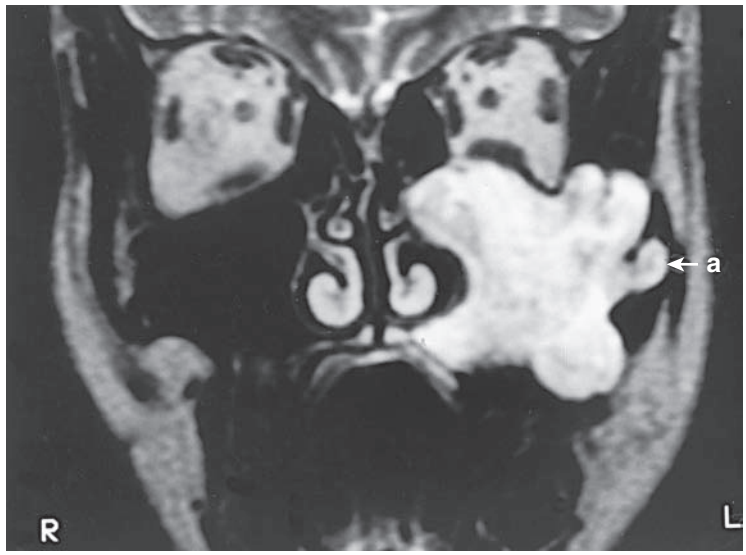


Fig. 3.16 Coronal magnetic resonance image (MRI) showing infiltrative lobularity by an odontogenic keratocyst. (Image kindly provided by Professor L.J. van Rensburg and previously published in *Oral and Maxillofacial Clinics of North America,* Vol. 15(3): 363–382 by van Rensburg, L.J., *et al*. Correlative MRI and CT imaging of the odontogenic keratocyst: a review of twenty-one cases. Elsevier Publishers, 2003, with permission.)

There is now little evidence to support such an origin for the OKC. Forssell (1980) has pointed out that the frequency of aplasia of the teeth is relatively high when compared with that of OKCs and that the site distributions of these cysts and supernumerary teeth differ greatly from each other. It is clear from many reported series that only a small number of OKCs can have developed at a site where a tooth is missing but has not been extracted. In a series of 130 OKCs reported by Reff-Eberwein *et al*. (1985), only two could have arisen in place of a tooth.The 'replacement' variety of OKC described by Main (1970a) may well have arisen from remnants of the dental lamina, particularly in view of more recent understanding of the genetic influences in their pathogenesis.

Evidence derived mainly from the examination of OKCs from patients with the NBCCS suggested that the cysts may arise directly from dental lamina (Soskolne and Shear, 1967). Satellite microcysts in the walls of the main cysts (Fig. 3.17) may be seen, some apparently arising directly from remnants of the dental lamina (Fig. 3.5). The stimulus for this phenomenon is not known, but as the NBCCS is transmitted genetically as an autosomal dominant (Gorlin and Goltz, 1960), as the occurrence of multiple OKCs in patients with the syndrome is a common finding (Meerkotter and Shear, 1964; Woolgar *et al*., 1987a,b; Dominguez and Keszler, 1988) and as multiple OKCs occur in many patients without other overt features of the syndrome (Ahlfors *et al*., 1984; Forssell *et al*., 1988), earlier thinking pointed to the likelihood that there was a predisposition in some individuals to form OKCs.

Browne (1969) and Rittersma (1972) had suggested that as the NBCCS could appear in varying degrees of completeness, the presence of a cyst without other features of the syndrome might represent the least complete form, but

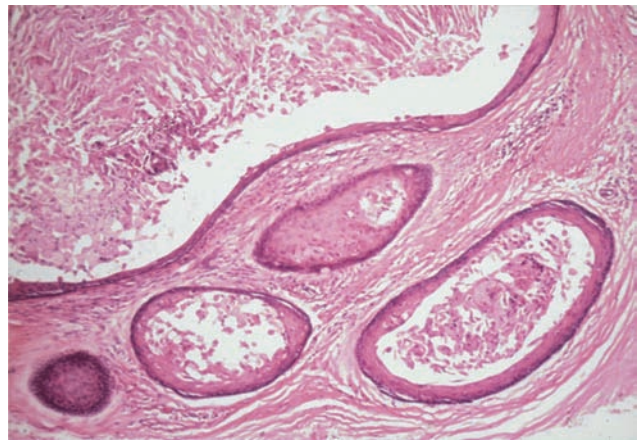


Fig. 3.17 Satellite microcysts in the wall of an odontogenic keratocyst.

Woolgar *et al*. (1987b) stated that the results of their study could be interpreted as evidence for or against that hypothesis. The frequent presence of satellite cysts, apparently derived from dental lamina, in the walls of OKCs, suggested to Browne (1975) that there was a clone of epithelial remnants of the dental lamina that were genetically abnormal and prone to exuberant proliferation.

The case for the origin of at least some OKCs from the proliferation of basal cells of the oral epithelium has been put mainly by Stoelinga and co-workers. In their histological studies they have demonstrated accumulations of epithelial islands in the mucosa superficial to excised OKCs, especially in the ascending ramus. This phenomenon was particularly notable in cysts removed from patients with the NBCCS. These epithelial islands may sometimes be seen dropping off the basal layer of the surface epithelium and the cysts may be attached to oral

mucosa through fenestrations in the bone (Fig. 3.6). Although acknowledging that remnants of the dental lamina in the tooth-bearing area can probably still be considered as a prominent source for the development of cysts in that region, they stressed that even these are located primarily in the gingiva and that gingival adhesions of these cysts may therefore be expected. They stated that frequently, however, OKCs are located in the ascending ramus and have no relationship to a tooth follicle or dental lamina. Such cysts, they concluded, may have arisen from basal cell offshoots or basal cell hamartias which originated from the overlying oral mucosa.

Shear and Altini (1976) suggested that such basal cell offshoots or hamartias may possibly be induced by residual ectomesenchymal influence in the tooth-bearing areas of the jaws. From the point of view of treatment, Stoelinga and various co-workers have proposed that overlying surface epithelium should be excised together with the cyst as this may avoid recurrences originating from residual epithelial islands and microcysts. They recognised, however, that after such excision, the repaired surface epithelium may have the same potential as the original epithelium for producing cysts.

Ostrofsky (1980) studied serial histological sections of 52 specimens of tissue excised from the retromolar mucosa of patients undergoing surgery for the removal of unerupted third molars. Of these, 39 specimens were found to contain cell nests, deep to the overlying oral epithelium, which resembled odontogenic epithelium. He concluded that these nests may be the 'hamartias' referred to by Stoelinga but was not able to determine whether they originated from dental lamina or from the basal layer of overlying oral epithelium. He felt, however, that the more mature cell rests may have arisen from dental lamina whereas the immature forms may have been relatively recent off shoots of the basal layer of oral epithelium.

The consistent finding of a keratinised layer in 'true' keratocysts, while this feature is so rarely seen in other jaw cysts, may be related to their origin from primordial odontogenic epithelium that has not yet differentiated and retains the potential inherited from its parent tissue, the stomadeal or oral epithelium (Shear, 1960a; Stoelinga, 1976). It has often been noted that dental lamina can give rise to keratin (Hjørting-Hansen *et al.*, 1969). Dentigerous cysts are lined by reduced enamel epithelium which only very rarely appears to have the capacity for keratinisation, and radicular cysts develop from cell rests of Malassez which likewise seem to have very little potential for keratinisation.

Pathology

Unless the cyst is small, the linings of OKCs are rarely received intact in the laboratory. They are usually thin-walled, collapsed and folded. However, if one is seen intact, the unequal growth that is responsible for the scalloped radiographic margins may be observed (Figs 3.8 and 3.9).

The histological features are characteristic and have been confirmed in numerous publications (Philipsen, 1956; Shear, 1960a; Pindborg *et al.*, 1962; Browne, 1971a; Brannon, 1977; Kramer *et al.*, 1992; Jordan, 2003; and others). The cysts are lined by a regular, narrow, keratinised, stratified, squamous epithelium which is usually about 5–8 cell layers thick and without rete ridges (Fig. 3.18). The form of keratinisation is exclusively parakeratotic in about 80–90% of cases, but is sometimes orthokeratotic (Fig. 3.19) and both forms may be found in different parts of some cysts (Brannon, 1977; Cohen and Shear, 1980; Voorsmit, 1984). A stratum granulosum is associated with the orthokeratin layer in some but not all cases. It is now clear that the orthokeratinised lesions should not be regarded as OKCs and this is

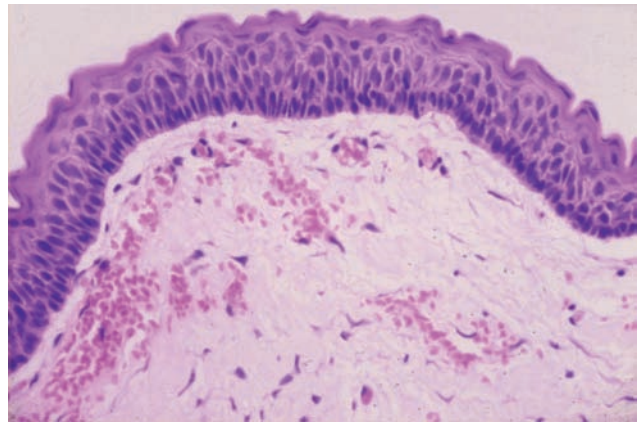


Fig. 3.18 Histopathology of an odontogenic keratocyst.

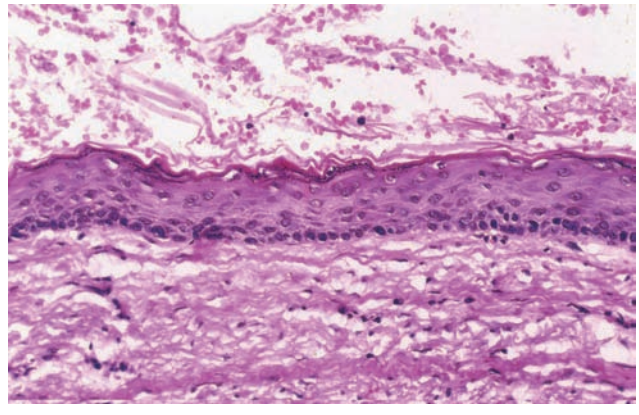


Fig. 3.19 Orthokeratinised jaw cyst, previously regarded as a variation of the odontogenic keratocyst but no longer considered to be so. The preferred name is now 'orthokeratinised odontogenic cyst', abbreviated OOC.

discussed in further detail later. The parakeratotic layers often have a corrugated surface. There is a well-defined, often palisaded, basal layer consisting of columnar or cuboidal cells or a mixture of both. Cuboidal basal cells occur relatively more frequently in relation to the orthokeratinised linings (Cohen and Shear, 1980). Flattened basal cells may also be found in some orthokeratinised linings (Wright, 1981; Siar and Ng, 1988). The nuclei of the columnar basal cells in the parakeratotic linings tend to be orientated away from the basement membrane and in the majority of cases are intensely basophilic. This is a particularly important feature in distinguishing 'true' OKCs from other keratinising jaw cysts (Forssell and Sainio, 1979). Desquamated keratin is present in many of the cyst cavities. The cells superficial to the basal layer are polyhedral and often exhibit intracellular oedema.

Mitotic figures are found in the basal layer but more frequently in the suprabasal layers (Browne, 1971a), and mitotic activity is significantly greater in OKCs from patients with the NBCCS than from patients without (Woolgar *et al*., 1987a). Occasional linings (Fig. 3.20) show features of epithelial dysplasia (Rud and Pindborg, 1969) and some workers, while stressing that malignant transformation in jaw cysts was extremely rare, have made the point that keratinising cysts appear to have a greater tendency to such change than others (Toller, 1967). Browne and Gough (1972) observed that there was little evidence that the OKC was associated with malignant change more commonly than other types of odontogenic cyst. However, Van der Waal *et al*. (1985) reported a well-documented case of an OKC that underwent change to a squamous cell carcinoma. Ahlfors *et al*. (1984) found four examples with epithelial dysplasia in their series of 319 OKCs but there was no case in which a carcinoma developed. MacLeod and Soames (1988) reported a case of an OKC that showed areas of epithelial dysplasia and transformation to an infiltrating well-differentiated squamous carcinoma. Other reports of squamous cell carcinoma arising in OKCs have been published by Moos and Rennie (1987), Minic (1992), Zachariades *et al*. (1995) and Makowski *et al*. (2001).

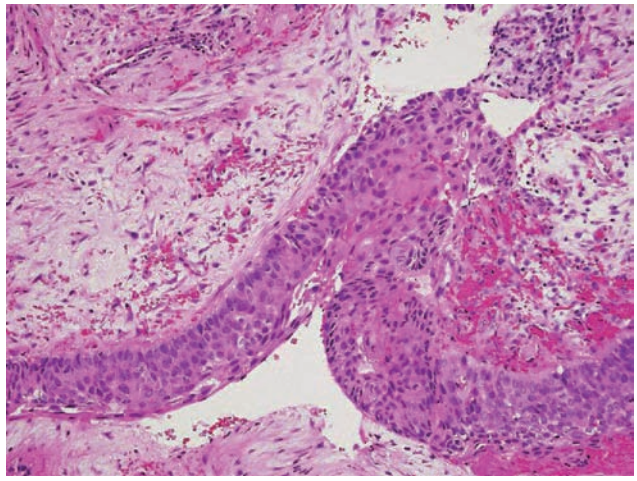


Fig. 3.20 Odontogenic keratocyst with dysplastic changes in part.

Does the epithelial lining of the OKC have a particular predilection to undergo change to squamous cell carcinoma? This has still to be resolved, but there is the possibility that in view of the OKC's reputation for aggressive behaviour, workers in the field may have been more likely to report malignant changes in OKCs than in other jaw cysts.

Some DNA, viral and other laboratory studies attempted to address the question. Using techniques that allowed flow cytometry to be performed on tissue stored in paraffin wax, High *et al*. (1987) examined the DNA content of cells from an OKC that underwent epithelial dysplasia and malignant transformation. They showed that the DNA distribution in control OKCs had a single large peak on the left-hand side of the channel number scale, representing cells in the G0/G1 phase that are diploid (2N) value. A smaller and less well-defined peak was seen to the right and represented cells that had passed through S-phase and were in G2 or mitosis (M) and had twice as much DNA (4N). Those cells intermediate in position were in DNA-synthesis (S-phase) at the time of staining. The OKC with epithelial dysplasia had a large additional peak to the right of the diploid G0/G1 peak and represented a DNA aneuploid G0/G1 component which has a DNA index of 2.0. The subsequent carcinoma demonstrated a smaller but significant DNA-aneuploid G0/G1 peak, also with a DNA index of 2.0. The authors were hesitant to suggest that the presence of aneuploidy in a single case might predict the future biological behaviour of these lesions, but suggested that as the measurement of DNA-aneuploidy from paraffin-embedded sections can be performed easily and routinely, there was considerable scope for further study.

Gunhan *et al*. (2003) concluded from nuclear densitometric studies that DNA indices of all OKCs in their sample were close to 1.0 and the cells were considered diploid.

Cox *et al*. (1991) extracted DNA from an OKC and detected human papilloma virus (HPV) type 16 DNA sequences. They resisted the temptation, however, to propose that HPV 16 infection might give rise to this group of lesions with a higher malignant potential. Their alternative proposal was that as HPV 16 was also found in a high percentage of keratinising oral mucosal lesions, with HPV replication presumed to be dependent on differentiating epithelial cells for the completion of the virus life cycle, certain conditions such as keratosis, squamous carcinoma and cystic lesions such as in their case, may merely provide the correct type of differentiating cell in which a previously latent HPV may replicate.

Gonzales-Moles *et al*. (2006) investigated 83 OKC samples, including 29 NBCCS-associated cases, for HPV DNA, and none gave a positive result. They concluded that HPVs did not participate in the etiology of the OKC.

Studies by Dabelsteen and Fulling (1971) had shown that there was a loss of blood group antigens A and B in dysplastic epithelium compared with normal oral epithelium. Following on this finding, Vedtofte and Dabelsteen (1975) used a double layer immunofluorescence staining technique to study the expression of blood group antigens A and B in eight ameloblastomas, 16 OKCs from patients with the NBCCS, 11 OKCs from patients without the syndrome, and 12 non-keratinising odontogenic cysts. All ameloblastomas reacted negatively, three of 16 cysts from the patients with the NBCCS reacted negatively, while the OKCs from patients without the syndrome, as well as the non-keratinising odontogenic cysts, all gave a positive reaction.

In a study similar to that of Vedtofte and Dabelsteen (1975), Wright (1979a) demonstrated a positive reaction for blood group antigens in all of four OKCs of unspecified origin in patients with blood group A. He pointed out, however, that in all positive cases, positive areas alternated with negative areas and only 5–50% of all the squamous epithelium present showed localisation of blood group A substance.

In a later study, Vedtofte *et al*. (1985) repeated some of the experiments carried out in the 1975 investigation. They demonstrated A, B and H type 2 antigens in OKCs and in dentigerous and radicular cysts. They did not, however, detect *N*-acetyl lactosamine in the OKCs as they did in the non-keratinised cysts. They emphasised the need to examine extensive areas of the cyst linings in order to ensure accurate sampling. None of these cell surface carbohydrates was demonstrable in a series of ameloblastomas, and the authors suggested that these immunohistochemical methods were useful in distinguishing the tumour from odontogenic cysts.

Early attempts at laboratory diagnosis of the keratocyst

Examining the cyst fluid

Toller (1970a) considered that estimation of the soluble protein level in aspirated cyst fluid might be a valuable aid in the preoperative diagnosis of OKCs. He showed that fluids from keratinising cysts had soluble protein levels below 3.5 g per 100 mL (mean 2.2 g per 100 mL), whereas the values for non-keratinising cysts were in the range 5.0–11.0 g per 100 mL with a mean of 7.1 g per 100 mL. Electrophoretic studies corroborated the finding that keratinising cysts were very low in soluble proteins and Toller postulated that a protein level of less than 4.0 g per 100 mL indicated a diagnosis of OKC. A value of over 5.0 g per 100 mL, however, would suggest a radicular, dentigerous or fissural cyst, or even an ameloblastoma. His view was that fully keratinised linings were impervious to all proteins whereas the usual type of radicular or dentigerous cyst wall would at least slowly transmit the smaller proteins. In the presence of a fairly pronounced inflammatory reaction in an OKC wall, the degree of keratinisation over these areas would be altered and this was likely to increase the permeability of the lining and result in a soluble protein level in the fluid higher than in the uninflamed keratinising cysts. Toller's estimates of protein levels in cyst fluids were confirmed by Ylipaavalniemi *et al*. (1976a) who considered that the inflammatory process itself would influence the protein content of the cyst fluid; not merely the nature of the epithelial lining.

Kramer (1970) suggested that a preoperative diagnosis of OKC might be made by aspirating cyst fluid and demonstrating keratinised squames in a stained film. In a later study, Kramer and Toller (1973) reported on the combined use of exfoliative cytology and protein estimations in the preoperative diagnosis of these cysts. In some instances, when aspirates were sent in the post, a period of up to 2 days had elapsed before smears were prepared, but whenever practicable smears should be carried out as soon as possible after sampling. Smears were made by placing a drop of fluid on a clean glass slide and spreading with the edge of a dry coverslip. Two smears of each specimen were allowed to air-dry and were stained respectively with haematoxylin and eosin and by the rhodamine B fluorescence method (Clausen and Dabelsteen, 1969). A third smear was allowed to dry to a tacky state and fixed in a solution containing 75% ethyl alcohol and 3% acetic acid prior to staining with the Papanicolaou procedure.

Kramer and Toller examined a total of 56 jaw cysts and of these, subsequent histological examination showed that 21 were OKCs, 32 were other jaw cysts and three were cystic neoplasms. Examination for squames gave the correct result, namely OKC or not OKC, in 47 of the 56 cases. When this cytological procedure was combined with protein estimation of cyst fluid, the correct diagnosis was reached in all 21 OKCs. There were six false positives among the other cysts and squames were also found in the fluid from a cystic carcinoma.

They found that examination of the exfoliative cytology smears achieved comparable diagnostic accuracy with each of the three staining methods and that this accuracy was similar to that achieved by use of the protein estimations. Although none of the methods gave complete accuracy, the number of incorrect diagnoses was reduced if smears stained by two or three methods, and protein estimations, were performed on each case. The smear technique required very little material and this could almost always be aspirated even if the cyst contents were thick.

These findings have been confirmed by Smith *et al*. (1986) who recommended the bromocresol green

dye-binding method for albumin and the glyoxylic acid method for globulins because they did not appear to suffer from the non-specific colour interference or turbidity seen in the biuret method. They also advised that the use of positive displacement pipettes rather than air displacement pipettes was essential for accurate sampling of cyst fluid because of the mucinous nature of some fluids. Fluid aspirates from their sample of 18 OKCs showed very much lower levels of albumin, total globulins and total protein (4.70±0.73 g per 100 mL) than fluids from radicular and dentigerous cysts. The higher proportion of albumin relative to total globulins in the OKC was reflected in the higher albumin:globulin ratio observed. They advised that protein analysis, qualitative protein electrophoresis and smears could be carried out on an aspirate of volume as small as 100 µL. In their experience, the combination of protein analysis and the demonstration of epithelial squames in the smear resulted in accurate diagnosis of the OKC in virtually every case.

Voorsmit (1984) reported a diagnostic accuracy of 100% when the combined techniques were used, using a total protein level in the cyst fluid of less than 4.8 g per 100 mL as an indication that the lesion was an OKC.

A keratocyst antigen

Kuusela *et al.* (1982) demonstrated an antigen in the fluid of OKCs that was not present in the fluids of other cyst types nor in plasma or saliva. A double-antibody fluorescence technique localised the antigen to the epithelial cells of the OKC and they called it keratocyst antigen (KCA). In a later study, Kuusela *et al.* (1986) showed that KCA existed in OKC fluid as a 60–68 000 Da polypeptide with an isoelectric point of pI 6.8. Immunoblotting analysis of various isolated keratins revealed a typical polypeptide pattern of each keratin when anti-KCA antiserum was used for staining. These findings suggested that KCA and keratin were related molecules and that KCA may be a soluble component of keratin. They proposed that the keratin may become soluble in the cyst fluid by proteolysis and, moreover, that the relationship of keratin and KCA would enable the use of commercially available antikeratin antibodies in the detection of KCA in the cyst fluids, thus making it possible to distinguish OKCs prior to surgery. No follow-up of this work appears to have been published.

Lactoferrin in keratocyst fluids

In the search for either a single protein or group of proteins that was characteristic of a particular cell type, Douglas and Craig (1986) used immunological techniques to search for components of non-serum origin in cyst fluids. Separate antisera were raised against OKC, dentigerous cyst and radicular cyst fluids and used to analyse a range of fluids from cysts of known type. Samples were subjected to crossed immunoelectrophoresis into homologous antiserum through an intermediate gel containing antibody to whole human serum, in order to screen out serum-derived components. Their investigation identified the presence of a major antigen in the fluid aspirated from the fluid of OKCs. This seemed to be of epithelial origin, but was not a keratin. It was present in all the OKC fluids assayed, despite total soluble protein concentrations ranging from 1.86 to 22.0 g per 100 mL. This antigen, which they named antigen X, was later identified as lactoferrin, a secretory substance present in the azurophilic granules of polymorphonuclear leucocytes and body secretions but not in serum (Douglas and Craig, 1987). They were unable to explain why lactoferrin consistently accumulated in OKC fluids. Its presence could not be attributed solely to the presence of inflammation, which is rare in OKCs compared with radicular cysts, and lactoferrin was only occasionally found in the cavity fluids of the latter. They speculated that lactoferrin may be derived from the OKC epithelium, but preliminary attempts at immunoperoxidase localisation of the substance in formalin-fixed OKC linings had been disappointing. Finally, they suggested that the polymorphonuclear leucocytes that do infiltrate the cyst wall act as the source of the lactoferrin in the fluid and, as it is unable to diffuse away into the surrounding tissues because of the relative impermeability of the OKC to proteins, its concentration may increase with time.

In the third of their series of papers on the subject, Douglas and Craig (1989) used a competitive enzyme-linked immunosorbent assay (ELISA) to measure the concentration of lactoferrin in fluids from OKCs, dentigerous and radicular cysts. OKC fluids contained significantly higher concentrations of lactoferrin than fluids from the other two cyst types, but the range of values obtained within each group was large, and the lactoferrin concentration could not therefore be regarded as an absolute marker for OKCs. The lactoferrin concentration correlated very strongly with the numbers of neutrophils present in OKC fluids, assessed in smears, but not with fluids from dentigerous and radicular cysts. The authors suggested that neutrophils were the source of lactoferrin in the three cyst types and developed the idea mooted in their earlier paper, that the relatively impermeable nature of the OKC lining probably accounted for the particularly high concentrations of lactoferrin found in their fluids. The molecular weight of lactoferrin is in the range 77–85 000 Da and its ability to diffuse through the OKC lining is likely to be impeded. Speculating further on the presence of neutrophils in OKC fluids, the authors suggested that they may be a response to the keratin in the cyst lining, possibly mediated by IL-1 which is chemotactic to neutrophils.

Using qualitative and quantitative immunodiffusion methods, fluid from 29 of 29 dental (radicular) cysts, 12 of 14 dentigerous cysts and 27 of 31 OKCs investigated by Smith, Matthews *et al.* (1988) were found to contain

lactoferrin. Although some of the highest concentrations of lactoferrin were detected in fluids from OKCs, they found no significant difference between lactoferrin concentrations among the three groups. Neutrophil elastase was detected in 20 of 24 samples tested, 22 of which also contained lactoferrin. Immunocytochemical localisation of both lactoferrin and elastase was confined to neutrophils infiltrating cyst walls. They concluded from these results that lactoferrin in the fluid of odontogenic cysts was derived from infiltrating neutrophils and that its presence in aspirated fluids was not a useful diagnostic marker for the OKC.

Toller and Holborow (1969) examined 15 jaw cyst fluids by immunoelectrophoresis and found that cysts with keratinised epithelial linings had the lowest levels of immunoglobulins.

Smith *et al*. (1987), in a study of immunoglobulin-producing cells in human odontogenic cysts, found that IgG-containing plasma cells were the predominant species in all cyst types with a much lower percentage of IgA- and few IgM-containing plasma cells. There were significantly fewer IgG and significantly more IgA plasma cells observed in the OKCs than in the radicular and dentigerous cysts. IgA plasma cells appear to represent a significantly higher proportion of the total plasma cell population in OKCs than in radicular and dentigerous cysts, although IgG cells still predominated. Generally, IgG plasma cells predominate in areas of diffuse chronic inflammation and the raised proportion of IgA plasma cells in the OKC may, the authors speculated, reflect the focal nature of the inflammatory infiltrate. They also found intense extracellular staining for IgG in the capsule and this they thought would support the view that the IgGs in odontogenic cyst fluids may be derived from local synthesis in the cyst capsules as well as from the inflammatory exudate. Further consideration of this subject is found in Chapter 11.

Browne *et al*. (1984) found crystalline deposits in aspirated fluid of 38% of OKCs examined, compared with 10% of radicular cysts and no dentigerous cysts. There was a high incidence of the crystalline calcium phosphates, hydroxyapatite and whitlockite in both types of cyst. Calcium and magnesium levels were within normal ranges for serum, but the levels of inorganic phosphate were considerably raised in the OKCs and slightly elevated in the radicular cysts. The higher levels of these ions in the cyst fluids may possibly be responsible for the higher frequency of deposits in their walls.

Behaviour of orthokeratinised OKCs. Should they be renamed 'orthokeratinised odontogenic cysts'?

Of considerable importance is that some studies have shown that the orthokeratinised OKCs (Fig. 3.19) in their material have had a substantially lower recurrence rate than those that were parakeratinised (Wright, 1981; Siar and Ng, 1988; Crowley *et al*., 1992; Lam and Chan, 2000) and later molecular studies, discussed elsewhere in this chapter, have shown significant differences between the two varieties (High *et al*., 1993; Li *et al*., 1998, Da Silva *et al*., 2002; Thosaporn *et al*., 2004).

Brannon (1977) pointed out that orthokeratinisation was uncommon in OKCs of patients with the NBCCS or of patients with multiple cysts and reported that orthokeratinised cysts did not often recur. Wright (1981) confirmed the low recurrence rate of orthokeratinised cysts and suggested that these be regarded as a distinct entity. In the series of Ahlfors *et al*. (1984), all orthokeratinised cysts were single and none had recurred; nor had any of the cases of Siar and Ng (1988). Brannon (1977), Wright (1981), Voorsmit (1984), Siar and Ng (1988) and Li *et al*. (1998) have all commented on the frequent association between orthokeratinised cysts and the crowns of unerupted teeth, and this leads one to speculate whether the relatively less aggressive behaviour of some of these may be because they are keratinised dentigerous cysts and not 'true' OKCs. Ultrastructural differences between parakeratinised and orthokeratinised varieties have been demonstrated by Wysocki and Sapp (1975).

Unfortunately, there is not yet clarity on the behaviour of OKCs that show both ortho- and parakeratotic areas histologically. On the basis of mounting evidence, the orthokeratinising cysts should be regarded as a separate entity with a less aggressive behaviour, and it has been suggested that they should be given a different name, 'orthokeratinised odontogenic cyst' (OOC) (Li *et al*., 1998; Shear, 2002c). However, if these cyst linings include also a substantial component of associated parakeratinised epithelium, the behaviour should probably be regarded as unpredictable, pending further evidence.

The fibrous capsule

The fibrous capsule of the OKC is usually thin with relatively few cells widely separated by a stroma which is often rich in mucopolysaccharide and resembles mesenchymal connective tissue (Fig. 3.21). Inflammatory cells are very infrequent but there may be a mild infiltration of lymphocytes and monocytes. In the presence of an intense inflammatory process, the adjacent epithelium loses its keratinised surface, may thicken and develop rete processes, or may ulcerate. In a series of 112 OKCs examined to study the relationship between inflammation and the epithelial cyst lining, Rodu *et al*. (1987) showed that inflammation without the aforementioned changes in the epithelium was found in 10 cases (8.9%). Conversely, no cysts were seen with such epithelial changes in the absence of inflammation. Hyalinisation is sometimes seen in the capsules of cysts removed from older patients (Browne, 1971a). In 11% of Brannon's large series, the cyst linings were intimately associated with surrounding soft tissues such as skeletal muscle, salivary gland and oral mucosa.

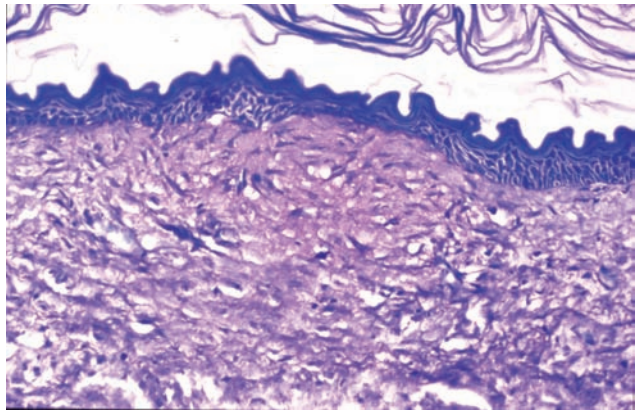


Fig. 3.21 Stained with toluidine blue, the stroma of the odontogenic keratocyst is strongly metachromatic.

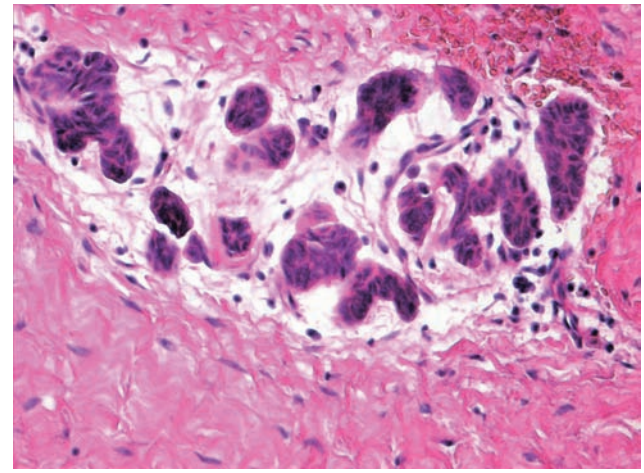


Fig. 3.22 Odontogenic epithelial cell rests in the wall of an odontogenic keratocyst.

The attachment between epithelium and the connective tissue capsule tends to be weak and in many areas separation occurs. The collapsed and folded thin-walled cysts may give an erroneous impression of multilocularity in histological sections.

At intervals there are 'infoldings' of the epithelial lining into the fibrous cyst wall with resultant inlets of the lumen or crypts (Ahlfors *et al*., 1984). In describing this feature, the authors postulated that these were not merely folds of the lining following collapse of the wall on removal of the cyst. This, they believed, could be gauged from the fact that the cyst capsules were narrower at these locations than elsewhere, and that the subepithelial collagen bundles followed the curvature of the fold while the main collagen bundles were arranged circumferentially. The authors considered that these infoldings may be the result of cyst epithelium being pushed into the capsule by active proliferation.

Satellite cysts, epithelial rests and proliferating dental lamina are sometimes seen in the cyst capsules, particularly in patients with multiple cysts and with the NBCCS (Figs 3.5 and 3.22). Although the epithelial linings of the cysts in the syndrome patients usually show the classic features of OKCs, Waldron (1969) has described some histological variants. In some of his syndrome cases the epithelial linings were considerably thicker than in classic cases and showed prominent nests of basaloid cells budding off from the cyst linings. Detailed histological studies on the frequency of satellite cysts, basal budding, odontogenic rests, epithelial islands and 'ameloblastomatoid' features in patients with solitary and multiple OKCs associated and unassociated with the NBCCS have been reported by Ahlfors *et al*. (1984), Woolgar *et al*. (1987a,c), Dominguez and Keszler (1988) and Myoung *et al*. (2001).

Ahlfors *et al*. (1984) demonstrated budding of the basal layer in 25% of their pooled sample and much more frequently in patients with multiple cysts or with the syndrome than in patients with postoperative recurrences; whereas Woolgar *et al*. (1987a,c) found no significant difference in the frequency of basal budding between cysts that did not recur, primary cysts which eventually recurred, their first recurrences, and cysts in patients with the syndrome. Ahlfors *et al*. found islands or remnants of odontogenic epithelium in the fibrous capsules in 23% of their sample, with a substantially higher frequency in patients with multiple cysts and the syndrome; while Woolgar *et al*. reported a significantly higher frequency of odontogenic rests and solid islands in their patients with the syndrome, but not between their control and recurrent samples. Dominguez and Keszler also found a significantly higher frequency of intramural odontogenic epithelium in their syndrome sample. Ahlfors *et al*. found satellite cysts frequently in the walls of those cysts in patients with the syndrome (50%) and where there were multiple cysts (27%), but only very rarely otherwise. Woolgar *et al*. observed satellite cysts significantly more frequently in patients with the syndrome (54%) than in their control sample of OKCs, as did Dominguez and Keszler. Woolgar *et al*. demonstrated solid proliferating islands of odontogenic epithelium significantly more frequently in the syndrome patients than in the controls, but not between their control and recurrent samples. Myoung *et al*. (2001) analysed the influence of satellite cysts and basal cell budding on recurrence rates, and found that the former carried some significance ($P=0.03$).

In the studies of both Ahlfors *et al*. and Woolgar *et al*., ameloblastomatoid formations were occasionally observed; in the latter study, only in patients with the syndrome. None of these workers has reported ameloblastomatous change in OKCs. Ahlfors *et al*. described the presence of suprabasilar clefts in the epithelial linings that were found more frequently in the recurrent, multiple and

syndrome-associated cysts. They interpreted the split as probably a preparation artefact, but as they had only rarely observed them in other types of jaw cyst, considered that their frequent presence in cysts from patients who were prone to develop them may reflect an intrinsic property of the cyst epithelium.

Melanin pigmentation has occasionally been observed in the epithelial linings of OKCs (Browne, 1971a; MacLeod *et al*., 1985; Takeda and Yamamoto, 2000).

Mucous metaplasia, hyaline bodies (Rushton, 1955) and cholesterol clefts are sometimes present in the walls of OKCs (Browne, 1971a; Brannon, 1977; Voorsmit, 1984; Woolgar *et al*., 1987a). Jensen *et al*. (1979) observed odontogenic epithelial cell rests embedded in nerve bundles in the fibrous capsules of two OKCs. Their ultrastructural studies confirmed that these were epithelial and not the neuro-epithelial organ of Chievitz. They emphasised that such epithelial islands in nerve bundles should not be misinterpreted as neural invasion by carcinoma.

Mast cells were found to be present in substantial numbers in OKC walls, as well as in the walls of dentigerous and radicular cyst walls (Smith *et al*., 1989). The highest concentration was in the subepithelial zone where the count was 5.71 ± 3.52 per microscopic field, the latter being defined as the area encompassed by a $1\,cm^2$ graticule. Mast cells were also observed in the epithelial linings, which the authors suggested implied a chemotactic stimulus to mast cells in odontogenic cysts, attracting them to the epithelial lining or luminal fluid contents. This work on mast cells followed three previous studies by the same group on glycosaminoglycans in OKCs, dentigerous and radicular cysts (Smith *et al*., 1984, 1988a,b) which have been referred to earlier in this chapter in the section on enlargement of OKCs.

Fornatora *et al*. (2001) described the presence of cartilagenous metaplasia with a benign histology in the connective tissue wall of an OKC in a 66 year old man and reviewed six other reported cases. Interestingly, similar cartilage was seen in a recurrence.

Ultrastructural studies

Ultrastructural studies of OKCs have been reported by Hansen and Kobayasi (1970b), Wysocki and Sapp (1975), Philipsen *et al*. (1976, 1992), Wilson and Ross (1978), Voorsmit (1984) and Herbener *et al*. (1991). Scanning electron microscopy of the parakeratinised forms showed a complex series of elevations and depressions on the cell surfaces; whereas scanning electron microscopy of the orthokeratinised variety revealed a uniform, flat surface covered with a thick layer of leafy squames of orthokeratin with no evidence of surface corrugations or deep epithelial infoldings (Wysocki and Sapp, 1975). Transmission electron micrographs of the surface of parakeratinised epithelium confirmed the presence of the cytoplasmic interdigitations and desmosomal junctions which give rise to the complex surface morphology. The orthokeratinised cysts showed a loose attachment between superficial shreds of orthokeratin and a compact layer of underlying keratin.

Using a series of 12 cysts from patients with the NBCCS as their material for an ultrastructural study, Philipsen *et al*. (1976) demonstrated that juxta-epithelially, deep to the lamina densa, the collagen showed signs of dissolution and often disappeared completely. They suggested that this process of collagenolysis might be produced by a collagenase or other proteases and it appears to be this phenomenon that is responsible for the ready separation of OKC epithelium from its supporting capsule. Tonofilaments occurred in increasing numbers from the basal towards the superficial layers, but unlike the situation in keratinising oral epithelium, cytoplasmic organelles such as mitochondria, endoplasmic reticulum and Golgi apparatus showed no significant changes in structure or number through the strata towards the keratinised cell layers. This was interpreted as indicating that the cells of the stratum spinosum should be regarded as rather poorly differentiated.

A feature of the cells of the stratum spinosum was the presence of considerable amounts of glycogen, a characteristic that was also observed by Wilson and Ross (1978), Voorsmit (1984) and Herbener *et al*. (1991).

In a later paper, Philipsen *et al*. (1992) described the parakeratinised OKC as showing a complex pattern of microplications on both upper and deep cell surfaces. The microplications were linear and often whorled, some ending abruptly, others with hairpin bends or ending in a loop or hook. A common configuration was dichotomous branching forming a Y. Isolated and dispersed dot-like microvilli were present between the microplications.

Scanning electron microscopy (SEM) at low magnification of OKCs and orthokeratinised cysts (OOCs) showed regular, flattened polyhedral cells with distinct intercellular boundaries. Several cells were partially detached, representing the process of desquamation. Round or oval central elevations indicated the positions of the nuclei of these cells.

At high magnification, the orthokeratinised OKC (or OOC) showed a reticular network of intercommunicating microridges surrounding depressions giving a honeycombed appearance to the entire surface. The deep surface of these cells was covered by a complementary array of short stubby microvilli, separated by narrow grooves. This pattern was identical to that described for oral epithelium in areas of masticatory mucosa.

El-Labban and Aghabeigi (1990) investigated the blood vessels in OKCs and dentigerous cysts, both stereologically and ultrastructurally. No significant differences were found between them stereologically, using the volume and surface densities of blood vessels as parameters, suggest-

ing that their overall vascularity may be similar. The ultrastructural study, however, showed considerable differences between blood vessels in the two cyst types. Fenestrated capillaries were found only in OKCs. Another feature of the OKC was degeneration of the epithelial lining, associated with thrombosis. The authors suggested that the fenestrated capillaries in OKCs and not in dentigerous cysts might indicate a rapid transfer of fluid to meet the demand of active proliferating epithelium. They also suggested that proliferation of OKC epithelium may be promoted by growth factors released from platelets in the thrombosed vessels, on the basis that other workers had reported that a platelet homogenate fraction added to culture medium, stimulated epidermal cell outgrowth and viability (Hebda *et al*., 1986).

Tissue and organ culture: attempts to produce experimental cysts

Atkinson (1972, 1976) has described the histological changes in experimental cysts produced by the transplantation of maxillary molars extracted from 10 day old C57B1 mice grafted subcutaneously into adult mice of the same strain. After initial degenerative changes in the enamel organ, the reduced enamel epithelium changed to a hyperplastic stratified squamous epithelium in which there was cystic breakdown. This led to the development of cavities lined by a thick parakeratotic stratified squamous epithelium which resembled the lining of an epidermoid cyst. As the cysts enlarged, the linings changed to a thin non-keratinised squamous epithelium.

Bartlett *et al*. (1973) transplanted the first maxillary molars of 2 day old C57B1/10 mice into the subcapsular space of of the kidneys of isologous mice. There was no rejection or inflammation. Splits developed and enlarged in the enamel organ epithelium and had developed into keratinising cysts in the 50-day specimens. No rete ridges or inflammatory cells were present, and the authors regarded the experiment as a model for OKCs despite the absence of other classical features of this lesion. Soskolne *et al*. (1976) developed a technique for the production of keratinising cysts in rat mandibles using autogenous grafts of interdental papilla implanted into prepared cavities. Ramanathan and Philipsen (1981) have carried out similar studies using intra-osseous implants of rat palatal mucosa. Ligthelm (1989) developed an original experimental cyst model in vervet monkeys and a genetically standardised line of rats (BD-IX-rats). He preformed the cyst walls by wrapping the animals' oral mucosa around a silastic tube with the epithelial surface against the tube. Donor tissue was transplanted into subcutaneous tissues and into prepared cavities in bone. Cysts developed in a very high proportion of the transplants. They initially had the histological appearance of the original epithelium, but the latter became thinner as the cysts enlarged.

Although these models were considered to be useful experimental techniques for the investigation of OKCs, it has to be emphasised that keratinisation is only one of the histological characteristics of OKCs, and these potential models have, as yet, made little contribution to our knowledge of the origin, pathogenesis or behaviour of OKCs.

In an important experiment that demonstrated the significant dependence of the OKC epithelium on its supporting ectomesenchymal stroma, Vedtofte *et al*. (1982) transplanted human OKC linings into athymic (nude) mice. The cyst epithelium proliferated, and sometimes formed a new cyst in the host tissue. The epithelium retained its typical histological features as long as it was supported by its own connective tissue capsule. However, epithelial outgrowths over mouse connective tissue showed an altered morphology. In most specimens the epithelium was keratinised but atrophic, and the basal cells were flattened. The possibility that the primary defect in an OKC might be in the mesenchymal capsule rather than in the epithelial cells themselves had been mooted by Browne in 1975, and other workers have referred to the mesenchymal influence in recurrences (Shear and Altini, 1976; Voorsmit *et al*., 1981).

Enzyme histochemistry

Stenman *et al*. (1986) grew fresh tissue specimens from three OKCs and three dentigerous cysts *in vitro*. There was a considerable difference in growth capacity. Within 2 days of explanting the OKCs, there was growth of epithelial cells which reached a peak after 14–16 days, after which growth slowed and stopped after 3–4 weeks. Fibroblast-like cells appeared in the cultures 10–14 days *in vitro* and after 2–3 passages most epithelial cells had disappeared and the cultures consisted mainly of the fibroblast-like cells. The growing epithelial cells showed moderate to high activity of NADH-diaphorase and acid phosphatase, which was most intense close to proliferating fibroblastic cells. The authors considered the high levels of enzyme activity in epithelial cells adjacent to the fibroblastic cells of particular interest in view of the findings of Vedtofte *et al*. (1982), referred to above, and suggested that the close relationship with the mesenchymal cells of the cyst capsule is essential for the maintenance of this metabolic capacity.

These histochemical reactions *in vitro* were similar to those demonstrated in tissue sections of OKCs compared with other odontogenic cysts (Magnusson, 1978). In his study, Magnusson demonstrated a high level of leucine aminopeptidase activity in the fibrous capsule of OKCs. This is an enzyme that has been implicated in the invasiveness of malignant tumours. This finding was confirmed by Chomette *et al*. (1985).

Static end-point and continuously monitored nitroblue tetrazolium-based histochemical methods were used by

Mason and Matthews (1996) to measure the levels of succinate, lactate, glutamate, glycerophosphate and glucose-6-phosphate dehydrogenases in the linings of OKCs and radicular cyst linings. End-point assays showed that the OKC linings contained higher levels of glucose-6-phosphate dehydrogenases (P <0.0002) and lower levels of lactate dehydrogenase (P <0.002) than those of radicular cysts. Succinate, glutamate and glycerophosphate dehydrogenase activities were similar in both cysts. Calculated enzyme activities from continuous assays were between 1.49 and 3.49 times higher than those from the end-point assays and confirmed that levels of glucose-6-phosphate dehydrogenase were significantly higher in the OKCs than in the radicular cyst linings (P <0.004). However, the succinate dehydrogenase activity was significantly higher in the radicular cysts, thereby highlighting the benefits of continuous monitoring methodologies.

They concluded that the high level of glucose-6-phosphate dehydrogenase found in OKC linings was consistent with their higher levels of proliferation and synthetic activities, whereas the higher level of lactate dehydrogenase in radicular cysts probably reflected the presence of local tissue damage in these inflammatory lesions.

In a histochemical study of the cell membrane carbohydrate components in paraffin sections of OKCs using horseradish peroxidase-conjugated lectins, Aguirre *et al.* (1989) demonstrated strong intra- and intercellular staining in the spinous and keratinised layers of three-quarters of their specimens using concanavalin ensiforme (Con A) following periodic acid oxidation. The basal cells stained only at their bases. Con A lectin binds the neutral sugars D-glucose and D-mannose. This Con A binding after periodate oxidation is attributed by the authors either to an unmasking of mannose hydroxyl groups, or to unmasking of glycogen. In a parallel study on a series of ameloblastomas, Aguirre *et al.* (1989) showed a higher concentration of receptors for Con A and periodic acid–Con A in this tumour than in OKCs. Saku *et al.* (1991) demonstrated that the lectins *Ulex europaeus* agglutinin I (UEA-I) and *Bandeirea simplicifolia* agglutinin I (BSA-I) bound to the epithelial linings of OKCs, dentigerous cysts and radicular cysts, but not to the epithelial component of ameloblastomas. They suggested that this could be useful for the differential diagnosis of cystic ameloblastomas and simple epithelial-lined cysts of the jaws.

Immunohistochemistry

Cytokeratins and other epithelial cell markers (Table 3.6)
In the period 1987–2005, a series of publications examined keratin expression by odontogenic cell rests and the more common odontogenic cysts. One objective of these studies was to determine whether particular patterns of cytokeratin staining could provide accurate diagnostic markers for the common odontogenic cysts: the OKC, dentigerous and radicular cysts. A second was to see whether comparative studies with oral mucosa and odontogenic epithelium at different stages of tooth development could assist in elucidating the pathogenesis of the cysts. Third, there was interest in determining whether cytokeratin patterns could provide clues in elucidating the aggressive nature of the OKC.

Cytokeratins are the main structural proteins in epithelial cells comprising a wide series of polypeptides ranging from 40 to 67 kDa molecular weight. They fall into acidic (type I or A) and basic (type II or B) sub-families according to their charges, immunoreactivity and amino acid sequences. Cytokeratin patterns differ in the types of oral epithelium: the non-keratinised stratified squamous epithelium of normal oral mucosa from the keratinised epithelium of the gingiva and from that on the dorsum of the tongue. Numerous studies have been carried out on cytokeratin expression and other tissue markers in dysplastic and neoplastic oral epithelium. Differences in the type and distribution of cytokeratins have been demonstrated in these lesions and have been reported in an extensive review (Scully and Burkhardt, 1993). It is not surprising therefore that these techniques should have been applied to OKCs, among other odontogenic tissues and lesions, to try to resolve the many outstanding questions about its behaviour.

A review of keratin patterns in odontogenic epithelium from the early stages of tooth development in rodents, primates and humans led to a conclusion that no two immunocytochemical studies were directly comparable (Smith and Matthews, 1991). Technical problems in the preparation of sections from calcified tissues clearly play a part, as do differences in reactivity between different monoclonal antibodies for the same cytokeratin.

Accumulated data in the review of cytokeratin patterns in the post-formative reduced enamel epithelium and the cell rests of Serres and Malassez indicated that the major keratins consistently found were 13, 14 and 19 (Smith and Matthews, 1991). The combination of keratins 13 and 14 and expression of keratin 19 by large numbers of odontogenic epithelial cells were thought to be unusual, and might be a potentially useful marker for the identification of odontogenic epithelium. However, a further difficulty in postulating precise cytokeratin profiles to any group of odontogenic epithelial cells was that the pattern appeared to change as odontogenesis proceeded, and as quiescent cells proliferated in pathological situations (Smith and Matthews, 1991; Gao *et al.*, 1988b). For example, it was found that in the resting cells of Malassez, keratin 5 was paired with keratin 19 while in periapical granulomas, keratin 14 was strongly expressed in the contained epithelium and keratins 8 and 18 were consistently observed in proliferating epithelium in granulomas and radicular cyst linings (Gao *et al.*, 1988b).

In earlier reviews (Shear, 1994), similar difficulties were pointed out in assessing the published work on cytokeratins in odontogenic cyst epithelium because, on the evidence available then, the diagnostic potential appeared to be limited, and the variability of the results from different laboratories suggested the need for further refinement and standardisation of the methodology. The same difficulty was encountered in two later reviews (Shear, 2002a–c, 2003a,b). It soon became apparent that although there was consistency in the results reported by different groups of workers in respect of some cytokeratins, there were also disagreements on others. A retrospective review of the different results is a complex task, not only because there was a range of at least 19 different cytokeratins being studied, but also because there was a broad range of antibodies in use for the same cytokeratin or group of cytokeratins. Moreover, there was not always standardisation of laboratory techniques in the selection and preparation of the sections being studied. These factors and possibly disappointment with the value of the findings led to a break of some 8 years before a few other papers on the subject appeared in 1999 and 2000. For ease of reference, the findings of the different studies have been summarised in Table 3.6.

Immunohistochemical staining with monoclonal antibodies was used in what appears to have been the first study that compared the cytokeratin content of different odontogenic cysts together with normal gingival epithelium and ameloblastomas (Hormia *et al*., 1987). These authors' findings have been reviewed previously (Shear, 1994) and are summarised in Table 3.6. The absence of cytokeratin polypeptides typical of keratinising epithelia – namely, numbers 1, 9, and 10/11 – from all OKC epithelia were typical of mature keratinocytes and it was suggested that their absence indicated that no true keratinisation took place in OKCs (Hormia *et al*., 1987). This led to the conclusion that the presence of true keratinisation alone was not a distinguishing feature of OKCs and that more reliable diagnostic features were the presence of an accentuated basal cell layer, maturation of the cells towards the surface and, immunohistochemically, the presence of keratins 8, 18 and 19 in the basal and suprabasal cells. Keratin 10 was also not found in another study using monoclonal antibodies LH2 and LH3, and these workers did not test for keratins 1 and 9 (Gao *et al*., 1989).

The findings of an investigation of keratin expression in the epithelial linings of 50 odontogenic cysts using an enhanced indirect immunoperoxidase method on acetone-fixed frozen sections (Matthews *et al*., 1988) are summarised in part of Table 3.6. Also investigated in this study was the distribution in these linings of epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) and rat liver antigen (RLA) as well as proliferating cells within the epithelium using the monoclonal antibody Ki-67 (see p. 45). In contrast to the earlier study (Hormia *et al*., 1987), keratins associated with cornified epithelia (keratins 10/11) were detected in the upper suprabasal layers in 17 of their sample of 18 OKCs and these conflicting results were ascribed to differences in the techniques used.

Cells negative or weakly positive for keratin 13 or 13/16 and 10/11 had a distribution similar to that of Ki-67-positive proliferating cells, and expression of these keratins in OKCs appeared to be related to epithelial cell maturation and proliferation rather than histogenesis or cyst type. Keratin profiles, it was suggested, were therefore unlikely to distinguish between an inflamed OKC that had lost its typical histological appearance, and other odontogenic cysts that had keratinised epithelial linings as a result of metaplasia (Matthews *et al*., 1988).

Expression of CEA and EMA, as with that of keratin 10/11, appeared to be dependent on epithelial structure and differentiation. Their expression by OKC epithelium was restricted to weak and patchy staining of the surface layers, although areas with 'disordered structure' showed cytoplasmic staining of most cells, particularly for EMA. In the dentigerous cysts, both antigens, more so EMA, were found in most epithelial cells, and in the radicular cyst their distribution was variable. RLA was expressed by most suprabasal cells in all three cysts (Table 3.6) (Matthews *et al*., 1988).

A parallel biochemical approach examined the specific keratin proteins in the lining epithelium of OKCs using one-dimensional SDS electrophoresis (sodium dodecyl sulphate polyacrylamide gel electrophoresis) and silver staining; and immunoblot analysis (Shuler and Shriver, 1987). For the latter purpose they used AE1–3, a mixture of two monoclonal antibodies reactive with both type I and II keratins. Their aim was to determine whether the unique histological appearance was reflected in a reproducible pattern of keratin proteins. Such a precise pattern of molecular differentiation, they thought, could reflect the presence of specific local factors responsible for the classic pattern of epithelial differentiation.

Their findings were consistent with other studies that had linked epithelial differentiation and keratin gene expression, and suggested a common pattern of gene expression underlying the characteristic histological pattern of the parakeratinised OKC. Their finding of lack of keratins of molecular weights in excess of 60 kD was compatible with the hypothesis that these were found only in orthokeratinised epithelium, and the orthokeratinised variant of the OKC might be expected to have a different set of keratin proteins (Shuler and Shriver, 1987).

In a criticism of the above paper, it was pointed out that the method and monoclonal antibody used were incapable of separating and identifying the keratins satisfactorily and that no conclusions could be drawn in respect of the

Table 3.6 Immunocytochemical expression of cytokeratins and other epithelial markers in the odontogenic keratocyst, compared with the dentigerous and radicular cysts. (After *Oral Oncology*, 2002, Vol. 38, pp. 409–10, with kind permission of Elsevier Publishers and the editor.)

Author(s)	OKC	Dentigerous	Radicular
Hormia *et al*. 1987	Results varied with different antibodies with some CKs a. CK 7, 17, 19 in all layers b. CK 13, 16 in suprabasal layers c. CK 8, 18, 19 in basal layers and few suprabasal layers d. CK 1, 9, 10/11 absent	Results varied with different antibodies with some CKs CK 7, 17, 19 in all layers 'Heterogeneous' staining for CK 8, 13, 16, 18, 19 Two cases ++ for 1, 9, 10, 11; –ve for 18. Another 2 cases had a layer of CK 18+ve cells	Results varied with different antibodies with some CKs CK 7, 17, 19 in all layers 'Heterogeneous' staining for CK 8, 13, 16, 8, 9 CK 1, 9, 10/11 not present
Morgan *et al*. (1987)	CK 19 in all layers CK 10 in superficial third	CK 19 in all layers	Not done
Shuler & Shriver (1987)	Immunoblot analysis with monoclonal antibodies AE1/3 indicated 7 keratin bands of approx MWs 46, 48, 50, 52, 54, 58, 59	Not done	Not done
Matthews *et al*. (1988)	a. CK 19 in all layers b. CK 10/11 in upper suprabasal layers c. No CKs 7, 8, 18 d. CK 13, 13/16 +ve e. CEA and EMA weak and patchy f. RLA expressed in majority of suprabasal cells	CK 19 in all layers 10/11 rarely expressed No 7, 8, 18 CK 13, 13/16 +ve CEA/EMA detected RLA as in OKC	CK 19 in all layers 10/11 rarely expressed CK 7 in 3 cases. No CK 8. One 18 + CK 13, 13/16 +ve CEA/EMA inconsistent RLA as in OKC
Morgan *et al*. (1988)	a. CK 4, 13, 14, 19 1,10,16 in upper layers	4, 13, 14, 19	4, 13, 14, 19
Howell *et al*. (1988)	CEA reactivity in 7/7 cases, but there was non-specific staining		No CEA reactivity in 2/2
MacDonald & Fletcher (1989)	Monoclonal antibody LP34 for intermediate MW CKs: Basal cells –ve in 9/9 cases; other layers moderately to strongly +ve	LP34 antibody: Basal cells, and all other layers strongly +ve in 9/9 cases	Not done
Matthews & Browne (1990) and Smith & Matthews (1991)	Unable to verify results of MacDonald & Fletcher using LP34 antibody. Suggest differences in laboratory technique		
MacDonald & Fletcher (1989)	Response to Matthews & Browne (1990). Emphasise need for standardised technique		

Gao *et al*. (1989)	a. CK 19 in suprabasal cells and some basal cells b. CK 4, 13 in suprabasal cells c. CK 5, 8 strongest in basal layers d. CK 16 strong in suprabasal layers in all cases e. CK 10 very weak	CK 19 in full thickness or only superficial cells CK 13 ++ in suprabasal layers	Not described
Smith & Matthews (1991)	a. CK 5/8 strong reactivity b. CK 6/18 strong reactivity c. CK 1/10/11 strong reactivity d. CK 13/16 strong reactivity e. CK 7, 8, 18 ('Simple') weak/variable f. CK 19 ('Simple') strong reactivity g. CK 13, 14, 16 ('Stratified') strong reactivity h. CEA, EMA weak variable; RLA moderate	CK 5/8 strong reactivity CK 6/18 strong reactivity No CK 10/11 CK 13/16 strong reactivity CK 19 ('Simple') strong CK 13, 14 strong; 16 weak CEA, EMA, RLA moderate	CK 5/8 strong reactivity 6/18 strong reactivity No CK 10/11 CK 13/16 strong reactivity CK 19 ('Simple') strong reactivity CK 13, 14, 16 strong CEA, EMA, RLA moderate
Li *et al*. (1998)	Show differences in cytokeratins, EMA and CEA distributions in OKC and orthokeratinised OKCs	Not done	Not done
Wagner *et al*. (1999)	CK 7, 20 expressed CK 19 not detected in OKCs. P53 only in OKCs	CK 7, 19, 20 expressed	CK 7, 19, 20 expressed
August *et al*. (2000)	CK 10	No CK 10	No CK 10
Meara *et al*. (2000)	OKCs in NBCC syndrome: a. CK 17 strong reactivity in all layers in 6/6 cases; b. CK 13, CEA, AE1/3 strong upper epithelium staining c. CK 18, no staining Sporadic OKCs: similar to above but – a. CK 17 less strong, less consistent & not all layers b. CK 18 more consistenly stained	CK 13, 17, 18, CAM 5.2, AE1/3 – all mild and variable reactivity. CEA –ve in 6/7 specimens	Not studied
Stoll *et al*. (2005)	CK 17 discernible in 93.3% of cases CK 19 negative	CK 17 present in 35% CK 19 in 43%	CK 17 present in 35% of cases CK 19 present in 43%

presence or absence of keratins 1 (68 kD), 10 (56.5 kD) and 11 (56 kD) (Smith and Matthews, 1991). Importantly, a 40 kD band corresponding to keratin 19 was not found in the study, while this keratin had been consistently found with immunocytochemical studies using several different monoclonal antibodies, as can be seen in Table 3.6. Confirmation of the presence or absence of cornification keratins in OKC epithelium, they believed, required further immunocytochemical and immunoblot studies with a variety of monoclonal antibodies reactive with keratins 1, 10, 11 together with biochemical analyses of epithelial extracts by two-dimensional elecrophoretic methods able to resolve all keratins.

A comprehensive review of the potential applications of cytokeratin immunocytochemistry in oral diagnosis demonstrated the ubiquity of keratin 19, a keratin found in some basal cells of stratified mucosal epithelia, in most simple epithelia, and also in normal and pathological odontogenic epithelia (Morgan *et al*., 1987). Unfortunately, the numbers of samples studied were not mentioned, and may have been single specimens, but cytokeratin positivity was observed in the cell rests of Malassez and Serres, at all levels of a dentigerous cyst and an OKC (with antibody LP2K). Keratin 10 was demonstrated in the superficial cell layers of the same OKC (using antibody LHP3).

A subsequent conference abstract from the same group reported that in their sample of OKCs, dentigerous and radicular cysts, all the epithelia expressed keratins 4, 13, 14 and 19, and OKCs alone expressed keratins 1, 10 and 16 in the upper layers (Morgan *et al*., 1988).

CEA immunoreactivity of varying staining intensity was demonstrated in all seven OKCs examined in a study of odontogenic tumours and cysts (Howell *et al*., 1988). Both radicular cysts investigated gave a negative reaction. However, there was a reduction in the staining intensity and the number of positive cases in the OKC sample when absorbed anti-CEA antiserum was used to obviate non-specific reactivity, which indicated results consistent with those reported above (Matthews *et al*., 1988).

Another attempt at finding a marker that would distinguish the OKC from the dentigerous cyst before definitive treatment was carried out used the monoclonal antibodies LP34 for intermediate, and CAM 5.2 for low molecular weight cytokeratins on sections cut from the original blocks, rehydrated and trypsin treated. Their material comprised nine OKCs and nine dentigerous cysts (MacDonald and Fletcher, 1989). Staining with CAM 5.2 was weak or absent in all cases of both cyst types. With LP34 most dentigerous cysts reacted strongly through the full thickness of epithelium. There was a different pattern with the OKCs in that the basal cells reacted negatively in all but two cases where the reaction was weak in areas of inflammation in adjacent fibrous cyst wall. The suprabasal and superficial layers for the most part showed moderate to strong reactivity. The authors concluded that basal cell staining with LP34 made it possible to distinguish dentigerous from OKCs and suggested that this basal cell staining was a property of the epithelial differentiation rather than a secondary effect of inflammation which in the OKC stained basal cells only in the presence of adjacent inflammation cysts (MacDonald and Fletcher, 1989).

This paper evoked a response in which it was contended that although other studies had suggested that there were no diagnostically important differences in keratin expression between cyst types, the OKC might be unique in coexpressing keratins 19 and 10 (Matthews and Browne, 1990). Nevertheless this 'OKC-specific' keratin phenotype could not be used for routine diagnostic purposes as the epitopes recognised by the monoclonal antibodies specific for keratins 19 and 10 were destroyed by formalin fixation and paraffin wax processing. Furthermore, they claimed that keratins 19 and 10 could also be demonstrated in other odontogenic cysts that had undergone metaplastic keratinisation as they had reported previously (Matthews *et al*., 1988).

The response to this was that their own material, unlike that of Matthews and Browne (1990), had not been decalcified and that there were other differences in the two methodologies (MacDonald and Fletcher, 1989). They emphasised also that reproducible results using monoclonal antibodies such as LP34 depended on following similar tissue processing and staining methods wherever possible. In a later paper (see p. 43), Smith and Matthews (1991) insisted that extensive studies by their group with this antibody on both frozen and paraffin sections indicated that OKC, dentigerous and radicular cyst epithelium could not be differentiated on the basis of LP34 reactivity.

In an immunocytochemical comparison of cytokeratins in odontogenic epithelium of dental follicles with the epithelium linings of odontogenic and non-odontogenic cysts, it was concluded that odontogenic epithelium and its derivatives: the rests of Malassez, OKCs, periapical and dentigerous cysts showed certain similarities in their patterns of cytokeratin expression, but differed from those of the non-odontogenic nasopalatine duct and epidermoid cysts (Gao *et al*., 1989). These authors, too, were surprised by the absence of keratin 10 expression in OKCs and thought it might be a reflection of the parakeratinisation process. They felt that their finding of strong keratin 16 staining in OKCs with monoclonal antibody LMM3, which had been associated with high proliferative activity, might reflect the high intrinsic growth potential of these lesions. They concluded, however, that small differences in cytokeratin expression in the different odontogenic cysts made it unlikely that the currently available antibodies made it readily possible to discriminate between them.

Brief reference has already been made to an extensive review of keratin expression and that of other epithelial cell markers in a range of developing and pathological odontogenic epithelia, which compared the findings in OKCs with dentigerous and radicular cysts (Smith and Matthews, 1991). This group used frozen sections and monoclonal antibodies against individual and small groups of cytokeratins and concluded that the major keratins consistently detected in odontogenic epithelium were keratins 13, 14 and 19, and that this combination provided a potentially useful marker for odontogenic epithelium. All of these were found in the epithelial linings of OKCs, dentigerous and radicular cysts. Keratins 13 and 14, they pointed out, were associated with non-cornified and all stratified epithelia, respectively, whereas keratin 19 was a major component in many simple epithelia and was also found in the basal cells of stratified epithelia including those of the oral mucosa (see Table 3.6).

These authors emphasised the need for care in the interpretation of negative results in immunocytochemistry, particularly in studies of keratins, as masking of some or all epitopes on a particular keratin in certain cells can occur. Further, differences in reactivity between different monoclonal antibodies for the same keratin were well documented, and this was certainly the case with keratin 19.

With regard to the detection of keratins characteristic of cornified epithelium such as keratins 1 and 10, two groups (Morgan *et al*., 1987; Smith and Matthews, 1991) had reported consistent positivity of OKC epithelium reacting with monoclonal antibodies specific for keratin 10 (LH3 and RKSE60) and for keratins 1, 10, 11 (KS8.60). On the other hand, two other groups (Hormia *et al*., 1987; Gao *et al*., 1989) had reported negative results using the same monoclonal antibodies (LH3, KS8.60) as well as a third antibody specific for keratin 10 (LH2).

Another point of interest in the series of studies by the Birmingham group was a greater expression of keratins 1/10/11, 13 and 16 by OKC epithelium than in remnants of dental lamina from which these lesions are believed to be derived. This raised the question of possible changes in keratin profile associated with transition of odontogenic epithelial remnants to pathological lesions. A final point was the strong reaction of OKC lining for keratin 16 which has been associated with high proliferative activity (Smith and Matthews, 1991).

The conclusion reached was that there did not seem to be any consistent differences in keratin expression between the OKC, dentigerous and radicular cysts and different types of odontogenic cell rests. They believed that if there was confirmation of the expression of cornification keratins by remnants of dental lamina and the OKC, the latter linked to expression of keratin 16, this might provide a useful marker differentiating them from dentigerous cysts, derived from reduced enamel epithelium, and radicular cysts, derived from remnants of the root sheath of Hertwig. Of importance was the fact that cornification keratins had been detected in more ordered epithelium in non-keratinising cyst linings. This tended to nullify the hopes of distinguishing OKCs in which the characteristic epithelium is masked by inflammation, from other odontogenic cysts with metaplastic keratinisation (Smith and Matthews, 1991).

Differences in cytokeratin, EMA and CEA immunocytochemical reactivity between the parakeratinised OKC and the orthokeratinised variety have been demonstrated and, as referred to earlier, the suggestion has been made that the latter, having a considerably less aggressive behaviour, is a different entity and should bear a different name, 'orthokeratinised odontogenic cyst' (OOC) (Li *et al*., 1998). Keratins associated with squamous differentiation or cornified epithelium (KL1, CKs 10/13 and AE1) showed pronounced staining in all but the basal cell layer of the OOC, whereas in the parakeratinised OKC staining was found only in the upper and surface parakeratin layers. Both EMA and CEA were consistently present in the surface parakeratin layer of the OKC but completely absent in the orthokeratinised linings. Ki-67 positive cells in the OKC linings were considerably more frequent than in the OOC linings (Li *et al*., 1998).

Unlike the findings in the earlier papers cited above, a more recent study did not detect CK19 in OKCs (Wagner *et al*., 1999).

A study of 18 fine needle aspiration biopsies obtained by traversing the cyst cavity and contacting the opposite cyst wall, compared the CK10 immunocytochemical expression of sampled epithelial cells with immunohistochemical CK10 expression of the postoperative biopsies (August *et al*., 2000). The authors reported that this technique accurately distinguished OKCs from non-keratinised dentigerous and radicular cysts in the entire sample.

Another recent paper reported strong expression of cytokeratin 17 in all layers of the epithelium in all of six OKCs from patients with the NBCCS. In a sample of seven sporadic OKCs, cytokeratin 17 expression was similar to the syndrome specimens in only two cases and showed weaker and irregular staining in the other five. Dentigerous cysts showed weak positivity for cytokeratins 13, 17 and 18. CEA expression was weakly positive in all the OKCs but was negative in all dentigerous cysts. It was suggested that cytokeratin 17 might be a useful marker to distinguish OKCs from other jaw cysts and even possibly to distinguish syndrome from sporadic OKCs. The authors were nevertheless cautious about drawing definite conclusions, citing observer subjectivity and problems with technical standardisation (Meara *et al*., 2000).

Stoll *et al*. (2005) concluded, from their comparative study using a panel of seven monoclonal antibodies, that cytokeratins 17 and 19 seem to be a valuable additional parameter distinguishing OKCs from other odontogenic cysts.

Epidermal growth factor and transforming growth factor

Epidermal growth factor (EGF), a potent mitogen, is a peptide growth hormone in human tissues that is important in the regulation of proliferation in normal and neoplastic cells. EGF activity is mediated by binding to its specific trans-membrane receptor EGFr. The latter is activated in its turn by the binding of another peptide, alpha-transforming growth factor (TGF-α). When EGF binds to the extracellular part of the receptor, it leads to the activation of a tyrosine kinase in its intracellular zone. This is thought to be the first step in a chain of reactions that culminate in mitosis. EGFr distribution occurs in normal epithelium, is expressed most intensely in undifferentiated basal cells and proliferating adnexal structures, and in both benign and malignant epithelial neoplasms (Carpenter, 1987; Shrestha *et al*., 1992; Li *et al*., 1993). Over-expression of this receptor has been reported to be a hallmark of squamous cell carcinoma by some, whereas others have found a loss (Shrestha *et al*., 1992).

A study was reported by the latter group on EGFr in odontogenic cysts and tumours (Shrestha *et al*., 1992). For reasons not explained by the authors, they separated what they called primordial cysts from OKCs. Combining the two, EGFr was demonstrated in 18 of 28 (64%) of these cysts, compared with 47% of dentigerous and 35% of radicular cysts. None of a range of benign odontogenic tumours showed any expression. In the OKC/primordial group, the positive staining of the cell membrane extended through the full thickness of the epithelium including the basal cell layer in some but not all of the cases. The authors speculated that the epithelium of odontogenic cysts (although they did not comment on the variability within the individual cyst groups) appeared capable of EGFr-mediated proliferation, whereas the odontogenic epithelial tumours appeared either to have no binding activity of EGFr or had lost their dependency on this factor for growth.

In the following year, a more detailed study on EGFr in odontogenic cysts was carried out (Li *et al*., 1993). Using three monoclonal antibodies for EGFr known to be reactive in paraffin sections, E30 and C11 with specificity for the extracellular domain, and F4 for the intracellular domain, they found that the epithelia of OKCs, dentigerous and radicular cysts were all positive in all specimens for all antibodies. The most consistent and intense epithelial staining was with E30. With all clones there was a trend indicating the most intense staining of the OKCs, followed by the dentigerous and then the radicular cyst linings. The lower EGFr expression in the radicular cysts tended to be found in epithelium adjacent to areas of inflammatory cell infiltration, and the same phenomenon was observed in OKCs that were inflamed in parts. In respect of distribution of EGFr within the epithelial linings, E30 showed the most consistent reactivity with strong epithelial cell membrane staining of basal and suprabasal cells. In nine of the 13 OKCs in the study the staining was most intense in the basal cells. With F4 and C11, there was high background reaction in paraffin sections and weaker and more variability between the cyst types.

In contrast with the findings in the study by Shrestha *et al*. (1992), all six ameloblastoma specimens they tested gave strong cell membrane reactivity for EGFr with E30 although there was more variable patchy staining with C11 and F4 antibodies. This disparity demonstrated, they believed, the importance of using a panel of antibodies for immunocytochemical studies of a complex and antigenically cross-reactive molecule like EGFr (Li *et al*., 1993).

The authors concluded that the high levels of expression in OKCs supported the view that these cysts have an intrinsic growth potential not present in other odontogenic cysts. The lesser EGFr expression that their study showed in the radicular cyst cells and the rests of Malassez from which they arose, contrasted with the maintenance of receptor expression in OKCs that are derived from dental lamina remnants. The reason for this, the authors speculated, might reflect epithelial–mesenchymal interactions and growth factor/receptor modulation. The loss of typical OKC structure adjacent to areas of inflammation and the corresponding diminution of EGFr expression emphasised the importance of mesenchymal integrity in shaping the OKC epithelium phenotype, a relationship well demonstrated in earlier explant studies (Vedtofte *et al*., 1982).

In a later similar study by the same group, the epithelial linings of all cysts showed reactivity for TGF-α mainly localised to the basal and suprabasal layers (Li *et al*., 1997). However, OKC linings expressed higher levels of TGF-α with 24 of 27 cases (89%) being strongly positive compared with five of 10 (50%) in both dentigerous and radicular cysts. EGF reactivity was similar in all cyst groups, weaker than for TGF-α and predominantly suprabasal. In fact, the most intense reaction for TGF-α was in the endothelial cells, fibroblasts and inflammatory cells in the fibrous tissue walls of all cyst types. They concluded that the differential expression of TGF-α, EGF and their common receptor (EGFr) in the different odontogenic cyst types suggested involvement of the growth factors in their pathogenesis.

Elafin

Elafin, also known as skin-derived antileucoproteinase inhibitor (SKALP), is an epithelial-specific, cationic elastase inhibitor that has been identified in cultured keratinocytes and its expression has been studied in OKC epithelium and compared with other jaw cysts, normal oral mucosa, dysplastic epithelia and some neoplastic lesions (Robinson *et al*., 1994, 1996). Using polyclonal anti-SKALP rabbit antiserum, all examples of uninflamed OKC epithelia (n=10 sporadic and 10 syndrome related) showed strong, uniform cytoplasmic staining in all layers,

but there was no staining where there was adjacent inflammation. The epithelium of dentigerous cysts showed only mild patchy staining in two of 10 cases and all radicular ($n=10$) and residual ($n=10$) specimens were also negative. There was increased expression of elafin in mild and moderate epithelial dysplasia while in severe dysplasias the staining was strong but not uniform. In general, there was increased elafin expression in neoplastic epithelium compared with normal oral epithelium. No staining was observed in the majority of ameloblastomas but moderate uniform staining was observed centrally in islands of acanthomatous ameloblastomas. The authors suggested that the increased levels of elafin in OKC epithelia and dysplastic tissue may be a cellular homoeostatic response to generate a protective barrier preventing proteolytic degradation of underlying elastic tissue, but they made no comment on whether its presence in OKC epithelium might influence its behaviour.

Bone morphogenic protein-4

Abnormal epidermal differentiation has been linked to abnormal expression of bone morphogenic protein-4 (BMP-4). The differences in histopathology of the lining epithelia of the OKC and dentigerous cyst led Kim *et al.* (2005) to postulate that different factors may be involved in both the development and recurrence tendency of the two lesions. They set out to determine whether the BMP-4 expression patterns of the two could be different. Their study sample comprised 34 OKCs and 43 dentigerous cysts. Goat primary polyclonal antibody against BMP-4 was used.

OKCs showed dense staining in 15 of 34 of the epithelial linings and in 17 of 34 of the mesenchymal cyst walls. By contrast, the epithelial linings of the dentigerous cysts showed negative staining in 37 of 43 specimens and in 30 of 43 of the mesenchymal cyst walls. The differences between the groups were statistically significant for both epithelial linings and mesenchymal cells ($P<0.001$). When the results of recurrent and non-recurrent OKCs were compared, BPM-4 was more intensely expressed in the epithelial linings of the recurrent cases ($P<0.036$) but not in the mesenchymal cells. The authors speculated on the reasons for these differences and concluded that the exact role of the BMP-4 could not yet be determined but that it might be related to the epithelial morphogenesis and invasive growth (Kim *et al.*, 2005).

Proliferation and genetic studies

Gp38 positivity in OKC epithelium suggests alteration in gene expression

Based on the finding that gp38, an epithelial-specific 38 kD cell surface glycoprotein, had been shown to be strongly expressed in basal cell carcinomas (BCC) but not in squamous cell carcinomas or various proliferative disorders of squamous epithelium, a study was carried out on the distribution of gp38 in the epithelial linings of 30 parakeratinised and six orthokeratinised OKCs, and also a wide range of other jaw cysts and normal oral tissues (High *et al.*, 1993). In view of the established association of OKCs and BCCs in the NBCCS, they hypothesised that the OKCs might express common proteins not expressed in normal oral epithelia. Routinely processed paraffin sections of the experimental material and, where available, frozen sections pretreated with α-chymotrypsin were treated with monoclonal antibody Mab MH99 which recognises an epitope on gp38. Results for frozen and paraffin sections were similar (High *et al.*, 1993).

There was consistent heavy cell surface staining of basal and suprabasal layers of all 30 OKCs, but no mention was made as to whether any of them were syndrome associated; the presumption is that they were not. Orthokeratinised cysts were all negative. In most cases the positive staining pattern was maintained even when inflammation distorted the classic histological pattern. The satellite cysts in the walls of 18 of the 30 OKCs also showed strong positivity. Most normal mucosal epithelia were negative but there was consistent strong positivity in the inner and outer layers of reduced enamel epithelium. Surprisingly, in view of this latter finding, the linings of all 10 dentigerous cysts sampled were negative, which led the authors to suggest that there must be some down-regulation in expression. Odontogenic epithelial cell rests were also negative (High *et al.*, 1993).

The strong specificity of this technique for parakeratinised OKCs suggested an alteration in gene expression that was also observed in BCCs but not in normal tissues and it was felt that this might support the view that the OKC had neoplastic potential. Of interest in this respect is that all histological variants of the nine ameloblastomas investigated were negative. The authors thought that the negativity of all the orthokeratinised cases ($n=6$) and the reported less aggressive clinical behaviour of this variety of OKC, including their absence of association with BCCs, justified their being regarded as distinct clinicopathological lesions warranting different treatment (High *et al.*, 1993).

p53, proliferating cell nuclear antigen, Ki-67, nucleolar organiser regions, calretinin

Numbers of papers have been published during the past decade on the expression of proliferating cell nuclear antigen (PCNA) (Fig. 3.23), p53 (Fig. 3.24), Ki-67 (Fig. 3.25) and, to a lesser extent, nucleolar organiser regions (AgNORs) in odontogenic cysts, and more particularly in OKCs, both sporadic and in association with the NBCCS. These markers have in common the fact that they are all expressed in actively proliferating cells, particularly in neoplasms. Given the accumulating evidence that the

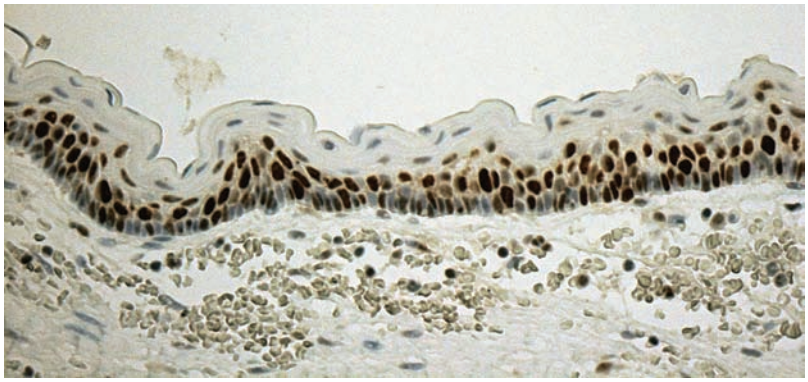


Fig. 3.23 Plentiful proliferating cell nuclear antigen (PCNA) positive cells in the basal and suprabasal layers of an odontogenic keratocyst.

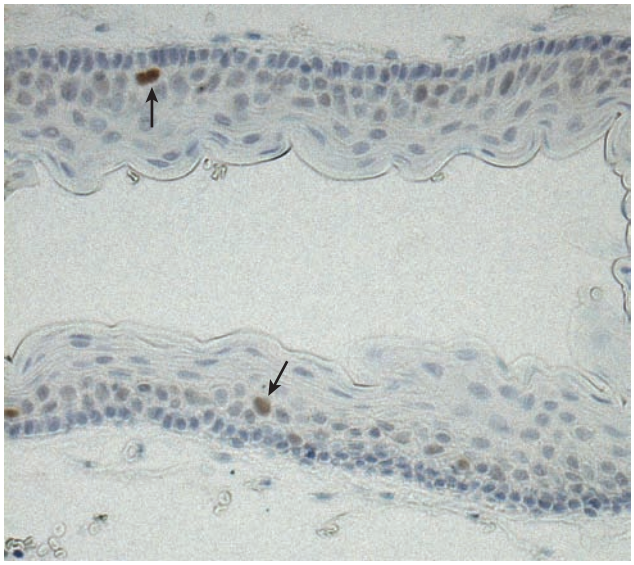


Fig. 3.24 Sparse numbers of p53-positive cells in the lining of this odontogenic keratocyst (arrows).

OKC was an aggressive lesion and the suggestions that it might be regarded as a neoplasm, it is not surprising that a spate of studies applied these methodologies to this cyst. They will be considered together chronologically.

The first investigation to demonstrate the increased expression of p53 protein in some OKCs was that of Ogden *et al*. (1992). p53 protein is a mutation product of the tumour suppressor gene p53. The p53 gene has a short half-life in normal cells and cannot be detected immunocytochemically, but when it mutates, the p53 protein product is more stable and can be detected using this procedure. Many studies have now demonstrated p53 protein in a wide range of malignant lesions but not in normal cells.

This first investigation was carried out on a series of 12 OKCs, 12 dentigerous and 12 radicular cysts using routinely fixed and processed sections. These were incubated with CM-1, a rabbit polyclonal antibody raised against the whole p53 protein. The presence of p53 protein in the nucleus was identified by positive staining. Further staining of the OKCs was performed using the monoclonal antibody PC10 which recognises PCNA. To assess the rate of cell division, the number of suprabasal mitoses was counted in a randomly selected area of 1500 epithelial cells in each OKC in the sample (Ogden *et al*., 1992).

The OKC was the only one of the three cyst types in which p53 was detectable, showing a positive reaction in five of the 12 cases. All the OKCs were positive for PCNA. PCNA staining indicated that the p53-positive cells were actively dividing, because similar regions were positive for both antibodies. p53 positivity was identified in most of the basal cells of the OKC, while PCNA staining was present in all basal cells and most parabasal cells. There was one patient with the NBCCS who had two cysts examined at different times. The first was p53-postive and the second, 3 years later, was negative. Two cysts from a second patient also showed p53 positivity in one and not in the other. Three of the 12 cysts in the series were recurrent and one of these was p53 positive. The number of suprabasal mitoses per 1500 cells varied from 0 to 4 but no difference could be shown between groups with p53-positive and p53-negative linings (Ogden *et al*., 1992).

The authors were cautious in the interpretation of their results emphasising that CM1 antibody recognised both wild and mutant forms of p53 and should not therefore imply that the positivity in some of the linings indicated an association with malignant disease. They also pointed out that the positivity in the OKCs was much weaker than that seen in oral cancers. Nevertheless, they felt that the well-documented features of tendency to recurrence, its association with the NBCCS, its frequent multiplicity, the high mitotic rate reported by some workers, and the PCNA positivity in all OKCs in their sample, might indicate some significance in the finding that only OKCs, and not the other jaw cysts, showed p53 positivity (Ogden *et al*., 1992).

Another study using the same monoclonal antibody PC10 to PCNA investigated the PCNA activity in routinely fixed paraffin sections of the OKC, dentigerous and radicular cysts (Li *et al*., 1994). PCNA was defined as a 36 kD nuclear protein associated with the cell cycle, being an auxiliary protein of DNA polymerase-δ, the distribution of which in the cell cycle increases through G1, peaks at the G1/S interphase and decreases through G2 phase. It was widely regarded as a marker of cell replication and

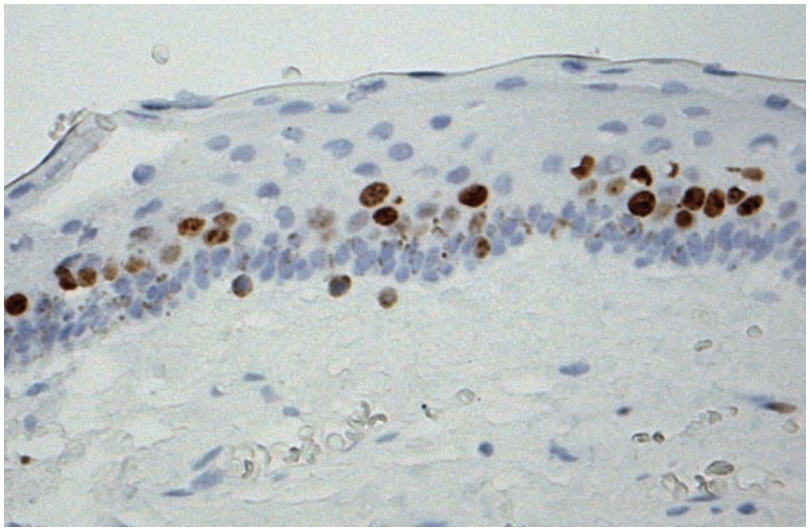


Fig. 3.25 Moderate numbers of Ki-67-positive cells are present in the suprabasal layers of this odontogenic keratocyst.

was also associated with DNA repair processes and stimulation by growth factors.

To quantify the PCNA activity after staining, PCNA-positive cells were counted manually and related to the length of basement membrane (mm) and the epithelial area (mm^2) using TV image analysis. Cell counts were expressed as total or PCNA-positive cells per mm of basement membrane or per mm^2 of epithelium. PCNA expression was generally in the nuclei. The epithelial linings of the OKCs ($n=11$) contained the highest number of PCNA-positive cells, most of which were in the suprabasal layers and fewer than 5% in the basal layers. The total PCNA count in the OKC had a mean value of 94.4±22.7 cells/mm and 1653±534 mm^2. This was significantly higher ($P<0.005$) than the dentigerous cysts ($n=10$) with a mean of 5.1±3.0 cells/mm; 164.7±122.7 mm^2, and the radicular cyst ($n=10$) with a mean of 11.0±4.1 cells/mm; 207.1±128.7 mm^2. These differences, the authors pointed out, were entirely the result of the significantly higher number of suprabasal cells in the OKC because there were no significant differences in basal cell positive counts. In fact there were significantly lower ($P<0.005$) basal:suprabasal cell ratios for PCNA-positive cells in the OKCs compared with the same ratios in the dentigerous and radicular cysts (Li *et al*., 1994).

The authors assessed critically the positive and negative aspects of the methodology for demonstrating PCNA reactivity and averred that in the absence of other supporting data it was not possible to attribute differences in PCNA expression directly to differences in proliferative activity. Nevertheless, they indicated that their results were consistent with earlier studies indicating greater proliferative activity in OKC linings, in accord with their aggressive clinical behaviour. They believed that much of the PCNA detected in OKC epithelium was associated with cell cycle related DNA synthesis. They were unable to determine whether the higher PCNA-positive cell numbers in OKCs represented a higher epithelial cell turnover rate or that a larger proportion of cells were dividing with a prolonged cell cycle time. As they had found that parakeratinised oral epithelium contained similar numbers of PCNA-positive cells per unit length of basement membrane to the OKCs, they wondered whether lateral rather than vertical migration of cells was greater in the OKCs, a factor that might explain the consistently narrow and regular OKC epithelium concomitant with active cyst growth cysts (Li *et al*., 1994).

Another point of interest was the predominant suprabasal distribution of PCNA-positive cells in the face of a low basal cell positivity in OKC linings. In their view, this was consistent with their own earlier finding of EGFr expression by the suprabasal cells of only the OKCs; and the high levels of p53 protein activity in the suprabasal cells shown by Ogden *et al*. (1992). The Ogden paper, however, reads somewhat differently, namely that 'CM-1 (for p53) was identified in most of the basal cells; staining with PC10 (for PCNA) was much more intense, being present in the basal cells and most parabasal cells' (Ogden *et al*., 1992).

The authors concluded that their study had demonstrated qualitative and quantitative differences in nuclear reactivity for PCNA between linings of the three major odontogenic cysts; and that the predominant suprabasal position of PCNA-positive cells together with the other studies that had shown increased expression of EGFr and p53 in OKC epithelium, suggested that a unique proliferative and differentiation process occurs in this cyst lining (Li *et al*., 1994).

Developing this same line of research, an immunocytochemical study of Ki-67 in sporadic, recurrent and NBCCS-associated OKCs used similar methodology to that in their PCNA study, with the inclusion of acetone-fixed fresh frozen sections of seven OKC specimens (Li *et al*., 1995). The routinely processed paraffin sections were deparaffinised and microwaved in 0.01 M citrate buffer for 50 min to retrieve the Ki-67 reactivity. Antibody clone Ki-67 was used. Ki-67 antigen was present in all active parts of the cell cycle. It rises during the latter half

of the S phase, reaches a peak in the G2 and M phases, and rapidly degrades after mitosis with a half-life of detectable antigen being an hour or less (Li *et al*., 1995). Its immunoreactivity has been found to correlate closely with other variables of cell proliferation. Its main limitation in assessing *in situ* cell proliferation has been the need for fresh frozen tissue, but this has been overcome by the use of the microwave procedure referred to above.

In this study, the staining pattern on the microwaved paraffin sections of the sporadic OKCs was similar to that for the fresh frozen sections. Positivity was essentially confined to the cell nucleus, particularly the nucleolus, but there was cytoplasmic staining of the basal cells. Quantification of Ki-67-positive cells showed no overall difference in positive numbers between paraffin and fresh frozen sections in the sporadic OKCs. However, there were significantly more positive basal cells in the fresh sections, which they believed might have been an overestimation because of the cytoplasmic staining in the basal layer (Li *et al*., 1995).

In comparing the Ki-67 distribution in the OKC (n=10) with the dentigerous (n=5) and radicular (n=5) cysts, they found that, overall, the pattern was the same as that of PCNA. OKC epithelium contained the highest number of Ki-67-positive cells, most of which were in the suprabasal layers. The positive number was similar to that for oral epithelium (n=7), but greater than for dentigerous and radicular cysts (P <0.006). The distribution of Ki-67-positive cells within the epithelium varied between the groups, with the basal cells of the OKCs being significantly lower than those of the oral epithelium and the other two cyst types (P <0.003). There was a significant correlation between Ki-67 and PCNA labelling (r=0.92; P <0.001) (Li *et al*., 1995).

There was no significant difference in the Ki-67 count between sporadic and recurrent (n=8) OKCs (P >0.30), but the number of Ki-67-positive cells in syndrome-associated lesions (n=9) was significantly greater than the other groups (P <0.009). Over 90% of the Ki-67-positive cells in all OKC groups were detected in the suprabasal layers. Only four of the nine syndrome-related specimens contained satellite cysts or solid epithelial lining in the fibrous walls. Generally, these contained fewer Ki-67-positive cells; the staining was weaker, and was mainly found in the basal cells (Li *et al*., 1995).

The authors postulated that it was not possible to attribute differences in PCNA expression unequivocally to differences in cell proliferation. Although PCNA expression has been shown to correlate with the S-phase of the cell cycle in many studies, it is not necessarily related to the cell cycle because it is associated with DNA repair processes and may be expressed in cells not synthesising DNA. Ki-67 antigen is a more specific marker of proliferating cells, maximally expressed during S-phase. The high level of correlation between their present Ki-67 study and their earlier PCNA study reflected cell proliferation. The higher level of epithelial cell proliferation in OKCs compared with the other odontogenic cysts, as assessed by Ki-67 reactivity in this study, supported the findings in other studies that had come to the same conclusion. Moreover, the present study, they suggested, confirmed the predominantly suprabasal distribution of proliferating cells (Li *et al*., 1995).

With regard to the high recurrence rates of OKCs they believed that their finding that there were no significant differences in cell proliferation as assessed by Ki-67 reactivity between the sporadic and the recurrent OKCs, suggested that incomplete removal, rather than intrinsic growth, was likely to be responsible for this well-documented feature. On the other hand, their finding that Ki-67-positive counts in the epithelial linings of syndrome-related OKCs were almost twice the level of those in the sporadic cysts indicated a greater level of proliferative activity in the former. This was reflected in the multiplicity of cysts and the increased numbers of satellite cysts and epithelial islands in the OKCs of NBCCS patients. This suggested that it was a genetic factor, possibly related to defective tumour suppression functions, that was reflected by the higher proliferative activity in their epithelial linings (Li *et al*., 1995). Genetic studies on the OKC are discussed below (see p. 53).

Caution in the interpretation of the level of PCNA activity in OKCs has also been mentioned because of the possibility of its detection in circumstances other than DNA synthesis, such as repair processes and the influence of epidermal and platelet-derived growth factors (El Murtadi *et al*., 1996). This study also demonstrated PCNA nuclear staining in all of a sample of 41 OKCs, predominantly in the suprabasal layer and occasionally in the basal and more superficial cells. The counts in the syndrome-related cysts was higher than in the sporadic group (P <0.05) and the PCNA count in the recurrent cases was lower than in the *de novo* sample although the difference here was not statistically significant (P=0.18).

Another investigation of the expression of PCNA in OKCs (n=12), dentigerous (n=8) and radicular (n=12) cysts and a variety of ameloblastomas (n=22) showed that of the cysts, the OKC contained the highest number of PCNA-positive cells (P <0.0001), most of which were located in the suprabasal layers although some basal cells were positive (Piatelli *et al*., 1998). Most of the positive cells in the dentigerous and radicular cysts were localised in the basal layer. All histological variants of ameloblastoma showed a higher PCNA count than the OKC (P <0.00001).

The question of whether inflammation in the OKC might influence the behaviour and treatment of this cyst led to a study on the influence of inflammation on the immunohistochemical expression of PCNA, Ki-67 proteins and the histochemical expression of AgNORs in 10

non-inflamed and 10 inflamed OKCs (de Paula *et al*., 2000). Using the same methodology as other workers in the field, they found that the total cell number as well as the PCNA-positive and Ki-67-positive cell counts were significantly higher in the inflamed than the non-inflamed OKCs ($P=0.01$). The mean number of PCNA-positive and Ki-67-positive cell counts were significantly higher in the suprabasal than in the basal layer in both inflamed and uninflamed cysts ($P=0.01$). Furthermore, inflamed OKCs showed significantly higher numbers of PCNA-positive and Ki-67-positive cells in the basal and suprabasal layers than in the non-inflamed sample ($P=0.01$); and a higher percentage of PCNA-positive and Ki-67-positive cells in the basal but not in the suprabasal layers ($P=0.01$). The mean number of AgNORs per nucleus was significantly higher in the inflamed than in the uninflamed sample ($P=0.01$).

In a study to determine whether AgNORs might be useful in distinguishing various odontogenic cysts from the unicystic ameloblastoma, Coleman *et al*. (1996) concluded that the AgNOR counts were not of diagnostic significance and could not be used for this purpose.

Epithelial hyperplasia in response to an inflammatory stimulus is a well-recognised phenomenon which is seen particularly in radicular cysts that are of inflammatory origin (Shear, 1992). Developmental odontogenic cysts, however, also display this change in the presence of an inflammatory stimulus, as the result of infection or trauma. Epithelial hyperplasia is reversible, whereas there is considerable evidence that the epithelial proliferation in the OKC, other than that induced by inflammation, is not. Presumably then, raised levels of PCNA and Ki-67 positivity in the OKC would reverse if and when the inflammatory stimulus subsided.

A combined study of p53 protein and Ki-67 in OKCs ($n=13$), as well as in dentigerous ($n=15$) and radicular ($n=6$) cysts, ameloblastoma ($n=9$) and odontogenic carcinoma ($n=2$), was carried out by Slootweg (1995). Immunocytochemistry was performed on deparaffinised sections using monoclonal antibody BP53-12-1 directed against both wild-type and mutant p53 protein (p53P); and monoclonal antibody MIB-1 which reacts with Ki-67 nuclear antigen. Instead of using microwave pretreatment for antigen retrieval, the deparaffinised sections were treated with a boiling solution of freshly prepared 10 mmol citrate/HCl buffer, pH 6.0 for 10 minutes on an electric hotplate.

The evaluation of his results was carried out by cell counts of single high power fields in areas of greatest labelling. Overall, the OKC contained larger numbers of Ki-67-positive cells with a more uniform distribution than the dentigerous and radicular cysts. In the OKC, the positive cells were found mainly in the layer just superficial to the basal layer (juxtabasilar), and positive basal cells were rarely observed. In the other two cyst types, the Ki-67 positivity was mainly in the basal layer, except in areas of inflammation when the positivity was present in all layers (Slootweg, 1995).

Nuclear staining for p53 protein was detected in 42 of the 45 cases examined. Most cases showed both light and dense staining. Densely stained nuclei were found most commonly in the OKC (11 of 13 cases), the ameloblastomas (six of nine) and the odontogenic carcinomas (two of two). The dentigerous and radicular cyst epithelia were mainly negative or contained only faintly staining cells. Correlation between Ki-67 and p53 positivity was found only in positions of dense nuclear labelling. All lesions in which the maximal area of Ki-67-positive cell labelling contained more the 100 cells per high power field were associated with the presence of densely stained p53-positive cells, suggesting a possible relationship. Nevertheless, the author included both faintly and densely p53-positive nuclei as positive in concluding that there were no differences in this respect between the three different cyst types. However, there was a relationship between the intensity of the staining and the lesions that clinically were characterised by proliferation: the ameloblastoma, odontogenic carcinoma and the OKC. Arising from this conclusion, he postulated that it was over-expression of p53 protein rather than increased numbers of p53-positive cells that was related to the proliferative capacity of the OKC (Slootweg, 1995).

A study by Saraçoğlu *et al*. (2005), who also used monoclonal antibody MIB-1, confirmed the finding that the numbers of MIB-1-positive cells were higher in the OKC lining epithelium than in other odontogenic cysts.

Another immunocytochemical study compared the p53 protein expression in single non-recurrent ($n=15$), with recurrent OKCs ($n=10$) and those in patients with the NBCC syndrome ($n=3$) (Lombardi *et al*., 1995). Routinely processed and paraffin-embedded tissue was used and immunostaining performed by reacting with polyclonal antibody CM-1. Immunopositivity for p53 protein was scored as positive or negative.

Positivity was recorded in 15 of 30 cases in the total OKC sample, of which eight of 15 (53.3%) were the non-recurrent cysts, four of 10 (40%) were recurrent, and three of five (60%) were in syndrome cases. These differences were not statistically significant. The staining intensity was variable and weak compared with the control cases of epithelial dysplasia or squamous cell carcinoma. Labelling was mostly solitary and scattered, only occasionally clustered, and localised to basal and suprabasal cells, not only in the main cyst lining but also in the satellite cysts and epithelial rests in the cyst walls. There was no significant relationship between p53 protein expression and the presence of basal cell budding, satellite cysts, or odontogenic epithelial islands in the fibrous cyst walls (Lombardi *et al*., 1995).

The frequency of p53 positivity in this study was similar to that in the Ogden study (Ogden *et al*., 1992) but the patterns and intensity of the staining were different in that most of the OKC basal cells in the latter were positive while in the paper under discussion staining was scattered. The Slootweg study, on the other hand, indicated a much higher positivity rate. The Ogden and the Lombardi studies used the antibody CM-1 while Slootweg used BP53-12-1. Both antibodies are directed against both wild-type and mutant p53 protein.

The authors (Lombardi *et al*., 1995) argued that while the relatively aggressive, locally invasive clinical behaviour of OKCs would be consistent with that of benign tumours and could explain the presence of mutant or otherwise inactive p53, other factors could be operative. The fact that p53 had been demonstrated immunocytochemically in a variety of reactive lesions and wild-type p53 in some physiological processes, indicated that p53 protein stabilisation mechanisms other than gene mutation might be involved.

A similar study on p53 protein expression in 11 sporadic, five recurrent and six NBCCS-associated OKCs, used three antibodies to p53, clone BP53-12, clone 1801 and polyclonal CM (Li *et al*., 1996). Five dentigerous and five radicular cysts were also investigated. Their objective was to determine whether there was any relationship between p53 immunoreactivity and epithelial cell proliferation as assessed by Ki-67 expression in their paper of the previous year (see above). They also wished to determine the presence of p53 gene mutations by screening, using the technique of combined polymerase chain reaction and single-stranded conformation polymorphism (PCR-SSCP) analysis for exons 5–10, followed by direct sequencing in two immunopositive cases using fresh frozen sections of one sporadic and one syndrome-related specimen. Their methodology and evaluation of sections for the first part of their study was the same as were used for their previously described PCNA and Ki-67 investigations (Li *et al*., 1994, 1995).

Of the three antibodies tested, BP53-12 gave the most intense and consistent nuclear staining. Using this antibody, p53-positive epithelial cells were detected in all three odontogenic cysts although staining intensity, numbers of positive cells and their distribution varied between cyst types. Subjectively, the OKCs invariably contained the greatest number and most densely stained positive cells, but even in the OKC the staining was variable and weak in comparison with squamous cell carcinomas. Quantitatively, the counts were significantly higher in sporadic OKC linings (25.5±11.0 cells/mm basement membrane) compared with the dentigerous cysts (9.3±4.9; $P < 0.01$), and radicular cysts (6.7±2.6; $P < 0.01$). The distribution of the positive cells in the OKC was predominantly suprabasal whereas the dentigerous and radicular cysts showed a significantly higher basal cell distribution ($P < 0.005$ for both). There were no significant differences in BP53-12 reactivity between the OKC subtypes ($P > 0.1$). Excluding data for the NBCCS cases, there was a significant correlation between the p53 and Ki-67 labelling ($P < 0.01$).

Their PCR-SSCP analysis for exons 5–10 of the p53 gene showed no abnormality in banding patterns; and DNA sequencing analysis of the two fresh frozen specimens revealed no mutations within exons 5–9 which covered the 'hot spots' of p53 mutations in various human tumours, including oral SCC. They concluded that immunocytochemical overexpression of p53 by OKC compared with the other odontogenic cysts was not the result of p53 gene mutation. Rather, they thought, the over-production and or stabilisation of normal p53 product appeared to be related to cell proliferation. The exception, they pointed out, was in the syndrome-related OKCs where heightened proliferative activity was probably the result of factors associated with the NBCCS gene locus on chromosome 9q22.3-q31. The most likely location of the gene had been to be between DNA markers D9S12 and D9S53 (Farndon *et al*., 1992; Li *et al*., 1996).

Calretinin has been shown to be expressed in a high proportion of solid, unicystic and multicystic ameloblastomas (Altini *et al*., 2000; Coleman *et al*., 2001). It is a 29 kDa calcium-binding protein which is expressed in the central and peripheral nervous systems as well as in many other normal and pathological human tissues. Piatelli *et al*. (2003) have investigated its expression in 70 odontogenic cysts. All radicular, dentigerous and OOCs were negative, but in eight of 12 parakeratinised OKCs there was a positive reaction to calretinin in the parabasal to intermediate layers of the epithelial linings. The authors commented that this distribution in the OKCs was similar to that of other markers such as PCNA and p53, and that this could point to an abnormal control of the cell cycle.

p63

Flores *et al*. (2000) wrote that 'although the p53 family members p63 and p73 are structurally related to p53, they have not been directly linked to tumor suppression, although they have been implicated in apoptosis'. Their experiments showed that the combined loss of p63 and p73 resulted in the failure of cells containing functional p53 to undergo apoptosis in response to DNA damage.

Lo Muzio *et al*. (2005) studied the expression of p63 in OKCs, orthokeratinised OKCs, dentigerous (follicular) and radicular cysts, one glandular odontogenic cyst, and four calcifying odontogenic cysts. Their experiments showed that OKCs displayed a more intense and diffuse p63 labelling other than in the superficial layers. In the orthokeratinised cysts, however, the staining was mainly in the basal and parabasal layers. Statistical analysis of their semi-quantitative data showed significantly higher p63 positivity in OKCs compared with the

orthokeratinised, radicular (both at P <0.001) and dentigerous cysts (P <0.01).

This group concluded that the more intense and diffuse expression of p63 in parakeratinised OKCs could help to explain the differences in the clinical and pathological behaviour of the OKCs, pointing to an abnormal control of the cell cycle leading to an intrinsic growth potential.

IPO-38 antigen

Thosaporn *et al.* (2004) used IPO-38 antigen to measure the respective proliferation patterns of the OKC, OOC, dentigerous cyst and ameloblastoma. They described IPO-38 antigen as 'an antigen of 14–16 kD whose expression is constant through most stages of the cell cycle except during mitosis where a 400-fold increase in concentration has been observed. [It] is expressed at this high concentration earlier than Ki-67 antigen at the beginning of the cell cycle.' IPO-38 antigen is expressed in a range of malignant tumours. The dentigerous cyst was in effect a control, given that it is known not to be a cyst with potential to recurrences.

The staining of IPO-38 showed variable patterns in the four lesions. The mean labelling indices of IOP-38-positive epithelial cells, per 100 cells, were 76.1±14.6 in the ameloblastoma (n=10); in the OKC (n=10) 75.8± 18.7; in the OOC (n=7) 32.9±21.1; and in the dentigerous cyst (n=8) 5.5±6.5. Mann–Whitney analysis showed no significant difference in the ameloblastoma and OKC labelling indices (P=0.910). However, the indices were significantly higher in the OKC than in the OOC (P= 0.002) and the dentigerous cyst (P=0.000). The count in the OOC was significantly higher in the OOC than the dentigerous cysts (P=0.011).

The authors concluded that their findings supported previous studies showing that the proliferation indices were useful in predicting the different biological behaviour of the odontogenic lesions, and moreover that the OKC should be regarded as a benign tumour rather than an odontogenic cyst. It also supported the growing evidence that the OKC and the OOC were different biological entities, with the latter having far less proliferative potential.

Expression of bcl-2 and bcl-1 (cyclin D1) oncoproteins, apoptosis

A further approach to this problem was an investigation not only of PCNA and p53 expression in sporadic and syndrome-related OKCs, but also the expression of bcl-2 and bcl-1 (cyclin D1) oncoproteins (Lo Muzio *et al.*, 1999). These authors wished to determine whether the aggressive behaviour of NBCCS-associated OKCs, when compared with the sporadic variety, reflected differences in cellular proliferation rates and/or in the expression of oncoproteins and tumour suppressor genes. They also discussed the work that had been carried out on the *PTCH* gene in this regard (see p. 54).

The bcl-2 gene, located at chromosome 18q21, is characterised by its ability to stop apoptosis (programmed cell death) without promoting cell proliferation. The bcl-2 protein is expressed physiologically in the basal layers of the nasopharynx and skin. Its over-expression has been reported in most human low-grade tumours and this inhibition of apoptosis has been regarded as being one of the most common pathways of tumorigenesis (Lo Muzio *et al.*, 1999). Other studies had shown that cyclin D1 (bcl-1), localised on chromosome 11q13 and expressed in the G1 phase of the cell cycle, was amplified, re-arranged or over-expressed in a wide variety of tumours including head and neck cancers (Lo Muzio *et al.*, 1999).

Unlike the findings of other groups shown above, all of which recorded some degree of positivity in sporadic cysts, they found p53 protein expression (antibody Dako-p53, DO-7) significantly associated with syndrome-related OKCs (n=16) and 'never' in sporadic OKCs (n= 16) (P <0.05). Nevertheless, using the same method of evaluation as previous workers (Li *et al.*, 1995, 1996), results were not uniform in the syndrome group. Positivity had been measured in four categories: 1 being zero; 2, 10–20% positive cells; 3, 20–50% positive cells; or 4, >50% positive cells. Fifteen of the 16 syndrome cases were positive to some degree. The over-expression of p53 in their sample of syndrome cysts, when considered in association with the greater PCNA activity in this group (see below), indicated a valid background for the existence of a more aggressive phenotype of the OKC that is found in the syndrome (Lo Muzio *et al.*, 1999).

The bcl-2 protein (antibody Dako-bcl-2, 124) was assessed as either positive or negative and there was no significant difference between the two groups (P >0.05). The positively stained epithelial cells were always located basally (Lo Muzio *et al.*, 1999).

PCNA-positivity (antibody PC10) was recorded as 1 (positive nuclei in basal or parabasal cells) or 2 (positive nuclei in intermediate/superficial layers or full thickness). All OKCs showed some degree of positivity, but the major part of the syndrome cysts exhibited appreciably higher levels of staining, frequently involving the full thickness of the epithelium, than the sporadic sample. This supported the view that the more aggressive behaviour of the syndrome cysts may result from the higher proliferation rate in their epithelial linings (Lo Muzio *et al.*, 1999).

Activity of bcl-1 (cyclin D1) (antibody cyclin D1, 5D4) was recorded as 0, no staining; 1, 10–20% with nuclear staining; and 2, >20% positive cells. There were significant differences between sporadic and syndrome-related OKCs (P <0.05) in that there was over-expression of cyclin D1 to varying degrees in the syndrome group while all the sporadic cysts were negative. Immunocytochemical techniques are reported to detect only cells over-expressing

cyclin D1, and not in normal proliferating cells. The positivity of bcl-1 in all the syndrome OKCs suggested to the authors that the expression of this oncogene had been altered in a step of cellular neoplastic progression that preceded that of the p53 gene. The bcl-1 negativity in all the sporadic OKCs in their sample constituted, they believed, further evidence that the syndrome OKCs exhibited a more aggressive cellular phenotype consistent with a progressing neoplastic lesion (Lo Muzio *et al*., 1999).

Kimi *et al*. (2001) asked similar questions in examining the immunohistochemical expressions of cell-cycle- and apoptosis-related factors to investigate the possible role of these factors in the OKC.

Caspase-3, a member of the IL-1b converting enzyme (ICE) or cell death effector-3 (CDE-3) family, is involved in the induction of apoptosis. Positive staining for caspase-3 was detected in the cytoplasm and nuclei of basal to suprabasal or superficial cells, the lining epithelium of all groups of OKCs, and again with no significant difference between these tissues.

Anti-ssDNA antibody reacted with nuclei in the superficial cells of the OKC linings.

The mean ssDNA-LI in NBCCS-associated OKCs was significantly higher than that in primary OKCs ($P=0.001$) or recurrent OKCs ($P=0.01$). Expression of cyclin D1 and p16 protein was detected in the basal and parabasal cells in the lining epithelium of OKCs and was found more frequently in NBCCS-associated OKCs than in primary or recurrent OKCs. These results suggested to the authors that both cyclin D1 and p16 might work as regulators, mainly in basal and parabasal cells of OKC lining epithelium (Kimi *et al.,* 2001).

Positivity for p21 protein was detected in basal to superficial cells, whereas that for p27 protein was located in parabasal to superficial cells in the OKC lining epithelium. DNA topoisomerase IIα reacted with nuclei in basal and parabasal cells of the lining epithelium of OKCs, and positive cells were observed in BCNS-associated OKCs significantly more frequently than in primary or recurrent OKCs.

Single-stranded (ss) DNA-positive nuclei were detected in the superficial cells of the OKC linings. Apoptosis involves a breakdown of the supercoiling organisation and the formation of individual superbreaks. This ssDNA formation in the nucleosomal linker region is thought to constitute a critical early step in apoptosis. Consequently, the antibody against ssDNA is a sensitive marker for the detection of apoptotic cells, especially those in early apoptosis. DNA-positive cells were observed in NBCCS-associated OKCs significantly more frequently than in primary or recurrent OKCs (Kimi *et al*., 2001).

Fas ligand (FasL) is a molecule that binds to a cell-surface receptor named Fas (also called CD95), and signals the cell to begin the apoptosis programme. Expression of Fas was detected in the cell membranes and cytoplasm of suprabasal to superficial cells in both control gingival and lining epithelium of OKCs, and Fas was more broadly distributed in BCNS-associated OKCs than in primary or recurrent OKCs. These results suggested that the expression of apoptosis-related factors in BCNS-associated OKCs differed from that in solitary OKCs. As these Fas and Fas-L distribution patterns were similar to those of normal stratified squamous epithelium, it suggested that Fas and Fas-L were similarly involved in apoptosis in lining epithelium of OKCs and stratified squamous epithelium.

These results suggest that BCNS-associated OKCs might be an entity distinguishable from solitary OKCs. There was no evidence of a distinct difference between primary and recurrent OKCs (Kimi *et al*., 2001).

Kichi *et al*. (2005) investigated cell proliferation, cell death and expression of apoptosis-related proteins to elucidate why OKCs form cysts but not tumour masses, despite their aggressive proliferative activity. They used the TUNEL method (Terminal deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling) for *in situ* detection of apoptotic cells. The method is based on the addition of labelled UTP to the 3′ ends of fragmented DNA by TdT. They showed that TUNEL-positive cells were detected exclusively in the surface layer of the OKC, as well as in a control of dentigerous cyst lining. In OKCs, however, about 25% of the lining cells in the surface layer were TUNEL-positive, indicating that marked levels of apoptosis occurred in these cysts. Although they showed that apoptosis occurred also in dentigerous cysts, the TUNEL-positive ratio of the latter was about one-fifth that of the OKC.

Their results with bcl-2 confirmed the findings of Lo Muzio *et al*. (1999) that this apoptotic protein was almost exclusively found in the basal cell layer of the OKCs. As the TUNEL-positive cells were predominantly in the surface layers of the OKCs, they concluded that bcl-2 inhibited apoptosis to facilitate cellular proliferation in the basal layer, whereas apoptosis maintained the homoeostasis of the thickness of the lining epithelium and allowed the synthesis of keratin on the surface. These findings, they suggested, indicated that although active cell proliferation occurred in the linings of the OKC, as evidenced by the p53, PCNA and Ki-67 positivity demonstrated in numbers of studies, this proliferation was regulated by the apoptotic activity, so that these lesions manifest as cysts and not as tumour masses (Kichi *et al*., 2005).

Kolář *et al*. (2006) contrasted the expression of various markers between NBCCS and sporadic OKCs and also between both groups of OKC and dentigerous, radicular and all odontogenic cysts, respectively. They found that NBCCS cysts were characterised by higher expressions of Bcl-2, $p27^{Kip1}$ and c-erbB-2 (an oncoprotein) compared with sporadic OKCs. They also observed lower

proliferative activity in the basal cells of the syndrome cysts, as measured by Ki-67, and a lower inflammatory response. Odontogenic cysts, other than the OKCs, differed in a wide spectrum of apoptosis and other cell cycle-related protein expressions. They pointed out that their results agreed with those of Lo Muzio *et al.* (1999) in some respects, but not in others. While the Lo Muzio group had found no significant difference for PCNA and Bcl-2, and a higher expression of p53 and cyclin D1 in the syndrome-related cysts, Kolář *et al.* found no significant difference in p53 expression in the two groups, and significantly higher levels of Bcl-2 positivity in the NBCCS cysts. They suggested that these results may have been attributable to the higher sensitivity of their detection system in the case of p52 and by the use of a more specific antibody against Bcl-2. In addition, they claim to have described a new finding of significantly higher expression of endogenous inhibitor of cyclin-dependent kinases $p27^{Kip1}$ and oncogene c-erbB-2 in the basal cells of NBCCS OKCs as well as lower expression of proliferation antigen Ki-67.

The NBCCS gene and the OKC

On the basis that the NBCCS gene mapped to chromosome 9q22 and probably functioned as a tumour suppressor by deletion of this region in many neoplasms related to the syndrome, an analysis of six OKCs from four NBCCS patients and 14 sporadic cysts for seven polymorphisms spanning chromosome 9, provided the first molecular evidence of a two-hit mechanism for the pathogenesis of these cysts (Levanat *et al.*, 1996). Five of the six syndrome cysts and four of the 14 sporadic group arose with allelic loss, at two or more loci, of 9q22. That is, these cyst linings had lost the normal copy of the NBCCS region, while they retained the mutant copy. Three samples that showed allelic loss were from two siblings. In conjunction with analysis of their affected mother, it was found that each cyst retained the mutant allele and lost the allele from the unaffected parent. Two cysts, from one syndrome patient, that occurred on opposite sides of the mandible, had the same pattern of allelic loss, leading the authors to suggest that this genetic mutation occurred at a very early stage of embryogenesis and created a large field of cells with loss of heterozygosity (LOH). As all adjacent oral tissues (surrounding connective tissue, bone, overlying mucosa) studied at the same time retained heterozygosity, they were confident that there was a clear relationship between the observed molecular change and the developmental defect (Levanat *et al.*, 1996).

The difference in the frequency of allelic loss between hereditary and sporadic cysts was statistically significant ($P < 0.05$; two-tailed Fisher's exact test). With regard to the significantly less common loss of heterozygosity found in the sporadic cysts, the authors suggested that those not showing this alteration may have undergone point mutation of both copies of the syndrome gene but that it was more likely that they arose by a different mechanism. Family studies showed that the normal homologue of the syndrome gene was lost and the mutant homologue retained in the hereditary cysts. The authors concluded that their results provided strong support for the view that inactivation of the NBCCS gene was an important step in the pathogenesis of the OKC (Levanat *et al.*, 1996).

There was further support for the view that the syndrome-related OKCs could be explained by a two-hit mechanism (Lo Muzio *et al.*, 1999). In an early progenitor cell of dental lamina, it was suggested, there could be a homozygous inactivation of the *PTCH* gene (see p. 54) leading to either abnormal migration, abnormal differentiation or failure to undergo programmed cell death. It was postulated that the *PTCH* gene inactivation in syndrome OKCs and over-expression of bcl-1 were not incidental findings but causative in their pathogenesis. With *PTCH* gene inactivation there was loss of control of proliferative activity in the lining of a sporadic OKC and this could act synergistically with the over-expression of cyclin D found in syndrome OKCs. This over-expression in the NBCCS, as in some human neoplasms, could be related to dysregulation of cellular proliferation and to carcinogenesis. The LOH considered together with the aggressive clinical behaviour and an over-expression of bcl-1 and p53, supported the hypothesis that the OKCs, at least those associated with the NBCCS, should be regarded as benign cystic neoplasms. Cyclin D1 and p53 tumour suppressor gene could, they believed, be two among the environmental and genetic modifying factors implicated in the wide spectrum and degree of clinical manifestations in NBCCS patients (Lo Muzio *et al.*, 1999).

Evidence of a genetic factor in the etiology of sporadic OKCs

At about the same time as the 1996 Levanat paper, it was argued that as the NBCCS gene had been mapped to chromosome 9q22.3-q31 and that as LOH for these DNA markers had been demonstrated in sporadic BCCs, the NBCCS gene might also be a significant factor in sporadic OKCs (Lench *et al.*, 1996). In what they described as a pilot study, they examined six sporadic OKCs. DNA isolated from their epithelium was analysed for LOH for a series of chromosome 9q22.3-q31 polymorphic markers. LOH for these chromosome markers was found in three of them.

The smallest region of overlap defined by the observed deletion breakpoints (between D9S287 and D9S180 centromeric and D9S176 and D9S127 telomeric) contained the region that had been defined in LOH studies in BCC as well as the NBCCS locus. This allelotype loss, they believed, provided evidence for involvement of a tumour suppressor gene at a particular chromosomal region.

Their results, they believed, strengthened the hypothesis that the NBCCS gene product functions as a tumour suppressor gene and they thought it possible that the OKC represented one of the first clinical manifestations of homozygous inactivation of the NBCCS gene. They pointed out that LOH in this region of chromosome 9q had been demonstrated in a range of epithelial neoplasms including BCC, squamous cell carcinoma and transitional cell carcinoma. Their results, they believed, strengthened the hypothesis that the OKC should be regarded as a benign neoplasm. They suggested, based on Knudson's theory of homozygous tumour suppressor gene inactivation (Knudson, 1971), that where multiple cysts are present in the patients with the NBCCS, a predisposing mutation is already present in the germ-line and only a single mutational event is required in the somatic cell to cause homozygous inactivation and neoplastic progression, whereas in sporadic cysts two independent mutational events are required in the somatic cell (Lench *et al*., 1976).

Pursuing this line of research, DNA from the OKCs of 16 NBCCS patients was screened by SSCP-PCR[3] and 10 exonic PCR products showing altered electrophoretic mobilities were detected and analysed further by DNA sequence analysis (Lench *et al*., 1997). Mutations were identified in four of these 10 following direct DNA sequencing of PCR-amplified exons. All 23 exons from the remaining 12 samples were amplified and sequenced and one additional mutation was detected by this method. They were unable to detect LOH or the presence of a second inactivating mutation in the OKC tissue examined. They believed that these mutations existed and that a limitation of the mutation screening procedure and/or the presence of contaminating stromal cells was responsible for masking mutant PCR products. The contaminating cells might have caused selective amplification of the normal allele of the *PTCH* gene[4] from DNA isolated from OKC tissue (Bale *et al*., 1995; Lench *et al*., 1997).

They considered these five novel germ-line mutations from NBCCS patients to be consistent with the role of *PTCH* as a tumour suppressor gene. They speculated on the similarities that *PTCH* shares with the APC[5] protein which is mutated in familial polyposis coli and sporadic adenomas. Both were cytoplasmic proteins involved in complex signalling cascades that might function as 'gatekeeper genes', whereby inactivation of a gatekeeper gene is required for passing the genetic threshold of the neoplastic process in a tissue. They suggested that mutations in *PTCH* and *APC* could lead to abnormal cell–cell adhesion resulting in loss of signalling between neighbouring cells and the formation of abnormally proliferating cells that are targets for further multiple genetic hits (Lench *et al*., 1997).

Further work on *PTCH* gene mutations was reported in a study of three sporadic and three syndrome-related OKCs using SSCP and direct DNA sequencing on each of the 23 exons of the PCR-amplified *PTCH* gene (Barretto *et al*., 2000). All six cysts were screened and all exons showing abnormal migration patterns were subjected to direct sequencing. Mutations were found in three cysts, two associated with the syndrome and one in a sporadic cyst. The positive sporadic OKC showed a deletion of five base pairs in exon 3 by direct sequencing, and this mutation was absent from the DNA in the patient's peripheral blood. The mutations found in one NBCCS case and in one sporadic case resulted in truncated PTCH protein and the mutation in the other syndrome case caused a (G → A) transversion. Using direct sequencing of the mutant and wild-type alleles in the cyst, they were not able to detect a second inactivating mutation in any of the syndrome-related cysts, and speculated that the mutations may exist but that they might have been masked by technical procedures.

They also invoked the 'two-hits' hypothesis in supporting the view that the syndrome-related BCCs and OKCs probably arose from precursor cells that contained a hereditary 'first hit' and the allelic loss represented loss of the normal allele. Sporadic BCCs and OKCs, they thought, might arise from susceptible cells in which two somatic 'hits' have occurred, one of which manifests as allelic loss. They also speculated that the *PTCH* may function as a 'gatekeeper' gene as described above. In terms of this model, the cells of the OKC, after losing the *PTCH* function, become targets of other genetic alterations. They concluded that their study provided further evidence for the role of *PTCH* in the formation of sporadic as well as syndrome-related OKCs. Furthermore, they indicated that because the loss of a tumour suppressor gene is by definition a feature of 'tumorigenic' tissue, this strengthened the hypothesis that the OKC should be regarded as a benign cystic neoplasm (Barreto *et al*., 2000).

Further evidence of a genetic origin for sporadic OKCs has come from a paper by Agaram *et al*. (2004). Their study sample comprised 10 sporadic OKCs, only one of which was a recurrent specimen. None of the patients was known to have the NBCCS. DNA was obtained and

[3] Single strand conformational polymorphism–polymerase chain reaction.

[4] As defined by Barreto *et al*., (2000): 'Recently, the gene for NBCCS was cloned and shown to be the human homologue of the *Drosophila* segment polarity gene *Patched (PTCH)*, a tumor suppressor gene (located at 9q22.3). The *PTCH* gene encodes a transmembrane protein that acts in opposition to the *Hedgehog* signalling protein, controlling cell fates, patterning, and growth in numerous tissues, including tooth.' For a detailed account of *PTCH* and *Hedgehog*, see Cohen (1999).

[5] Adenomatosis polyposis coli gene.

amplified in all cases. The average number of informative genetic loci per case was seven. Loss of heterozygosity in the gene loci studied was not seen in the patients' normal tissues, but was seen in at least one tumour suppressor gene locus in the epithelial linings of seven of the 10 specimens. The frequency of allelic loss (FAL) averaged 27% among all the cases, with a range of 0–80%.

The tumour suppressor genes most commonly found to have allelic losses were *p16*, *p53*, *PTCH* and *MCC*. These showed FALs of 75, 66, 60 and 60%, respectively. Of particular note was the high FAL at the 9q22 locus, which contains the *PTCH* gene.

The presence of daughter cysts correlated significantly with the FAL. All of five cases with daughter cysts demonstrated at least one mutation, while only two of five without daughter cysts had mutations ($P=0.02\%$). However, budding did not correlate with mutations, but were more frequent in the older patients ($P=0.02$) and the larger lesions ($P=0.03$). The FAL did correlate with the presence of inflammation (35% with inflammation and 7% without inflammation; $P=0.05$). The one recurrent OKC did not show mutations.

The authors concluded that their study showed significant loss of heterozygosity of tumour suppressor genes in sporadic OKCs. They believed that the presence of allelic imbalance of tumour suppressor genes in the majority of lesions studied, and the high FAL at the 9q22 locus that contains the *PTCH* gene, was strong supportive evidence that sporadic OKCs, like those associated with the NBCCS, were neoplastic. The higher FAL associated with daughter cysts suggested that the presence of these daughter cysts in histological sections might be an indicator of extension or local invasion of lesional tissue.

The purpose of a later paper by Barretto *et al.* (2002) was to examine expression of *PTCH* in a range of odontogenic cysts and tumours that could also arise with mutations in *PTCH*: 15 radicular cysts, 29 OKCs, one glandular odontogenic cyst, six dentigerous cysts, three odontogenic myxomas, six calcifying odontogenic cysts, and eight ameloblastomas. Sequencing analysis of the *PTCH* gene had previously been performed on seven of the 29 OKCs included in their present study (Barreto *et al.*, 2000). The single glandular odontogenic cyst included in this study did not present a *PTCH* gene mutation (Barreto *et al.*, 2001). Immunohistochemical methods were used to assess *PTCH* expression at the protein level.

To validate their technique, they examined PTCH protein in BCC. Although the tumour cells over-expressed *PTCH* mRNA, they pointed out that PTCH protein would not be expected to be present in BCC. The reason was that the vast majority of these tumours had truncating *PTCH* mutations 5′ to the region encoding the peptide against which their antibody was made. As expected, there was virtually complete lack of immunostaining of PTCH in the peripheral and central cells of tumour sheets. Immunostaining of the odontogenic lesions revealed the presence of PTCH protein in virtually all cysts and tumours. All tissue examined showed positive intracytoplasmic staining of PTCH of variable intensity. PTCH staining was found in the intermediate and superficial cells of the epithelium in all OKCs. In addition, two OKCs showed staining of the basal cell layer with loss of the characteristic OKC features in the presence of a dense inflammatory infiltrate.

Positive staining in the intermediate and superficial layers of the cystic epithelium was detected in 14 of 15 radicular cysts, with the basal layer also staining in two of them. As pointed out later, the dentigerous cyst can also be caused by the functional loss of PTCH (Levanat *et al.*, 2000) and further work on the subject by the same group is also dealt with in Chapter 4 (Pavelić *et al.*, 2001). In the present study, Barreto *et al.* (2002) demonstrated positive staining in the epithelium of the dentigerous cyst. Citing Hardcastle *et al.* (1998), they noted that the positive labeling for PTCH in epithelial lesions (radicular cyst, glandular odontogenic cyst, calcifying epithelial odontogenic cyst, and ameloblastoma) and in a mesenchymal tumor (myxoma) was in agreement with both cell types expressing this protein during early odontogenesis. The staining in all lesions was more intense and evident than in the epithelium of normal oral mucosa, consistent with a model whereby the Hedgehog pathway was activated in these lesions. They believed that it was unlikely that *PTCH* itself was mutated in all of these lesions, because most inactivating *PTCH* mutations would be expected to result in low levels of PTCH protein (as in BCC). They observed that more studies were needed to determine how this pathway was switched on.

Referring to the papers by Lench *et al.* (1996) and Levanat *et al.* (1996), who had previously reported loss of heterozygosity in *PTCH* in seven sporadic OKCs, Barreto *et al.* (2002) pointed out that two of the OKCs reported in their study had *PTCH* mutations predicted to result in a truncated protein. While they had expected no immunostaining of the epithelial cells of these lesions, surprisingly an immunoreactivity was detected, indicating that the epithelial cells may be heterozygous for the *PTCH* mutation. These results therefore suggested that the OKC may arise with haploinsufficiency of *PTCH*. They pointed out that this observation was consistent with the reported demonstration of the retention of one normal copy of PTCH in a mouse medulloblastoma with a heterozygous *PTCH* mutation as reported by Zurawel *et al.* (2000).

The above evidence suggesting that the OKC may arise through haplo-insufficiency of *PTCH*, which is the loss of of only one allele, was taken up in a brief letter to the editor by members of the same group (Gomez and De Marco, 2005). They referred to further recent work that

considered haplo-insufficiency to be an important mechanism in the development of some human neoplasms (Santarosa and Ashworth, 2004). These latter authors had pointed out that classic tumour suppressor genes had been thought to require mutation or loss of both alleles to facilitate tumour progression, but that it had become clear over the last few years that for some genes, haploinsufficiency, which is loss of only one allele, may contribute to carcinogenesis. These effects, they wrote, could either be directly attributable to the reduction in gene dosage or might act in concert with other oncogenic or haplo-insufficient events.

To clarify the role of Sonic hedgehog (Shh) signalling in OKCs, the expression of Shh, PTCH, SMO, and GLI-1 and mutations of *PTCH* were examined in 18 sporadic, four syndrome-associated OKCs and seven control gingivae (Ohki *et al*., 2004). The role of the *Patched* (*PTCH*) gene in these lesions has been discussed earlier. Its product has a role in the Sonic hedgehog (Shh) signalling pathway involving Smoothened (SMO) and GLI-1. The authors pointed out that SMO also has a role in reception and transduction of the Shh signal and was responsible for triggering intercellular signalling and the subsequent activation of target genes such as GLI-1. In the absence of Shh, PTCH interacts at the membrane with SMO, rendering it inactive. However, when SHH binds to PTCH, the inhibition of SMO signalling was released and downstream genes transcriptionally up-regulated. GLI-1 is a transcription factor, the authors wrote, that is thought to form a cytoplasmic complex and mediate Shh signalling from cytoplasm to nucleus.

Shh, *PTCH*, SMO, and GLI-1 were detected in all OKC and gingiva samples by reverse transcriptase polymerase chain reaction (RT-PCR). Immunoreactivity for Shh and GLI-1 was markedly higher in epithelial components than in subepithelial cells, while immunoreactivity for *PTCH* and SMO was similar in epithelial components and subepithelial cells in OKCs. The positive rate of *PTCH* and SMO expression in subepithelial cells of OKCs was significantly higher than that in the gingivae. The positive rate of GLI-1 expression in the subepithelial cells of NBCCS-associated OKCs was significantly higher than that in sporadic OKCs. These results suggested to the authors that the Shh signalling might be involved in the pathophysiologic nature of OKCs. While mutations of the *PTCH* gene could not be detected in four NBCCS-associated OKCs by direct DNA sequencing, three of five sporadic and four of four recurrent OKCs had several mutations of this gene. They concluded that *PTCH* mutations were probably related not only to NBCCS-associated OKCs but also to sporadic OKCs, hence supporting earlier work that had reached the same conclusions (Ohki *et al*., 2004).

It is well known that dentigerous cysts, which develop by accumulation of fluid between the reduced enamel epithelium and the crowns of unerupted teeth, occur only in some individuals even though unerupted and usually impacted teeth are a much more common phenomenon. Similarly, radicular cysts occur very much less frequently than do periapical infections associated with non-vital pulps. So some individuals appear to be prone to the development of certain cysts while others are not, which suggests that a genetic factor is possibly involved. Studies of this kind need to be pursued to identify possible genetic factors that might be involved in the genesis of the dentigerous, radicular and other jaw cysts.

Numbers of papers have cited in support of a neoplastic theory for the OKC the fact that the epithelium of the cyst has a particular propensity to dysplasia or malignant change. We do not believe that this is true. While there are well-documented cases of this, they are very rare in relation to the large numbers seen in many laboratories without such changes. The evidence from these molecular studies and the clinical behaviour of the cysts are much more cogent support for the neoplasia theory, at the very least for those associated with the NBCCS.

A general review of molecular approaches to the diagnosis of sporadic and NBCCS-associated OKCs has been provided by Todd and August (2003).

Conclusions

PCNA, Ki-67, p53 protein and IPO-38 antigen have in common that they are all expressed in actively proliferating cells, particularly in neoplasms. The evidence provided by laboratory studies on the expression of these substances is that, in general, they are expressed more strongly in OKCs than in other odontogenic cysts and more particularly so in the OKCs associated with the NBCCS. Furthermore, the evidence of mutation of the NBCCS gene *PTCH* in OKCs of patients with the syndrome, and at least some sporadic OKCs, has made an important contribution to the understanding of these cysts, and has provided supportive evidence that the OKC is a benign neoplasm.

Treatment

Earlier in this chapter, attention was drawn to the high rates of recurrence of OKCs in an extensive series of reported cases (see p. 13). What is clear is that each case must be assessed with great care before a treament modality is chosen and undertaken. In the 2003 monograph on the odontogenic keratocyst, one of the series ‘Oral and Maxillofacial Surgery Clinics of North America’, no fewer than five chapters were devoted to the different treatment modalities that may be chosen. The chapter titles are:

1 Surgical management of the odontogenic keratocyst (Ghali and Connor, 2003)

2 The use of liquid nitrogen cryotherapy in the management of the odontogenic keratocyst (Schmidt, 2003)
3 Excision of the overlying, attached mucosa, in conjunction with cyst enucleation and treatment of the bony defect with Carnoy solution (Stoelinga, 2003b)
4 Decompression and marsupialisation as a treatment for the odontogenic keratocyst (Pogrel, 2003b)
5 Treatment options for the odontogenic keratocyst (Bell and Dierks, 2003)

It is not the intention in this book to include detailed descriptions of the different surgical techniques, as these are fully dealt with in texts and journals of oral and maxillofacial surgery, and covered admirably in the five chapters referred to above. Where appropriate, however, brief comments are made on the principles that drive the different treatment approaches.

Ghali and Connor (2003) have emphasised the need for thorough evaluation before deciding on the form of treatment. Various factors that should be considered include size and extent, location, presence of perforation or soft tissue involvement, age of individual and primary or recurrent nature of the lesion. Long-term follow-up should be part of the protocol because late recurrences are known to occur.

They have pointed out that conservative methods of treatment such as enucleation and marsupialisation have produced less than optimal results, but that this did not preclude the use of the latter procedure as an adjunct to the more conventional surgical options. Simple cyst enucleation without curettage was no longer advocated, as given the thin and friable linings of the OKC and the often difficult access, removal as a single piece was a difficult option.

Peripheral ostectomy was recommended as an adjunct approach to enucleation when resections could be avoided. This involves the use of rotary instruments to remove as much bone as seems necessary to ensure the elimination of all residual lining, but there still remains some uncertainty that the ablation has been entirely successful.

En bloc osseous resection may have to be considered for some cases. This may be a marginal resection that preseves continuity, or segmental resection that violates continuity and will require additional reconstruction (Ghali and Connor, 2003).

Schmidt and Pogrel (2001) and Schmidt (2003) evaluated the management of patients with OKC treated with a combination of enucleation and liquid nitrogen cryotherapy. In the first of these papers, 23 of 26 (88.5%) patients had no evidence of clinical or radiological recurrence over a range of 2–10 years. Schmidt (2003) has pointed out that this combination technique would not be the treatment of choice for all OKC patients, but that the data do suggest that liquid nitrogen does help to reduce the recurrence rate, especially for lesions that have recurred previously. Other indications are large complex mandibular lesions in which enucleation of the lining might be difficult and in which conventional management might involve structures such as the inferior alveolar nerve. This procedure, it is believed, is preferable to decompression.

Stoelinga (2003b) has proposed a treatment strategy based on the well-documented behavioural patterns of the OKC. He suggested that all unilocular cystic lesions in the mandible and maxilla should be enucleated except for those in the mandibular third molar region that tended to extend into the ascending ramus. He advised that when an OKC was diagnosed, a 'wait and see' policy, with strict follow-up, was necessary but he believed that 'a recurrence can easily be handled'. Large maxillary cysts, particularly those that originated in the posterior maxilla, he believed should be treated as OKCs. His protocol includes wide excision of the mucosa in the tuberosity area, and the cyst enucleated. 'Carnoy's solution may be used in the alveolar region but preferably not in the maxillary sinus to prevent necrosis of the sinus walls.' Unilocular lesions in the mandibular third molar region and extending into the ascending ramus should be treated with careful enucleation, including excision of the overlying mucosa, after which the defect should be treated with Carnoy's solution or liquid nitrogen. An incisional biopsy was recommended for multilobular or multilocular lesions in either jaw. If an OKC was diagnosed, cyst enucleation with excision of the overlying mucosa was advised, and electrocoagulation or Carnoy's solution may be used selectively in areas where the cyst was attached to the soft tissues.

Marsupialisation has generally not been accepted as a suitable surgical procedure for the treatment of OKCs because studies on their behaviour, histopathology and molecular biology lead one to believe that retention of part of the cyst lining means lesional tissue with potential for further growth and infiltration. Pogrel (2003b) treated 13 patients with OKCs, selected for inclusion because their medical histories made more aggressive surgery inadvisable; or they had large cysts of which conventional treatment would have meant the sacrifice of teeth or the inferior alveolar nerve; or a 'discontinuity defect' of the mandible; or problems with the maxillary antrum or nasal cavity. Standard marsupialisation procedures were carried out, with cavities kept open and cleaned at home by vigorous syringing. The patients were followed for periods ranging from 1.9 to 6.9 years. In this and in a follow-up paper (Pogrel and Jordan, 2004), the OKCs of all patients in the series completely resolved both clinically and radiographically. Histological and immunohistochemical examination of the retained cyst wall at the bases of the healed cavities showed normal epithelium only, with no signs of cystic remnants, daughter cysts or budding of the basal layer of the epithelium. Commercially available

cytokeratin-10 antibody staining failed to show a difference between normal mucosa and OKC lining. The bcl-2 protein expression was strictly limited to the basal layer of the initial biopsy of the OKC lining. After clinical healing, both the mucosa from from the base of the cystic cavity and the adjacent oral epithelium were bcl-2 negative.

It is difficult to explain this unusual and important finding. What has happened to the OKC epithelium with all its potential for active and infiltrative growth? Pogrel and Jordan (2004) explained it in this way:

'. . . bcl-2 is an antiapoptotic protein and was selected because it has been shown to be strongly and consistently expressed by all basal cells of OKCs but not in other odontogenic cysts (Piatelli *et al*., 1998). Studies have shown that bcl-2 is rarely expressed by some basal keratinocytes of normal epithelium. Hence, it was likely that bcl-2 could be used to differentiate keratocyst lining from normal epithelium. Although the exact nature and significance of this bcl-2 expression in the OKC remains in some doubt, it shows that after decompression only normal oral mucosa remains. The fate of the cystic epithelium remains unresolved. It may undergo metaplasia to normal mucosa, or it may undergo a creeping substitution by normal mucosa from the edges of the lesion, which may grow in and replace the cystic epithelium.'

Earlier, Marker *et al*. (1996) had set out to determine the course of healing, the frequency of recurrence and the changes in the epithelium of OKCs after decompression treatment. Their sample comprised 23 patients with OKCs, who had been divided into two groups, 12 and 11 patients, respectively. In one group, a polyethylene drain was inserted and a biopsy specimen was taken from the cyst wall. In the second group, a cystectomy was performed and the drain was removed approximately 1 year later. Biopsy material from both groups was examined. Reduction in cyst volume together with bone healing occurred in all cases, although there was recurrence in two patients. Decompression resulted in substantial histologic changes in the epithelium in 19 cases (83%). No evidence of OKC epithelium was detectable after decompression. The authors concluded that decompression resulted in new bone formation and thickening of the cyst wall; that this treatment modality conserved bone and anatomical structures and that the frequency of recurrence was low.

Ninomiya *et al*. (2002) had investigated the effects of marsupialisation on the retained epithelium of OKCs. The expression of IL-1α mRNA in OKCs was measured by *in situ* hybridisation before and after the procedure. The expression of IL-1α and Ki-67 was also measured immunohistochemically. The intensities for mRNA were correlated with the proliferating activities of the epithelial cells, and both the expression of IL-1α mRNA and the epithelial cell-proliferating activities were reduced proportionally by marsupialisation, strongly suggesting a close association between positive intracystic pressure, IL-1α expression and epithelial cell proliferation in OKCs. They concluded that marsupialisation may reduce the size of the OKC by inhibiting IL-1α expression and the epithelial cell proliferation.

Blanas *et al*. (2000) undertook an extensive review of all citations of English language articles in the *Index Medicus*, 1956–1966, followed by *Medline Database*, 1966–2000, which described either treatment or outcome for the OKC. Of 2290 'hits', 14 papers were selected that met the authors' strict inclusion criteria. They were able accurately to identify the treatment modalities and recurrences of 578 cysts. They recommended that ideally a biopsy should be performed to confirm the diagnosis before definitive treatment. From their data, they concluded that simple enucleation resulted in an unnecessarily high recurrence rate (28.7% of 387 cases). Adding Carnoy's solution to the cyst cavity for 3 minutes after enucleation results in a recurrence rate comparable to that of resection without necessarily aggressive surgery (1.6% of 60 cases). For a routine OKC in a person who is likely to return for follow-up treatment, Carnoy's solution appeared to be the least invasive procedure with the lowest recurrence rate. If the cyst was very large, decompression of the cyst followed by enucleation, they suggested, would also have a low recurrence rate. If a patient was unlikely to return for follow-up, these authors recommended resection.

A paper by Morgan *et al*. (2005) reported the follow-up over a range of periods of 40 OKC patients who had received different forms of treatment. There were nine recurrences and the greatest number (six of 11) of these had been treated by enucleation. Two had been treated by enucleation followed by Carnoy's solution and one of these recurred. There were two recurrences among 11 patients who had peripheral ostectomies, and there were no recurrences among 13 patients who had peripheral ostectomies combined with Carnoy's solution.

Zhao *et al*. (2004) have cautioned that while large OKCs may be marsupialised initially and then enucleated at a later stage in order to avoid pathological fracture of the mandible, they may still recur after this two-stage procedure.

Many other articles have been published in recent years on the treatment of OKCs, but for purposes of this chapter, the work referred to above is probably adequate to provide students and workers in the field with the information they need to direct further reading.

4
Dentigerous Cyst

A dentigerous cyst is one that encloses the crown of an unerupted tooth by expansion of its follicle, and is attached to its neck (Fig. 4.1a,b). It is important that this definition be applied strictly and that the diagnosis of dentigerous cyst is not made uncritically on radiographic evidence alone, otherwise keratocysts (OKCs) of the envelopmental variety (Main, 1970a), follicular OKCs (Altini and Cohen, 1982, 1987) and unilocular ameloblastomas involving adjacent unerupted teeth, are at risk of being misdiagnosed as dentigerous cysts. These latter presentations are considered later in this chapter.

Browne and Smith (1991) stressed that the term 'dentigerous cyst' is preferable to that of 'follicular cyst', as the latter implies a derivation from the tooth follicle which is a mesodermal structure. A further reason for not using the term follicular cyst is that this is most commonly used to refer to follicular cysts of the ovary, and also to hair follicle cysts. As Browne has pointed out, the literal meaning of dentigerous is 'tooth bearing', and this term is most appropriate for the lesion.

Clinical features

Frequency

Over a 46-year period, 1958–2004, 599 of 3498 jaw cysts recorded in the Department of Oral Pathology of the University of the Witwatersrand, Johannesburg (see Table 1.1) have been dentigerous cysts (17.1%). This translates to about 13 cases a year and as this material is drawn from numbers of sources, individual surgeons and departments are apparently dealing with far fewer than this number each year. In a study of the incidence of dentigerous cysts on the Witwatersrand (Shear and Singh, 1978), it was shown that the age-standardised incidence rates for dentigerous cysts, standardised against a world standard population, per million per year, were 1.18, 1.22, 9.92 and 7.26 for black men, black women, white men and white women, respectively (Table 4.1).

In an analysis of an extensive Canadian sample of 6847 odontogenic cysts carried out by Daley *et al.* (1994), dentigerous cysts accounted for 1662 (24%). An Israeli study of a series of 69 paediatric patients with cystic lesions of the jaws found that 31 (45%) were dentigerous cysts (Bodner, 2002); and in the series of 7121 odontogenic cysts documented by Jones *et al.* (2006), 1292 were dentigerous (18.1%).

Age

The age distribution of 343 patients in this series is shown in Fig. 4.2. The age-specific morbidity rates for black and white men and women on the Witwatersrand are shown in Table 4.2. Although dentigerous cysts occurred in the first decade more commonly than other jaw cysts, the frequency in that period was nevertheless considerably lower than in the subsequent three decades. This is because the mandibular third molar teeth and the maxillary permanent canines, which are the teeth most frequently involved in dentigerous cysts, are at an early stage of development (Fig. 4.3). The frequency increased sharply in the second decade and reached a peak in the third, after which there was a gradual decline.

The age distribution in the South African sample was similar to that of Mourshed's (1964c) US group and that of Roggan and Donath (1985) from Germany. In the Canadian sample of 1545 dentigerous cysts, the peak frequency also occurred in the third decade with a similar gradual decline (Daley and Wysocki, 1995). In a Mexican study of 108 dentigerous cysts, most cases occurred in the second and third decades, with a rather higher frequency in the first decade (16%) compared with our own 9% (Ledesma-Montes *et al.*, 2000). Similarly, a Japanese study of 259 dentigerous cysts showed that 60% were in patients under the age of 20 years (Nakamura *et al.*, 1995). In the sample of 1292 dentigerous cysts analysed in the Sheffield study, there were substantial numbers of cases in virtually all age groups, with a peak in the age group 41–50. In our age-standardised studies, the peak incidence for white women was found at a younger age than other groups (Table 4.2).

Figure 4.3 illustrates diagrammatically that in a series of 175 cases for which both age and involved tooth were

known, 17 cases occurred in the first decade. The mandibular first premolar was involved in six, the mandibular second premolar in four, the first permanent molar twice, and the maxillary permanent central, lateral, canine and premolars were each involved once. In the second decade, there was a substantially higher frequency than in the first (41 cases), most of the cysts involving the maxillary permanent canine (12), the mandibular third molar tooth (8) and the upper (5) and lower (8) second premolars. The third and fourth decades showed the peak involvement of the lower wisdom teeth (23, 22) and it was during the third decade that the upper wisdom tooth was involved for the first time. During the subsequent decades there was a gradual decline in frequency, with the mandibular wisdoms and maxillary permanent canines most often involved (Fig. 4.3).

Gender

The frequency of dentigerous cysts in the South African sample was significantly greater in men than women ($P = 0.001$). In a sample of 356 patients with this cyst, 227 (64%) were men and 129 (36%) women, a ratio of 1.8:1 (Table 4.3). These figures were similar to those of Mourshed's US sample and of Roggan and Donath (1985), although the series of both Browne and Killey *et al.* showed an even greater preponderance of men. In the Canadian sample of 1661 dentigerous cysts, 60% occurred in men and 40% in women (Daley and Wysocki, 1995). In the study by Jones *et al.* (2006), 722 of 1114 patients were males and 392 were females, a male:female ratio of 1.84:1. Our age-standardised incidence rates showed a male preponderance for white patients but not for black patients (Table 4.1).

Although there might be a temptation to assume that the less frequent occurrence in women is because they have a lower prevalence of unerupted teeth, this assumption was not borne out by data such as that collected by Mourshed (1964a) and Brown *et al.* (1982). In surveys of large series of radiographs, both groups found that there was no gender difference in the frequency of unerupted teeth. In the study of Brown *et al.* (1982), however, there was a difference in the frequency of impactions between black men and women ($P < 0.001$) although there was no significant difference between men and women either in whites or in the total sample. These data suggested that there was another factor, as yet not identified but possibly innate, that may influence the development of

Table 4.1 Age-standardised incidence rates for dentigerous cysts on the Witwatersrand area of South Africa, 1965–1974, standardised against standard European, World and African populations. (From Shear and Singh, 1978.)

	Per million per year		
	European	**World**	**African**
Black men	1.09	1.18	1.22
Black women	1.18	1.22	1.39
White men	9.93	9.92	10.83
White women	7.30	7.26	8.04

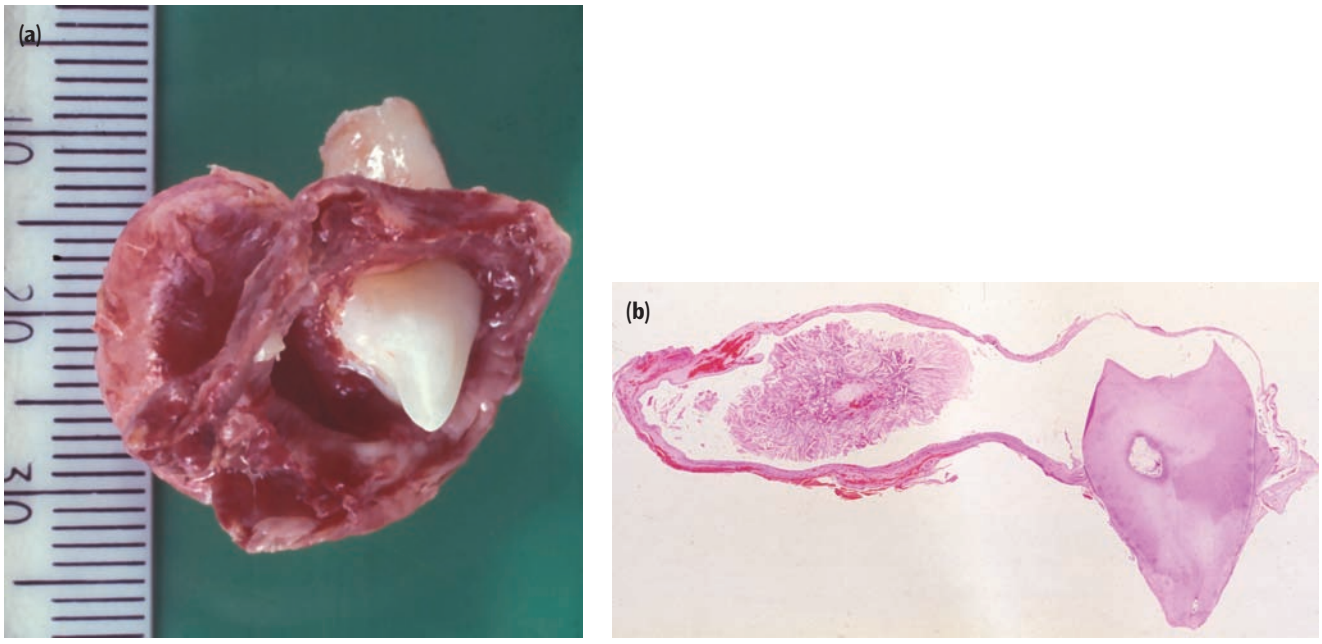


Fig. 4.1 (a) Gross specimen of a dentigerous cyst opened in the laboratory. The cyst encloses the crown of the tooth and is attached to its neck. (b) Macroscopic section of a dentigerous cyst showing attachment of its lining to the cervical margin of the tooth, enclosing its crown. (Courtesy of Professor J.J. Hille.)

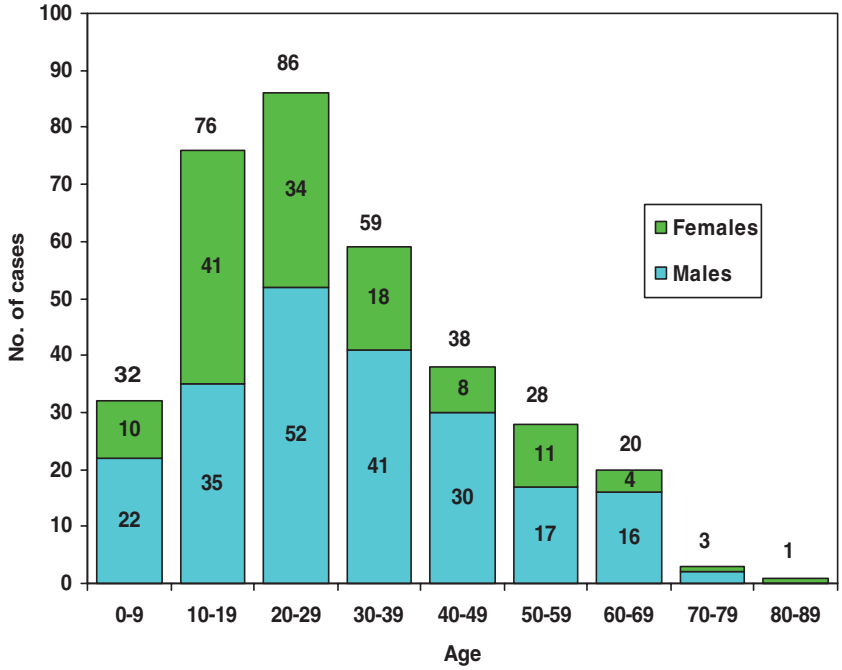


Fig. 4.2 Age distribution of 343 patients with dentigerous cysts.

Table 4.2 Average annual incidence rates for dentigerous cysts on the Witwatersrand, South Africa, 1965–1974.

	Average annual incidence per million by age group (years)							
	0–9	10–19	20–29	30–39	40–49	50–64	65–74	75+
Black men	0.64	1.94	2.62	0	0.85	1.27	0	0
Black women	0.69	1.47	1.57	1.90	2.71	0	0	0
White men	7.51	6.83	14.90	15.39	10.87	11.58	0	0
White women	1.95	12.04	9.41	10.46	7.29	6.46	0	8.90

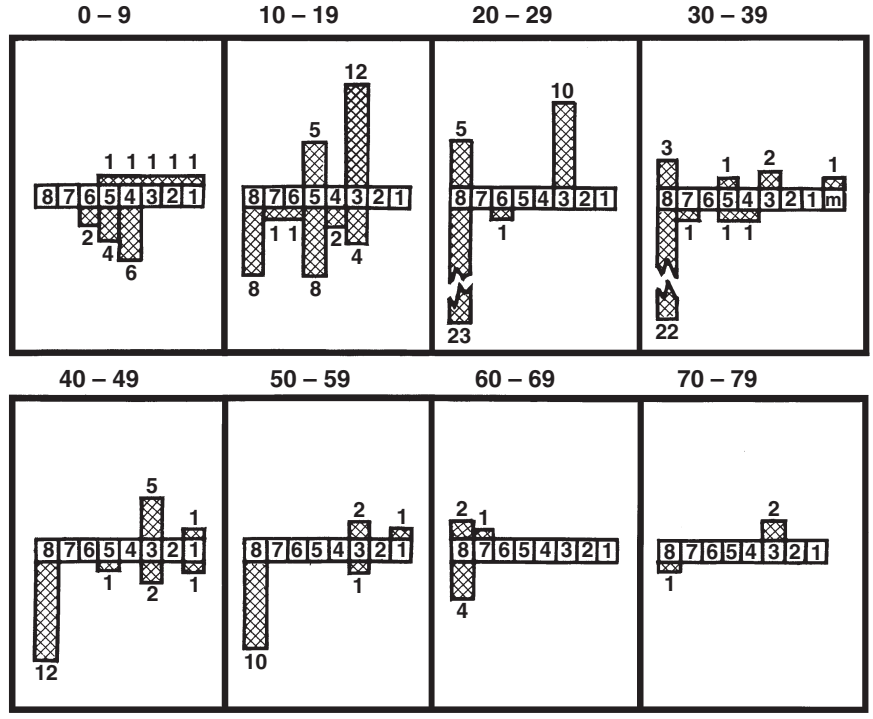


Fig. 4.3 Distribution of dentigerous cysts at different decades.

dentigerous cysts other than the mere physical fact of their origin in unerupted teeth. This possibility is discussed later in this chapter.

Race (Tables 4.1–4.3)

In the South African material, there was a higher frequency of dentigerous cysts in white than in black patients. Of 356 patients, 219 were white and 137 were black, a ratio of 1.6:1. The age-standardised study confirmed the higher incidence among whites in the population sampled and it seems that blacks may have a lesser tendency than whites to develop dentigerous cysts. In Mourshed's series, there was also a considerable preponderance of white patients compared with black, but Mourshed discounted this on the grounds that the biopsy service at his school dealt predominantly with material from white patients.

However, if the difference in racial incidence is a real one, then the reason for this must be sought either in differences in the frequency of impacted teeth or in the as yet unidentified factor which may be responsible for the greater preponderance in males than females, or in both. In a study on the Witwatersrand of 576 patients with impacted teeth observed in a series of 1853 radiographs (Brown *et al.*, 1982), white patients had a higher frequency of impactions (455 or 34.8% of the white sample) than black patients (121 or 22.2% of the black sample). This difference was highly significant statistically (P <0.0001) and is likely to be a factor influencing the higher frequency of dentigerous cysts in white patients.

Table 4.3 Gender distribution of 356 black and white patients with dentigerous cysts.

	Men	Women	Row total	M:F ratio
Black	97	40	137 (38%)	2.4:1
White	130	89	219 (62%)	1.5:1
Column total	227 (64%)	129 (36%)	356	1.8:1
W:B ratio	1.3:1	2.2:1	1.6:1	

Site

The anatomical distribution of 184 dentigerous cysts, in relation to tooth involved, is shown in Fig. 4.4 and this has already been discussed with regard to the age distribution. A substantial majority involved the mandibular third molar. The maxillary permanent canine was next in order of frequency of involvement, followed by the mandibular premolars and the maxillary third molar. Similar distributions were reported by Roggan and Donath (1985), and Jones *et al.* (2006).

Lustmann and Bodner (1988) reported on dentigerous cysts associated with supernumerary teeth. In a review of 42 such cases from their own material and those reported in the literature, they found that about 90% were associated with a maxillary mesiodens. Kaugars *et al.* (1989) documented the occurrence of dentigerous cysts associated with a substantial number (27.6%) of a series of 351 odontomas.

Clinical presentation

Like OKCs, dentigerous cysts may grow to a large size before they are diagnosed. Most of them are discovered on radiographs when these are taken because a tooth has failed to erupt, or a tooth is missing, or because teeth are tilted or are otherwise out of alignment. Many patients first become aware of the cysts because of slowly

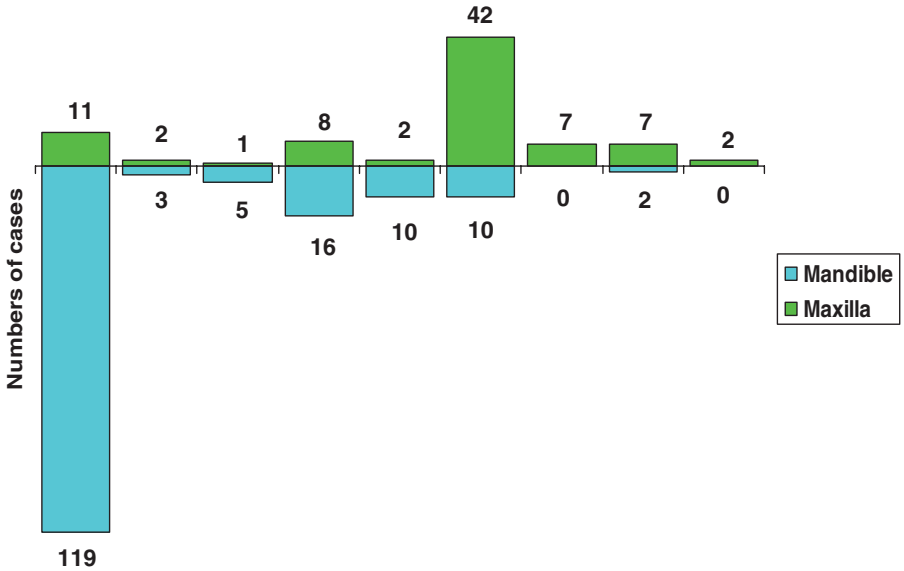


Fig. 4.4 Anatomical distribution of 247 dentigerous cysts.

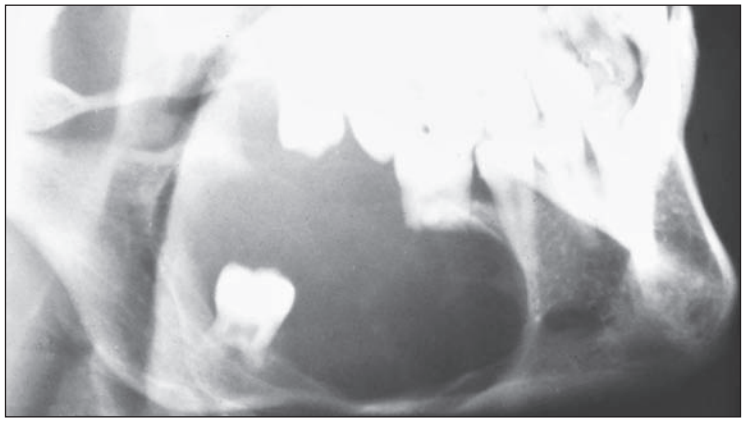


Fig. 4.5 Radiograph of a central type of dentigerous cyst. Note resorption of the root of the first mandibular molar. (Courtesy the late Professor J.J. Pindborg.)

enlarging swellings, and this is the common form of presentation with edentulous patients in whose jaws unerupted teeth have inadvertently been retained. Dentigerous cysts may occasionally be painful, particularly if infected. Although patients may give a history of a slowly enlarging swelling, Seward (1964) has shown radiologically that lesions 4–5 cm in diameter may develop in 3–4 years.

Radiological features

Radiographs show unilocular radiolucent areas associated with the crowns of unerupted teeth. The cysts have well-defined sclerotic margins unless they become infected. Occasionally, trabeculations may be seen and this may give an erroneous impression of multilocularity. The unerupted teeth may be impacted as a result of inadequate space in the dental arch or as a result of malpositioning such as by a horizontally impacted mandibular third molar or an inverted tooth. Supernumerary teeth may develop dentigerous cysts (Mourshed, 1964b; Lustmann and Bodner, 1988).

Three radiological variations of the dentigerous cyst may be observed. In the central variety (Fig. 4.5) the crown is enveloped symmetrically. In these instances, pressure is applied to the crown of the tooth and may push it away from its direction of eruption. In this way, mandibular third molars may be found at the lower border of the mandible as in Fig. 4.5, or in the ascending ramus and a maxillary canine may be forced into the maxillary sinus as far as the floor of the orbit. A maxillary incisor may be found below the floor of the nose (Fig. 4.6). The lateral type of dentigerous cyst (Figs 4.7 and 4.8) is a radiographic appearance that results from dilatation of the follicle on one aspect of the crown. This type is commonly seen when an impacted mandibular third molar is partially erupted so that its superior aspect is exposed (Fig. 4.7). The so-called circumferential dentigerous cyst in which the entire tooth appears to be

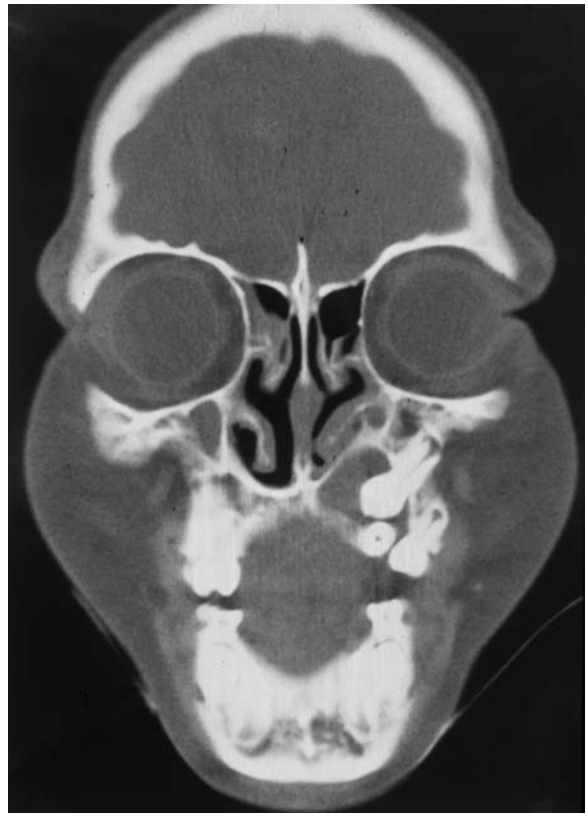


Fig. 4.6 CT scan of a maxillary dentigerous cyst extending to, and impinging on, the floor of the nose. (Courtesy Dr Mark Cohen.)

enveloped by cyst (Fig. 4.9), results when the follicle expands in the manner illustrated in Fig. 4.10c. It is important that this variety be differentiated from the envelopmental type of OKC.

Radicular cysts arising from deciduous teeth may mimic dentigerous cysts radiologically (Lustmann and Shear, 1985; Wood *et al*., 1988).

Dentigerous cysts appear to have a greater tendency than other simple jaw cysts to produce some resorption

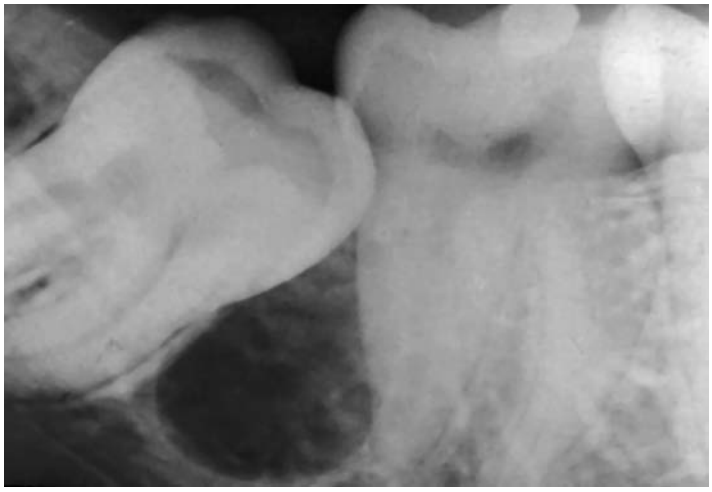


Fig. 4.7 Radiograph of a lateral type of dentigerous cyst.

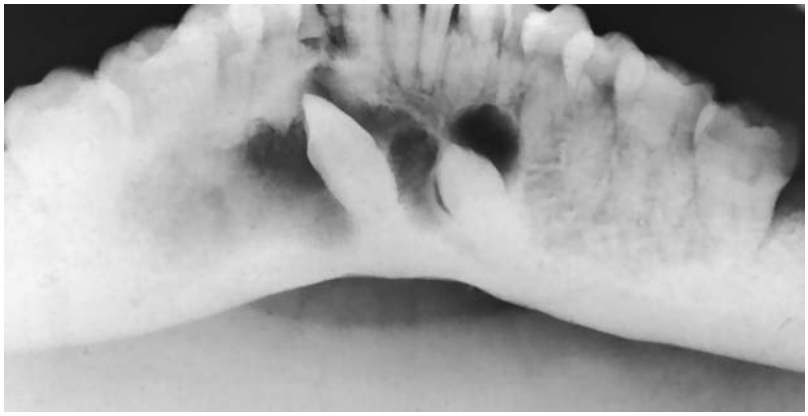


Fig. 4.8 Radiograph of two dentigerous cysts in the same patient. The cyst on the right is a lateral type; that on the left is a circumferential type.

of the roots of adjacent teeth (Struthers and Shear, 1976). In a radiographic study of root resorption produced by jaw cysts, Struthers and Shear (1976) observed root resorption in 11 of 20 dentigerous cysts (55%) in which there was contiguity of cyst and root (Figs 4.9 and 4.11). By comparison, root resorption was detected in only six of 33 radicular cysts (18%) and in none of their sample of 26 OKCs. They suggested that the dentigerous cyst's potential for root resorption may be derived from its origin from dental follicle and the ability of the latter to resorb the roots of the deciduous predecessors of the teeth, the crowns of which they surround. They felt that variations in root resorptive potential could not be explained by differences in intracystic pressure as Toller (1948) had shown that dentigerous and radicular cysts have very similar intracystic pressures. The important role of dental follicle in the resorption of bone has been demonstrated experimentally by Cahill and Marks (1980).

Experimental studies on bone resorption are described later in this chapter.

In the chapter on the odontogenic keratocyst (see Chapter 3) reference has been made to the use of computerised tomography (CT) scanning and magnetic resonance imaging (MRI) to assist in the differential diagnosis and treatment planning of the different jaw cysts.

Distinguishing dilated follicles from dentigerous cysts

Some unerupted teeth have a slightly dilated follicle in the pre-eruptive phase. This does not signify a cyst, nor even necessarily a potential cyst unless the pericoronal width is at least 3–4 mm. Daley and Wysocki (1995) have pointed out that it can be difficult to distinguish between a small dentigerous cyst and a large dental follicle despite the availability of both radiographical and histological information. Their comparative study of 1662 dentigerous cysts and 824 dental follicles showed considerable overlap in age distribution and site predilection, and they concluded that distinguishing reliably between a small dentigerous cyst and a large dental follicle may only be resolved by identifying a cyst cavity at the surgical operation.

The approach taken by Damante and Fleury (2001) was to verify the relationship between the

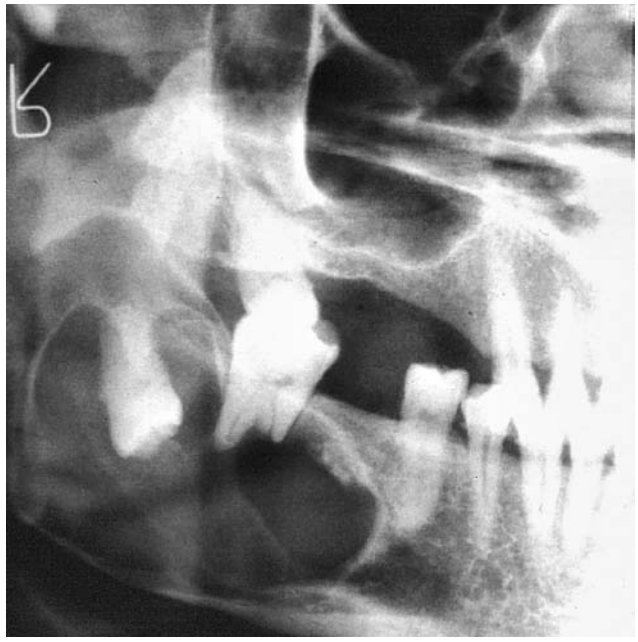


Fig. 4.9 Radiograph of a circumferential type dentigerous cyst associated with a mandibular third molar. The tooth of origin is displaced and the cyst wall has resorbed part of the root of the adjacent molar.

radiographically measured width of the pericoronal space and the microscopic features of the follicle, in order to contribute to the differential diagnosis of small dentigerous and paradental cysts. Their sample comprised 130 unerupted teeth and 35 partially erupted teeth. These were radiographed and then extracted. The widths of the pericoronal spaces were measured radiographically. The results of the radiographic analysis were compared with those of the histopathological examination of the dental follicle. The widths of the pericoronal spaces ranged from 0.1 to 5.6 mm. The most frequently observed lining of the follicles was a reduced enamel epithelium in 68.4% of unerupted teeth, and a hyperplastic stratified squamous epithelium in association with the partially erupted teeth in 68.5%. Inflammation was present in 36.1% of the unerupted teeth and in 82.8% of the partially erupted group. There was a statistically significant association between the presence of stratified squamous epithelium and pericoronal space enlargement for unerupted teeth ($P < 0.05$).

A trend was noted in the association between inflammation and enlargements of the pericoronal spaces in partially erupted teeth and possibly in unerupted teeth, but there was no measurable statistical significance.

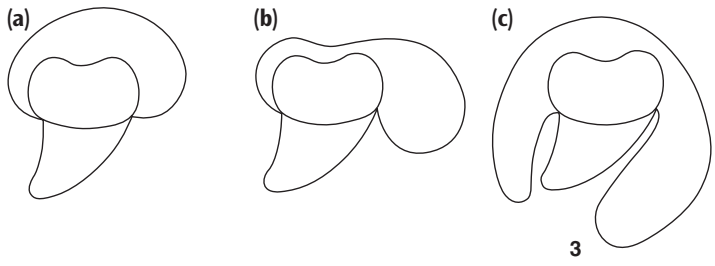


Fig. 4.10 Diagram illustrating the manner in which the dental follicle may expand to produce the radiographic appearances of (a) central; (b) lateral; and (c) circumferential types of dentigerous cysts.

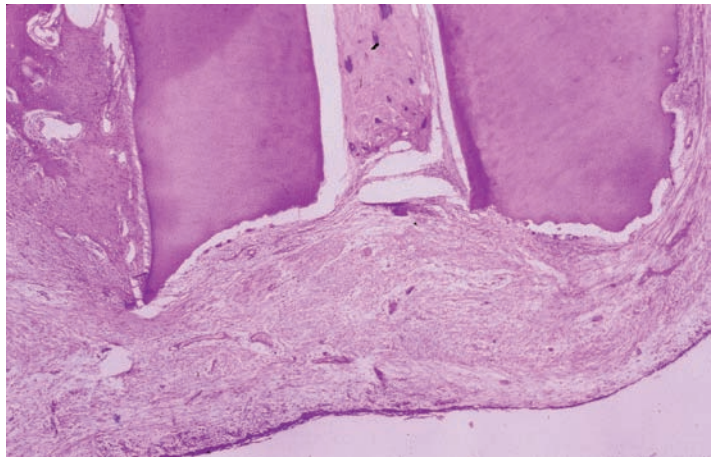


Fig. 4.11 A dentigerous cyst wall with resorption of the contiguous root of an adjacent tooth.

Surgically, the authors detected no bone cavitation or luminal cystic contents in pericoronal spaces smaller than 5.6 mm. They suggested that the first radiographic diagnosis for a pericoronal space enlargement, in most of the routine clinical cases, should be of 'inflammation of the follicle'. A differential diagnosis of 'dentigerous cyst' or 'paradental cyst' might be considered. The final differential diagnosis between a small dentigerous or a paradental cyst and a pericoronal follicle depended on clinical and/or surgical findings, such as the presence of bone cavitation and cystic content.

Curran *et al.* (2002) reported that in a sample of 2646 pericoronal lesions over a 6-year period, as many as 67% were follicular tissue with no evidence of pathology. Of the remaining cases, 752 were dentigerous cysts, 79 of which showed mucous metaplasia in the epithelial linings. Among the other pathological lesions in this material were 71 OKCs, 19 odontomas, 13 ameloblastomas, six carcinomas, six calcifying odontogenic cysts, four calcifying epithelial odontogenic tumours and one odontogenic myxoma.

Edamatsu *et al.* (2005) examined the expression of Fas, bcl-2, and single-stranded DNA (ssDNA) in dental follicles and dentigerous cysts to clarify the possible role of these apoptosis-related factors in a sample of follicles and in the pathogenesis of dentigerous cysts. The results were compared with Ki-67 immunoreactivity, used as a marker of cell proliferation.

As described in the chapter on the OKC (see Chapter 3), apoptosis, also known as programmed or physiological cell death, has an important role in embryogenesis, homoeostasis, and certain pathologic events (Kimi *et al.*, 2001). Edamatsu *et al.* (2005) have cited numbers of publications in describing how apoptotic reactions are modulated by many proteins, including Fas, TNF-α, p53, bcl-2, and caspases. Fas is a cell surface glycoprotein that transmits apoptotic signals from the cell surface into the cytoplasm, while the bcl-2 proto-oncogene encodes a protein that inhibits apoptosis. Also referred to in Chapter 3 were the studies that have shown that anti-single-stranded DNA (ssDNA) antibody recognises DNA fragmentation in the nuclei during programmed cell death as well as deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labelling (TUNEL). These apoptosis-related factors are detected in tooth germ tissues and several types of epithelial odontogenic cysts and tumours.

Their material comprised specimens of dental follicles associated with impacted lower third molars that were surgically removed from 80 patients, and specimens of 27 dentigerous cysts associated with impacted lower third molars were similarly prepared for comparison.

Expression of Fas and ssDNA was detected in superficial epithelial cells of both follicles and cysts. Expression of bcl-2 and Ki-67 was found in epithelial cells neighbouring the basement membrane. The positive ratio of bcl-2 in the follicles was significantly lower than that in the cysts ($P < 0.05$). ssDNA-positive cells were slightly more numerous in the follicles, while Ki-67-positive cells were slightly more numerous in the dentigerous cysts. In the follicles, epithelial tissues with proliferative rete processes showed significantly higher Ki-67 labelling than did those without proliferative rete processes. The dental follicles with marked inflammatory changes showed slightly higher rates of ssDNA and Ki-67 positivity than did the follicles without marked inflammation (Edamatsu *et al.*, 2005).

In considering their results, the authors believed that the impaction state and pericoronal radiolucency did not significantly correlate with the expression of apoptosis-related factors or cell proliferation markers in the dental follicles. This lack of a correlation suggested to them that impaction status and pericoronal radiolucency did not necessarily reflect the pathophysiologic status of the follicles. The Ki-67 labelling indices of follicles with proliferating rete processes of their epithelial linings were significantly higher than that of the Ki-67 labelling of epithelium with other morphological characteristics, indicating a high proliferative potential. Dental follicles with marked inflammatory changes had slightly higher ssDNA and Ki-67 labelling indices than did the follicles without marked inflammation. These features suggested that inflammatory changes in the follicles up-regulated the cell turnover of their epithelial components.

They concluded that apoptosis-related factors and proliferation markers differed between dental follicles and dentigerous cysts. Apoptosis and cell proliferation had a role in the pathogenesis of the cysts. In the follicles, however, expression of apoptosis-related factors and proliferative marker was most likely modulated by morphological characteristics of epithelial components as well as inflammatory changes (Edamatsu *et al.*, 2005).

Further immunohistochemical studies on the dentigerous cyst

The work of Flores *et al.* (2000) and Lo Muzio *et al.* (2005) on p53 expression in odontogenic cysts has been referred to in Chapter 3 (odontogenic keratocysts). Flores *et al.* wrote that 'although the p53 family members p63 and p73 are structurally related to p53, they have not been directly linked to tumor suppression, although they have been implicated in apoptosis'. Their experiments showed that the combined loss of p63 and p73 resulted in the failure of cells containing functional p53 to undergo apoptosis in response to DNA damage.

Lo Muzio *et al.* (2005) studied the expression of p63 in dentigerous cysts among other odontogenic cysts. Statistical analysis of their semi-quantitative data showed significantly higher p63 positivity in OKCs compared with the orthokeratinised, radicular (both at $P < 0.001$) and dentigerous cysts ($P < 0.01$). They found that in almost all the dentigerous cysts, p63 positivity was confined to the basal and parabasal layers of the epithelial linings. Only two of 30 cases showed a positivity in the intermediate layer. In all cases the staining was only nuclear, and in the majority only between 0 and less than 5% of the cells were stained. This group concluded that the more intense and diffuse expression of p63 in parakeratinised OKCs could help to explain the difference in the clinical and pathological behaviour of the OKCs, pointing to an abnormal control of the cell cycle leading to an intrinsic growth potential.

Abnormal epidermal differentiation has been linked to abnormal expression of bone morphogenic protein-4 (BMP-4). The differences in histopathology of the lining epithelia of the OKC and dentigerous cyst led Kim *et al.* (2005) to postulate that different factors may be involved in both the development and recurrence tendency of the two lesions. Their study sample comprised 34 OKCs and 43 dentigerous cysts. Goat primary polyclonal antibody against BMP-4 was used.

The findings in respect of the OKCs are discussed in Chapter 3. In comparison with the OKCs that showed dense staining in 15 of 34 of the epithelial linings and in 17 of 34 of the mesenchymal cyst walls, the epithelial linings of the dentigerous cysts showed negative staining in 37 of 43 specimens and in 30 of 43 of the mesenchymal cyst walls. The differences between the groups were statistically significant for both epithelial linings and mesenchymal cells ($P < 0.001$). The authors speculated on the reasons for these differences and concluded that the exact role of the BMP-4 could not yet be determined but that it might be related to the epithelial morphogenesis and invasive growth (Kim *et al.*, 2005).

Experimental studies on bone resorption

There is evidence that vital cyst tissue in culture releases a potent bone-resorbing factor that is predominantly a mixture of prostaglandins (PG) E_2 and E_3 (Harris and Goldhaber, 1973; Harris *et al.*, 1973; Harris and Toller, 1975; Harris, 1978). The source of this resorbing factor was thought to be the capsule and its leucocyte content. Arendorf (1981) has suggested that PGE_2 may have a similar role in the resorption of cementum and dentine. Data reported by Harris (1978) indicated a lower level of prostaglandin-like material (measured as PGE_2) released by dentigerous cysts (12.2±9.4 ng/mg) than by radicular (16.6±13 ng/mg) or by OKCs (20±11 ng/mg). Of interest, however, is the fact that the four lesions with the highest activities regardless of group, including the ameloblastoma, with a mean of 59.25±17.5 ng/mg, all resorbed the apices of adjacent teeth.

Matejka *et al.* (1985b) also found that PGE_2 was the predominant prostaglandin synthesised by radicular cysts but also found evidence of PGI_2 synthesis in a large number of radicular cysts. They believed that the surrounding granulation tissue with its associated inflammatory cells was the likely site of this synthesis and is thus one of the factors responsible for the osteolytic effects of radicular cysts. They suggested that these effects appear to be mediated at least in part by the synthesis of leucotrienes (with which prostaglandins share a common precursor, arachidonic acid), with a resultant increase in the production of PGI_2. The two dentigerous cysts that they investigated were the only two in their sample of 12 in which they found $PGF_{2\alpha}$. Further evidence that PGI_2 generation in human radicular cysts is stimulated by leucotrienes C_4 and D_4 in chronic inflammatory processes was reported by Matejka *et al.* (1985a).

Meghji *et al.* (1989) investigated the possibility that interleukin-1 (IL-1) may be produced by odontogenic cysts and may account for the raised levels of prostaglandin and collagenase synthesis by the cyst capsules. They referred to previous work that had shown that IL-1 and tumour necrosis factor accounted for much of the bone resorbing activity attributed to osteoclast activating factor produced by mononuclear leucocytes. These cytokines are particularly associated with chronic inflammatory lesions. Using radicular and dentigerous cysts, they demonstrated synthesis *in vitro* of a macromolecular factor with osteolytic activity that has the characteristics of IL-1. The stimulation of fibroblast collagenase and PGE_2 synthesis in their cyst wall culture media, as well as stimulation of fibroblast and osteoblast proliferation, also suggested IL-1 activity to the authors. They believed that the source of the interleukin could be the monocyte–macrophage infiltrate, the stromal fibroblasts and the epithelial cyst linings, and that the IL-1 released by the cysts could lead to a number of osteolytic cell reactions: the stimulation of osteoclasts to resorb bone, and the connective tissue cells to produce prostaglandins that will be responsible for further osteoclast activation. It also stimulates connective tissue cells to produce collagenase which is involved in the destruction of bone matrix.

The work of Li *et al.* (1997) on the immunocytochemical expression of parathyroid hormone related protein (PTHrP) in odontogenic jaw cysts has been discussed in relation to the OKC in Chapter 3. These authors investigated the immunocytochemical expression of PTHrP in odontogenic cysts because of evidence that OKCs had less bone resorbing capacity than the dentigerous and radicular cysts. They found, however, that the OKC

linings expressed significantly higher levels than those of both the dentigerous (P <0.003) and the radicular (P <0.003) cysts. The fibrous walls of all three varieties of cyst were reactive for PTHrP, with the OKC showing a higher intensity of staining.

These authors speculated that PTHrP might modulate growth and bone resorption in odontogenic cysts and might act synergistically with IL-1 to increase bone resorption or stimulate osteoblasts and inhibit osteoclasts, resulting in reduced resorption, through its transforming growth factor beta-like activity.

Pathogenesis

There can be little doubt that dentigerous cysts develop around the crown of unerupted teeth, whatever causes failure of eruption of the latter. In an analysis of the distribution of 761 unerupted teeth in 304 patients, Mourshed (1964a) showed that the vast majority were mandibular (378) or maxillary (328) third molars. Maxillary canines were next, a long way behind (15), followed by mandibular second premolars (11), maxillary second molars (8), mandibular second molars (7), mandibular canines (6) and maxillary second premolars (4). The mandibular and maxillary first premolars, a maxillary central incisor and a supernumerary tooth were each involved once.

A similar study was carried out in Johannesburg to determine the distribution of 1259 impacted teeth in a consecutive sample of radiographs taken in various departments of the dental hospital in the course of a single year (Brown *et al*., 1982). The distribution and frequency of individual impacted teeth determined in this way is compared in Table 4.4 with the anatomical distribution of 184 dentigerous cysts as illustrated in Fig. 4.4. In the case of mandibular third molars, the frequency of impaction (48.1%) is roughly the same as the frequency of cyst formation (45.7%). The maxillary third molars, however, have a comparatively much higher frequency of impaction (29.6%) than cyst involvement (5.4%), suggesting that this tooth might have a relatively lower risk of developing a dentigerous cyst than its mandibular counterpart. By the same token, maxillary canines would appear to have a somewhat higher relative risk of developing dentigerous cysts than mandibular canines. The relative risks of the other teeth, using the same assumptions, are shown in the extreme right-hand column of Table 4.4.

Mourshed (1964a) has calculated that the frequency of dentigerous cysts is 1.44 in every 100 unerupted teeth. Toller's estimate (1967) was that possibly 1 in 150 unerupted teeth might develop a dentigerous cyst, and the risk seemed to be greater in individuals over 30 years than in those who were younger. The anatomical environment of an unerupted tooth is probably of some significance in determining the development of a cyst. However, the differences in gender and race incidence suggest that there is some other factor, as yet unidentified, but possibly innate, that may have some role in determining whether a cyst will develop. This possibility is considered later.

It has been suggested that dentigerous cysts may be of either extrafollicular or intrafollicular origin and that those of intrafollicular origin may develop by accumulation of fluid either between the reduced enamel epithelium and the enamel, or within the enamel organ itself.

Atkinson (1972, 1976, 1977) described the formation of cysts derived from the enamel organ around the crowns of mouse molar teeth transplanted subcutaneously into an inbred strain (C57B1) of mice. In his 1976 paper,

Table 4.4 Comparison of frequency of impacted teeth with frequency of dentigerous cyst formation in two independent South African samples.

	Impacted (I)		Dentigerous cyst involvement (DC)		C%
Tooth	**(No.)**	**(%)**	**(No.)**	**(%)**	**I%**
Mandibular third molars	606	48.1	84	45.7	0.95
Maxillary third molars	372	29.6	10	5.4	0.18
Maxillary canines	150	11.9	36	19.6	1.65
Mandibular canines	44	3.5	7	3.8	1.09
Mandibular second premolars	41	3.3	14	7.6	2.30
Maxillary second premolars	27	2.2	7	3.8	1.73
Maxillary second molars	6	0.5	1	0.5	1.00
Mandibular first premolars	5	0.4	9	4.9	12.25
Maxillary central incisors	2	0.2	3	1.6	8.00
Mandibular second molars	1	0.1	2	1.1	11.00
Maxillary first premolars	1	0.1	1	0.5	5.00
Other teeth	4	0.3	9	4.9	16.33
Total	1259	100	184	100	

Atkinson showed that after initial degeneration, the enamel organ took the form of a squamous epithelium in which squamous hyperplasia took place after 5–6 days. Cystic degeneration within the hyperplastic epithelium produced cavities lined with a thick, parakeratotic, stratified squamous epithelium but as the cysts enlarged, the lining changed to a thin, non-keratinised, stratified, squamous epithelium.

Riviere and Sabet (1973) transplanted unerupted molar tooth germs from 7 day old mice to the mammary fat pads of adult mice of the same inbred line. Cysts with a dentigerous relationship to the crown of the tooth developed in every instance that the graft retained its viability and they developed at about the same rate in all animals over a 3-week period.

Al-Talabani and Smith (1980) studied the cysts that formed adjacent to the developing crowns of tooth germ isografts in hamster cheek pouch. In isografts from 5 day old animals, cysts frequently formed as a result of enamel organ degeneration soon after transplantation. Enamel hypoplasia was often a feature of the related teeth. They then examined 86 teeth associated with human dentigerous cysts and 43 of these showed areas of enamel hypoplasia on their occlusal surfaces or incisal edges. In tooth germ transplants from 2 day old hamsters, cysts formed in about half of the specimens only after completion of enamel formation, 6 weeks after transplantation. In this group, the cysts developed by separation between the cells of the reduced enamel epithelium and enamel hypoplasia was not a conspicuous feature. The authors considered that there was a strong possibility of a direct relationship between the development of cysts and the occurrence of enamel hypoplasia in the involved teeth. They suggested the possibility that there may be two types of dentigerous cyst, with different causes and arising at different stages of tooth development. One would arise by degeneration of the stellate reticulum at an early stage of development and is likely to be associated with enamel hypoplasia. The other would develop after completion of the crown by accumulation of fluid between the layers of the reduced enamel epithelium. Enamel hypoplasia would not be a significant feature of this variety. This concurrence of dentigerous cyst with enamel hypoplasia of the contained tooth is an interesting one as the relationship occurs too frequently to be fortuitous. Another explanation for the association, not suggested by Al-Talabani and Smith (1980), may be that the presence of foci of enamel hypoplasia diminishes the adherence of reduced enamel epithelium to crown and provides the starting point for the development of the cyst.

There can be no good reason for the extrafollicular theory of origin of dentigerous cysts, as the evidence is that those reported as arising in this manner all appear to be envelopmental or follicular OKCs. The case reported by Gillette and Weinmann (1958), and which was frequently quoted in support of extrafollicular origin, is clearly an envelopmental OKC (see Fig. 3.12). Occasional dentigerous cyst linings show projections which resemble Tomes' processes of the ameloblasts protruding into the lumen from the superficial layer of epithelial cells. This suggests that in these instances the superficial cells were derived from the ameloblasts and provides evidence that, in these cases, dentigerous cysts arose by accumulation of fluid between the reduced enamel epithelium and the enamel, and not in the stellate reticulum. Furthermore, it must be unusual to be able to demonstrate a fully circumferential, intact cyst lining around the crown of the unerupted tooth. There is considerable evidence that the epithelial lining of a dentigerous cyst terminates at the neck of the involved tooth. Therefore, while not excluding the possibility that dentigerous cysts may develop within the enamel organ in the tooth germ transplant experiments, this author's experience is that in humans these cysts form between the reduced enamel epithelium and the enamel.

Another theory of origin that has been proposed is that the crown of a permanent tooth may erupt into a radicular cyst formed at the apex of its deciduous predecessor. This phenomenon possibly does occur, but only exceptionally rarely, because radicular cysts involving the deciduous dentition are so uncommon (Lustmann and Shear, 1985). In such a case, the erupting tooth may indent rather than penetrate the wall of the radicular cyst and this should be apparent histologically, if not macroscopically (Fig. 4.12a,b) (Gebhardt and Lenz, 1985; Wood *et al*., 1988).

A variation of this concept is that inflammation at the apex of a deciduous tooth may lead to the development of an inflammatory follicular cyst (Shaw *et al*., 1980; Main, 1985; Benn *et al*., 1990; Benn, 1991). Benn's 1991 study included 15 patients ranging in age from 5 to 12 years. In 12 cases, the inflammation arose from a non-vital deciduous predecessor, while two patients had Garré's osteomyelitis. The mandible was involved in 10 cases and the maxilla in five. The premolar teeth were associated with the cysts in nine cases, the canines in three and the second molars in two cases, presumably in the patients with Garré's osteomyelitis. Macroscopically, all the cysts were attached to the necks of teeth showing virtually no root formation. Histologically, the most commonly occurring feature was the presence of non-keratinised, stratified, squamous epithelium of varying thickness with focal areas of arcading. All cases showed some degree of inflammation.

Shibata *et al*. (2004) carried out a retrospective review of 70 patients under the age of 16 years who had histologically confirmed dentigerous cysts which had developed between the central incisors and the second premolars. Most of the cases (54) were in the premolar region. Of these, 44 showed some clinical and radiological evidence

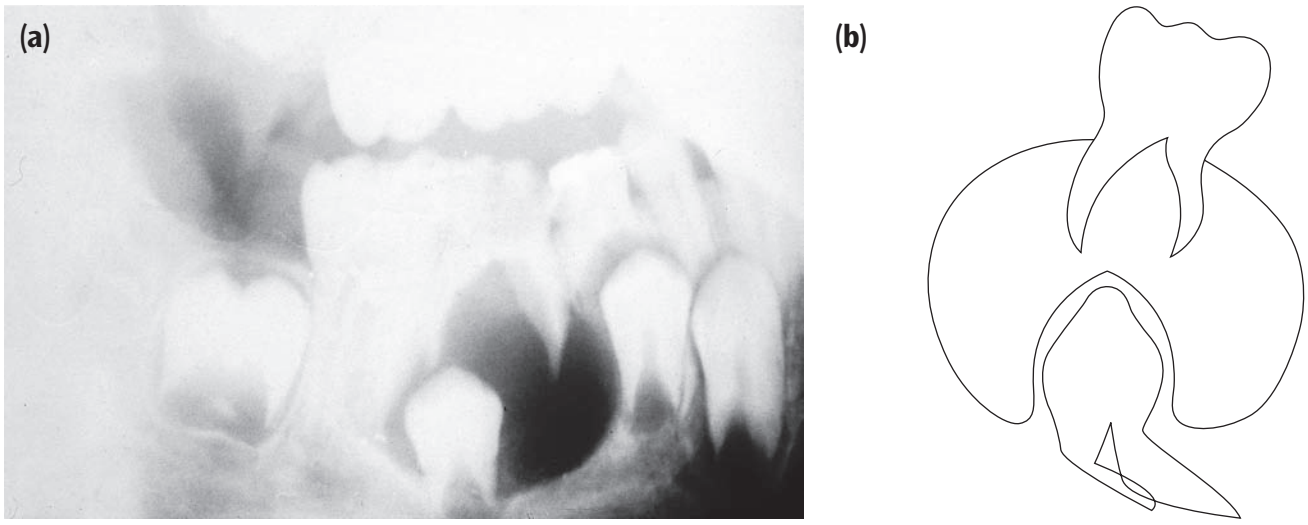


Fig. 4.12 (a) A radicular cyst associated with a deciduous mandibular second molar appears to be in a dentigerous relationship with the erupting premolar. (b) A diagrammatic representation of the probable relationship, where the erupting tooth has indented the radicular cyst wall. (Radiograph courtesy of Dr J. Lustmann.)

of inflammation of the deciduous teeth associated with the dentigerous cyst. They concluded that inflammatory change at the apex of a deciduous tooth may be responsible for initiating a dentigerous cyst of the permanent successor.

There would therefore appear to be some evidence of an inflammatory etiology in the pathogenesis of some dentigerous cysts. Nevertheless, individual cases need to be assessed critically. Attachment of the cyst wall to the neck of the associated tooth is an essential feature, and microscopically, the cyst lining should demonstrate a readily identifiable component of reduced enamel epithelium before a diagnosis of dentigerous cyst is made. Most of the cases reported by Shaw *et al.* (1980) were resolved after extraction of the involved primary tooth and curettage of the socket, and their brief description of the histological findings is consistent more with radicular than with dentigerous cyst linings. These are more likely to be rare examples of radicular cysts associated with deciduous teeth that have been indented by the erupting permanent successors, as indicated in Fig. 4.12.

Assuming then that the dentigerous cyst develops around an unerupted tooth by accumulation of fluid between the reduced enamel epithelium and the enamel, or between layers of reduced enamel epithelium, how does this happen? Main (1970b) suggested that the pressure exerted by a potentially erupting tooth on an impacted follicle obstructs the venous outflow and thereby induces rapid transudation of serum across the capillary walls. The increased hydrostatic pressure of this pooling fluid separates the follicle from the crown, with or without reduced enamel epithelium. With time, capillary permeability is altered so as to permit the passage of greater quantities of protein above the low concentration of the pure transudate.

In a later study, Main (1989) used a computer-aided image analyser to measure cystic areas on orthopantomograms of 30 uninfected, wholly intracortical cysts associated with third mandibular teeth. Fifteen cases each of two size categories, small and large, were correlated with the radiographic variables of cyst relationships to tooth crown, and angulation and nature of the impaction of the enclosed tooth. He found that cyst enlargement was most active in the third and fouth decades. The smaller cysts were associated with teeth impacted against adjacent teeth or bone, while the larger cysts developed predominantly from horizontally angulated teeth intruded endosteally. These findings, Main contended, lent support to the haemodynamic concept of dentigerous cyst enlargement linked with dysfunctional eruptive forces.

Studies by Skaug (1973), Skaug and Hofstad (1973) and Browne (1975) on dentigerous cyst fluids have indicated total soluble protein levels, albumin:globulin ratios and immunoglobulin levels similar to those in serum. Browne (1975) suggested therefore that in dentigerous cysts the fluid arises as an exudate from the vessels in the capsule and is only slightly modified by any local immunoglobulin synthesis in the cyst wall. However, immunoglobulins and immunoglobulin-containing cells are present in the walls of odontogenic cysts, and in an immunohistochemical study of immunoglobulin-containing plasma cells in OKCs, dentigerous and radicular cysts, Smith *et al.* (1987) showed that immunoglobulin G (IgG)-containing plasma cells were the predominant species in all three, with a much lower percentage of IgA- and few

IgM-containing plasma cells. There was a significantly higher percentage contribution of IgG-containing plasma cells and a significantly lower percentage of IgA-containing plasma cells in dentigerous cysts than in OKCs. There was also intense extracellular staining of IgG in the dentigerous cyst. The authors suggested that the immunoglobulins found in odontogenic cyst fluids may be derived from local synthesis in the cyst capsule as well as an inflammatory exudate.

Glycosaminoglycans, predominantly hyaluronic acid but also appreciable amounts of heparin and chondroitin-4-sulphate, are present in the fluids and walls of dentigerous cysts (Skaug and Hofstad, 1972; Smith *et al*., 1984, 1988a,b, 1989). Release of the glycosaminoglycans from the walls and their diffusion into the cyst fluid is thought to have an important role in expansile cyst growth by increasing the osmolality of the cyst fluid and hence raising the internal hydrostatic pressure of the cyst. A more detailed account of the role of glycosaminoglycans in odontogenic cysts is given in Chapter 3.

Many dentigerous cysts show evidence of a degree of acute and chronic inflammation in their walls, and in these instances exudation must play some part in the expansion of the cyst. Moreover, the passage of desquamated epithelial cells and inflammatory cells into the cyst cavity must contribute to the increase in intracystic osmotic tension and thereby probably to further expansion of the cyst. Toller (1970b) has shown that the mean cyst fluid osmolality of seven dentigerous cysts was 10 mOsm higher than the mean serum osmolality but that this increase was not statistically significant. He believed (Toller, 1967) that the likely origin of dentigerous cysts was a breakdown of proliferating cells of the follicle following impeded eruption. Although he conceded that the factors favouring fluid accumulation that were postulated by Main may possibly have a role, he believed that raised osmolality of the cyst fluid made an important contribution to cyst expansion. As the cyst expanded, there may be some compensatory epithelial proliferation to cover the greater surface area of connective tissue, but this is slight, as demonstrated by the low mitotic rate in dentigerous cyst epithelium (Browne, 1975). Furthermore, Stenman *et al*. (1986) have shown that dentigerous cyst epithelium has little capacity for *in vitro* growth, compared with OKC epithelium.

The role of prostaglandins in resorption of bone, and consequently the enlargement of dentigerous as well as of other cysts, has been dealt with earlier in this chapter.

Main (1970b) made the point that the pooling fluid separated the follicle from the crown, with or without reduced enamel epithelium, on the basis of the work of Stanley *et al*. (1965) who studied 70 non-cystic follicles from the third molars of patients ranging in age from 13 to 69 years. They concluded that follicles separated from enamel in patients below 22 years of age tended to leave the still-cuboidal reduced enamel epithelium attached to tooth, while above this age the progressively more squamous epithelium became increasingly more readily detached. The frequent occurrence of 'epithelial discontinuities' described by Toller (1966a) in about one-third of uninfected dentigerous cysts suggested that in some of these cysts the reduced enamel epithelium may separate in parts and adhere to the enamel in other parts.

Having resolved the question of whether dentigerous cysts, which develop by accumulation of fluid between the reduced enamel epithelium and the crowns of unerupted teeth, occur only in some individuals even though unerupted and usually impacted teeth are a much more common phenomenon, are there possible intrinsic factors that may have a role?

Dentigerous cysts and the PTCH *gene*

In Chapter 3, reference was made to a paper by Barretto *et al*. (2002) in which the authors investigated the expression of *PTCH* in a range of odontogenic cysts and tumours. This study included six dentigerous cysts. Immunohistochemical methods were used to assess PTCH expression at the protein level. These experiments revealed the presence of PTCH protein in virtually all cysts and tumours. Positive staining was demonstrated in the epithelium of the dentigerous cysts. All tissue examined showed positive intracytoplasmic PTCH staining of variable intensity.

The decision by Levanat *et al*. (2000) to examine the dentigerous cyst for *PTCH* alterations, was based on the expression of the Sonic hedgehog gene (*Shh)* in odontogenic epithelium in the early stages of tooth development. Seven dentigerous cysts were selected for the study as well as seven OKCs. Four markers were used, three of which belonged to the 9q22.3 region and one from the distal side in 9q31. Deletions throughout the 9q22–9q31 region have often been found in tumours associated with the naevoid basal cell carcinoma syndrome (NBCCS). Clear loss of heterozygosity (LOH) was scored in three dentigerous cysts and in four OKCs. Also, one cyst in each group showed LOH for two markers and one cyst in each group was clearly heterozygous for all markers used.

The authors hypothesised that the LOH observed in the epithelial lining of the dentigerous cysts suggested that a decisive initiating event in their development, as in the development of the OKCs, is *PTCH* inactivation in a progenitor epithelial cell from which the entire epithelial lining is later cloned. This autoregulating *PTCH* role, they stated, which ensures limited programmed proliferation, failed if the gene was altered by mutations or deletions. The result was uncontrolled cell proliferation, as well as a continuous and useless synthesis of the non-functional PTCH protein.

In a further study by the same group (Pavelić *et al*., 2001), the authors explored more carefully the

possibility of *PTCH* involvement in the development of dentigerous, OKCs and radicular cysts. They examined their initial LOH results on larger samples and then looked for abnormal *PTCH* expression in the cyst lining as the most direct evidence of gene malfunctioning. Finally, they compared the response of all three cyst types – dentigerous, radicular and OKCs to the non-metastatic marker Nm23.

Ten dentigerous cysts, without evidence of inflammation, were selected. Of the four markers used, three belonged to the 9q22.3 region because deletions throughout the 9q22–9q31 region had often been found in tumours of Gorlin's syndrome patients, and the markers in this study had often been used in NBCCS-related disorders. While no loss of heterozygosity was found in radicular cysts, five dentigerous cysts showed LOH for at least one polymorphic marker (Pavelić *et al*., 2001).

Based on the high incidence of LOH detected in half of the dentigerous cysts studied, the authors considered it reasonable to assume that the *PTCH* gene had been altered in all dentigerous cyst samples, only in a less dramatic way. A further argument for such a hypothesis came from comparison with OKCs, for which *PTCH* alterations had been recognised as the most likely cause. Their results for LOH in the dentigerous cysts were 'strikingly similar' to those they had previously found in their OKC samples, both by overall incidence of LOH and by relative contributions of particular markers.

Their PCR bands indicated that the *PTCH* gene was expressed in dentigerous cysts. From the five samples for which LOH had been found, two dentigerous cysts were selected that were most suitable for mRNA extraction from the remaining archival material in paraffin blocks. For comparison, they also included one of their archival OKC samples with LOH.

They concluded that the *PTCH* expression in the dentigerous cyst samples was clearly similar to that in the OKC specimen. They also found that *PTCH* mRNA detected in these dentigerous cysts showed that the gene was expressed despite alterations or deletions that were detected as LOH, so at least the other allele was being transcribed. They concluded that since the expression indicated Shh/Ptch/Smo continued signalling, that allele must also have mutated; otherwise, its product would have blocked the pathway signalling (Pavelić *et al*., 2001).

In addition to investigating potential *PTCH* involvement in the genesis of the three odontogenic cyst types, Pavelić *et al*. (2001) wanted to compare them for a more general indication of a possible neoplastic character of their epithelial lining proliferation. They therefore investigated the expression of *nm23* genes (non-metastatic clone 23) in the dentigerous cysts and also in OKCs and radicular cysts because of evidence that these were involved in the control of normal development and differentiation. They selected *nm23-H1*, the first of eight documented in humans, because reduced expression of *nm23-H1* had been associated with an aggressive clinical course in several human tumour cohorts, and studies *in vitro* had shown that up-regulation of Nm23 promoted differentiation by inducing growth arrest. They cited work that had found that in mouse development increased levels of Nm23 in organs of epithelial origin coincided with their functional differentiation and that terminally differentiated tissues retained high levels of the protein. All these properties of *nm23-H1* and its close homologues suggested to them that the level of the protein in the cyst epithelial lining might be inversely correlated, potentially, to the neoplastic character of lining proliferation.

Their semi-quantitative immunohistochemical findings were that for OKCs, all 10 specimens had quite consistent staining intensities at or near (+) value on a four-point visual estimate scale. The average for radicular cysts staining was about midway between (+) and (++), while for dentigerous cysts it slightly exceeded (++). Low *nm23* expression in OKCs was consistent, they believed, with their recognized aggressiveness and their potential for recurrence.

These authors believed they could argue that dentigerous cysts, just like OKC, might be caused by *PTCH* inactivation in a progenitor cell of the respective remnant tissue (reduced enamel epithelium as against dental lamina). However, unlike other malformations, they could find no compelling argument that cystic growth was triggered during early development. They suggested that although their frequency decreased with advanced age, both cyst types could occur at various times in life; and if the immediate triggering event for this proliferation was assumed to be an Shh signal reaching a progenitor cell, *PTCH* inactivation in this cell could have happened at any time before the Shh protein arrived at its membrane. Even if, in the case of dentigerous cysts, there was some hesitation in claiming that *PTCH* alone was responsible for their development, they believed that the missing band in the LOH readings was convincing evidence that the lining was cloned from a single progenitor cell.

Pathology

Sometimes the cyst is removed intact but more often the thin wall is torn during the surgical procedure. Pathologists should perform a careful dissection of the gross specimen to determine that the cyst surrounding the crown of the tooth is indeed a dilated follicle and that it attaches at the amelocemental junction. Some OKCs may appear, in the gross specimen, to be dentigerous cysts, but

their extrafollicular location will be demonstrable on dissection except with examples of follicular OKCs, the nature of which will only be revealed on histological examination. In an inflamed dentigerous cyst the wall may be thickened.

A few cases have been personally observed of early adenomatoid odontogenic tumour that have appeared radiologically and in the gross specimen as dentigerous cysts. The presence of adenomatoid odontogenic tumour may be suspected in the gross specimen by the observation of small white or yellow nodules on the luminal surfaces of the cyst walls. Similarly, the presence of the nodules of plexiform unicystic ameloblastoma may be predicted by careful examination of the gross specimen. Histological sections should, of course, always be prepared from these areas of irregularity.

Histological examination usually shows a thin fibrous cyst wall which, being derived from dental follicle, consists of young fibroblasts widely separated by stroma and ground substance rich in acid mucopolysaccharide. The epithelial lining, which is in fact reduced enamel epithelium, consists of 2–4 cell layers of flat or cuboidal cells (Fig. 4.13). Characteristically, the epithelial lining is not keratinised and most of those that have been described as keratinised have probably been adjacent OKCs. Discontinuities in the epithelial lining may be seen in the presence of an intense inflammatory infiltrate in the adjacent capsule, or, as suggested by Toller (1966a), through partial adherence to enamel. Sometimes, the superficial layer of the epithelial lining is low columnar and retains the morphology of the ameloblast layer which, of course, it originally was.

In some cysts, part of the epithelial lining may contain mucus-producing cells. Browne (1972) found them in 36% of mandibular and in 53% of maxillary dentigerous cysts in his series, and made the interesting observation that the frequency of such mucous cells increased in proportion to the age of the patients. Ciliated cells occurred very rarely. The presence of these mucous and ciliated cells is thought to result from metaplasia. Another rare example of metaplasia in dentigerous cysts is provided by the occasional presence of sebaceous glands in their walls (Gorlin, 1957; Spouge, 1966). Hyaline bodies (Rushton, 1955) are sometimes seen.

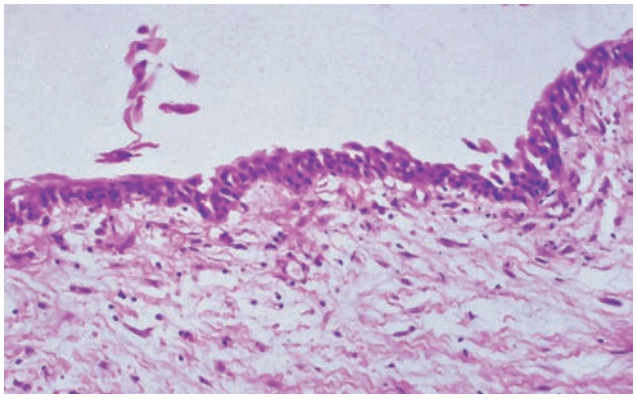


Fig. 4.13 Wall of a dentigerous cyst lined by a thin epithelium of 2–4 layers of undifferentiated cells derived from the reduced enamel epithelium. The fibrous cyst wall is relatively uninflamed and sparsely cellular.

In a sample of 130 dentigerous cysts, Takeda *et al.* (2005) found mucous cells in the linings of 31 (23.8%). Fourteen (10.8%) in the same sample showed ciliated cells in the epithelial linings, indicating that both can be present together. In their study, only areas devoid of moderate to severe inflammatory cell infiltration were selected, and several blocks were examined in each case. Variable numbers of clear or vacuolated cells were observed close to the mucous cells, as reported previously by Slabbert *et al.* (1995).

In several cysts of both developmental and inflammatory origin, intra-epithelial gland-like structures lined with mucous cells were observed in the hyperplastic regions of the epithelial linings. Such gland-like structures resembled the glandular structures in 'glandular odontogenic cysts (GOCs)' (see pp. 97 and 98). The authors were of the view that this was supportive evidence for the notion that GOCs were odontogenic in origin, rather than originating from intraosseous ectopic salivary glands (Takeda *et al.*, 2005).

Takeda and Yamamoto (2000) have reported a case of a dentigerous cyst containing granules of melanin pigment and dendritic melanocytes in the basal cells of the lining epithelium. There was also macroscopically visible pigmentation in the cyst wall.

Localised proliferation of the epithelial lining may occur in response to inflammation. Occasional bud-like thickenings of the epithelium may be seen in the absence of inflammation and sometimes there may be budding of the basal cells into the fibrous capsule. Nests, islands and strands of odontogenic epithelium are often seen in the capsule. Wright (1979b) reported the presence, in the capsules, of a series of dentigerous cysts, of epithelial proliferations that resembled the squamous odontogenic tumour (Pullon *et al.*, 1975). None of the cases has recurred following conservative surgery.

Undifferentiated epithelium lining dentigerous cysts, like reduced enamel epithelium of dental follicles, yielded consistently negative results for blood group antigens A and B in the hands of Wright (1979a). On the other hand, Vedtofte *et al.* (1985) were able to demonstrate the A, B and H type 2 antigens in follicular, radicular and OKCs. They ascribed the variation between their findings and those of Wright (1979a) to technical and sampling differences. Gardner and O'Neill (1988) also found that five of seven dentigerous cysts that they studied were markedly positive for blood group antigens A, B and H type 2. Two exhibited only a few positive cells.

Cytokeratins, epidermal growth factor and transforming growth factor, elafin, bone morphogenic protein-4, epithelial membrane antigen, carcinoembryonic antigen and rat liver antigen

Numerous immunohistochemical studies have been undertaken in the past few years, using a range of antibodies, to compare the cytokeratin content of dentigerous cyst epithelium with that of the OKC and radicular cyst. Other studies compared the content in these cyst linings of epidermal growth factor (EGF) and transforming growth factor (TGF), elafin, bone morphogenic protein-4 (BMP-4), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) and rat liver antigen (RLA). The observations in these studies will not be repeated here as they have been described in detail in Chapter 3, and summarised in Table 3.7. Many of these investigations were carried out to facilitate the diagnoses of the different cysts, particularly the OKC.

More specifically, Hormia *et al*. (1987) addressed themselves to the question of whether dentigerous cysts arose between the reduced enamel epithelium and the enamel, or by a split in the enamel organ itself. They proposed that their results suggested that two histogenetic entities could occur that could not be distinguished by routine histological examination. They also pointed out that their results indicated that dentigerous, but not other cyst types, may share with some cases of ameloblastoma, the expression of cytokeratin polypeptide No. 18. They speculated that cytokeratin 18-positive cells could have a specific histogenetic origin and could consequently have distinct functional characteristics. Another possibility, they suggested, was that the expression of cytokeratin polypeptide No. 18 in dentigerous cysts was a sign of oncofetal transformation in these lesions (Pavelić *et al*., 2001).

The dentigerous cyst as a potential ameloblastoma

Numbers of workers have claimed that many ameloblastomas arise in dentigerous cysts but the present author has seen no evidence to support such a contention. Indeed, the fact that dentigerous cysts are rarer in South African blacks, compared with whites, whereas ameloblastomas are very much more common in blacks (Meerkotter, 1969; Shear and Singh, 1978) provides contrary evidence. While ameloblastomas, being of odontogenic epithelial origin, may theoretically arise from dentigerous cyst lining as well as any other odontogenic epithelium, the belief that it commonly arises in this situation and that the dentigerous cyst should therefore be regarded as pre-ameloblastomatous, should be viewed with caution. Much of the confusion has probably arisen for three reasons. First, an ameloblastoma, like an OKC, may involve an unerupted tooth, particularly a third molar at the angle of the mandible, and this may be incorrectly interpreted as a dentigerous cyst on radiographs (Fig. 4.14). When subsequently the lesion is removed and diagnosed histologically as an ameloblastoma, the erroneous conclusion may be reached that the ameloblastoma developed from the dentigerous cyst.

The second possible reason for believing that many ameloblastomas develop from dentigerous cysts is that biopsies of ameloblastomas may be taken of an expanded locule lined apparently by a thin layer of epithelium. If the surgeon's provisional diagnosis is dentigerous cyst because of the radiological picture, the pathologist may well regard such histological features as consistent with this diagnosis. When the tumour is removed entirely and a diagnosis of ameloblastoma is made, once again this may be misinterpreted as having developed from a dentigerous cyst.

Third, as Lucas (1954) has pointed out, apparently isolated islets or follicles of epithelium are sometimes found

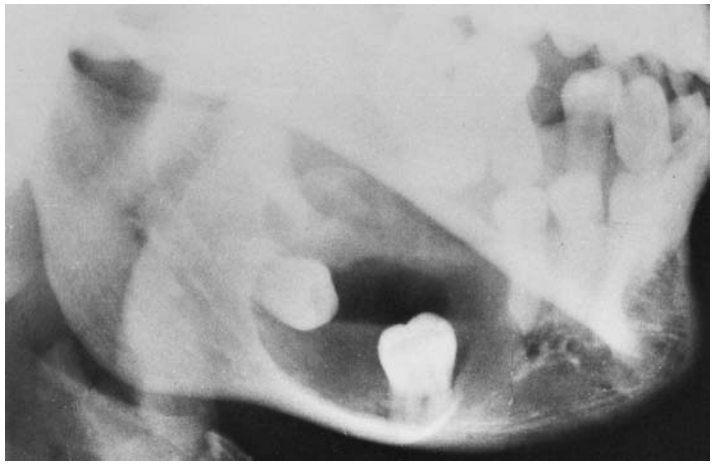


Fig. 4.14 Radiograph of a unilocular ameloblastoma that appears to be a dentigerous cyst.

in the cyst wall some distance from the epithelial lining. These have been interpreted as ameloblastoma although they bear only a superficial resemblance to the tumour.

It is likely that in the past, cases of unicystic ameloblastoma may have been misdiagnosed as dentigerous cysts. This lesion has now been well documented in the literature as a benign cystic neoplasm, and is not explored further in this book.

Treatment

Much of the literature on the treatment of dentigerous cysts has dealt with the procedures followed in handling these lesions in children. The emphasis is on conservative surgical treatment, combined with orthodontics, in order to retain the involved teeth and to ensure eruption into normal occlusion. Hyomoto *et al.* (2003) performed a retrospective investigation into the eruption of teeth associated with dentigerous cysts involving 47 mandibular premolars and 11 maxillary canines in pre-adolescent children. In one group, 81% of the mandibular premolars and 36% of the maxillary canines erupted successfully about 100 days after marsupialisation without traction. In the second group, the teeth had either undergone orthodontic traction, or the cysts had been removed entirely together with the associated tooth. The authors suggested that a period of 100 days after marsupialisation was the critical time for deciding whether to extract or to use traction. The eruption potential, they contended, was closely related to root formation, so that teeth with incomplete root formation had good potential to erupt, whereas those with fully formed roots could not. They recommended that on the basis of their study, position, angulation and root maturity of the cyst-related teeth should be considered in the treatment plan.

Other research papers and case reports supporting similar treatment approaches are those of Miyawaki *et al.* (1999), Counts *et al.* (2001), Bodner (2002), Jones *et al.* (2003), Jena *et al.* (2004) and Marchetti *et al.* (2004).

Motamedi and Talesh (2005) have detailed their experience in treating 40 large dentigerous cysts involving three or more teeth, referred to them over an 11-year period. Their view was that dentigerous cysts were usually easy to treat when small, but that the more extensive cysts were more difficult to manage.

Their treatment approaches were based on patient age, cyst site and size, involvement of vital structures by the cyst, and the potential for normal eruption into occlusion of the impacted tooth involved. Aspiration with a 16 or 18 gauge needle was performed to confirm that they were dealing with cysts and not tumours, and these were followed by incisional biopsies to make definitive histological diagnoses.

Cyst enucleation along with extraction of the impaction(s) was indicated in 34 patients. In these patients the impacted teeth were deemed unlikely to be useful, or lacked space for eruption. Cyst enucleation with preservation of the impacted tooth was indicated in six patients: five by enucleation of the cyst while preserving the associated maxillary or canine teeth, while one was treated by decompression. These teeth erupted normally when root formation was incomplete. Orthodontics was used in cases requiring aided eruption or alignment. Decompression was used in only one case where there was an extensive cyst in an 11 year old girl involving the mandibular body and angle, and impinged on the inferior alveolar nerve and term germs.

5
Eruption Cyst

An eruption cyst is in essence a dentigerous cyst occurring in the soft tissues. Whereas the dentigerous cyst develops around the crown of an unerupted tooth lying in the bone, the eruption cyst occurs when a tooth is impeded in its eruption within the soft tissues overlying the bone.

Clinical features

Frequency

Eruption cysts are not commonly seen in pathology departments and only 27 have been recorded in the archives of the Department of Oral Pathology, University of the Witwatersrand over a period of 46 years (0.8%) among a total of 3498 cysts of the jaws (see Table 1.1). In a series of 69 paediatric patients with cystic lesions of the jaws, 15 (22%) were eruption cysts, indicating a higher frequency in children with these cysts, than in a general population (Bodner, 2002). It is likely that they occur more frequently clinically and that as some burst spontaneously these are not excised and are therefore not submitted for histological examination.

Clinical presentation

The cysts are found in children of different ages, and occasionally in adults if there is delayed eruption. In a series of 27 patients with 36 eruption cysts reported by Aguilo *et al.* (1998), the lesions occurred within an age range of 5–9 years; while in the study of 24 patients reported by Bodner *et al.* (2004), the ages ranged from 1 month to 12 years with a mean of 4.4 years. In Seward's (1973) sample, one patient was 21 years old; and Woldenberg *et al.* (2004) documented an unusual case that occurred in a 40 year old woman. This patient presented with a 1-cm diameter gingival swelling over the right maxilla. Radiographs showed that the maxillary canines were impacted bilaterally and the crown of the canine on the right side was in proximity with the mucosal swelling.

Deciduous and permanent teeth may be involved, most frequently anterior to the first permanent molar. Aguilo *et al.* (1998) found that their most frequent location was in relation to the maxillary permanent dentition. In six of their 27 patients, two or more eruption cysts were found. In three of these, the lesions were bilateral, symmetrical and concurrent. In the series of Bodner *et al.* (2004), the cysts were associated with natal teeth in two cases, with primary teeth in 10, and with permanent teeth in 12 cases. The mandibular central primary incisors and first permanent molars were the teeth most frequently involved, and boys were affected twice as often as girls in their sample.

The eruption cyst produces a smooth swelling over the erupting tooth, which may be either the colour of normal gingiva or blue (Fig. 5.1). It is usually painless unless infected and is soft and fluctuant.

Sometimes more than one cyst may be present, and Ramon Boj and Garcia-Godoy (2000) have reported a case of a 15 month old child with six eruption cysts that had developed concurrently. There is often a brief history of about 3–4 weeks' duration during which they enlarge to approximately 1–1.5 cm. They are usually exposed to masticatory trauma. Transillumination is a useful diagnostic aid in distinguishing an eruption cyst from an eruption haematoma (Seward, 1973).

Radiological features

The cyst may throw a soft-tissue shadow, but there is usually no bone involvement except that the dilated and open crypt may be seen on the radiograph.

Pathogenesis

The pathogenesis of the eruption cyst is probably very similar to that of the dentigerous cyst. The difference is

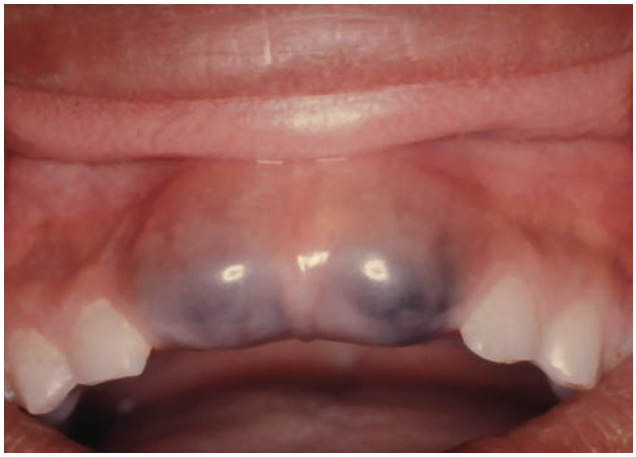


Fig. 5.1 Eruption cysts involving the maxillary permanent incisors.

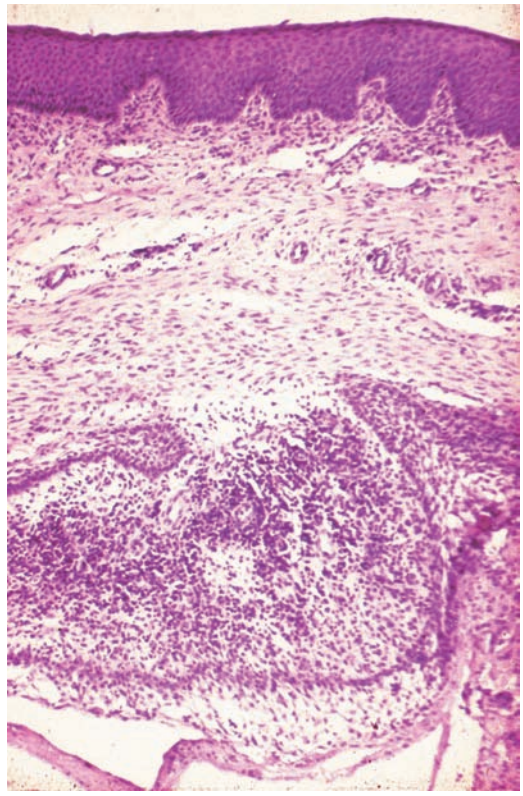


Fig. 5.2 Histological features of an eruption cyst. The surface epithelium is at the top and the cyst lining at the bottom of the photomicrograph. The intense chronic inflammatory cell infiltrate is a response to masticatory trauma.

that the tooth in the case of the eruption cyst is impeded in the soft tissues of the gingiva rather than in the bone. As Browne and Smith (1991) have argued, 'as the crown of the tooth associated with an eruption cyst usually projects into the cyst lumen, it is widely believed that the epithelium is derived from the reduced enamel epithelium, as in the dentigerous cyst'. The factors that actually impede eruption in the soft tissues are not known, but the presence of particularly dense fibrous tissue could be responsible.

Interestingly, two recent publications have demonstrated that the administation of ciclosporin may lead to the development of eruption cysts. The first article (O'Hara *et al.*, 2002) reported the development of multiple eruption cysts in neonatal dogs given oral ciclosporin concomitantly with intramuscular injections of adenoviral gene constructs, as part of an investigation of the efficacy of adenoviral-mediated gene therapy in a canine model of Duchenne muscular dystrophy. The cysts resolved within 1 month when ciclosporin administration was discontinued. In the second report (Kuczek *et al.*, 2003), eruption cysts developed in a boy treated with ciclosporin A following a heart transplant. The child was given periodontal treatment and the ciclosporin A was switched to tacrolimus, following which no further eruption cysts developed. These findings cannot impute any general aetiological role in eruption cyst formation, but are important to note as a possible side-effect when ciclosporin medication is being considered.

Pathology

As most eruption cysts are treated by marsupialisation, the pathologist usually receives part of the cyst wall. The superficial aspect is covered by the keratinised, stratified, squamous epithelium of the overlying gingiva. This is separated from the cyst by a strip of dense connective tissue of varying thickness which usually shows a mild chronic inflammatory cell infiltrate. As the cysts are so frequently exposed to masticatory trauma, the inflammatory infiltrate invariably increases in intensity towards the cyst lining, adjacent to which it is most intense. Sometimes it is possible to distinguish a line of demarcation between gingival and follicular connective tissues. The gingival connective tissue is relatively acellular and densely collagenous, and so has an eosinophilic hue. The follicular connective tissue is more densely cellular, less collagenous and has a more basophilic hue, presumably because of a higher content of sulphated glycosaminoglycans in the ground substance. Odontogenic epithelial cell rests may be present in the connective tissue.

In non-inflamed areas, the epithelial lining of the cyst is characteristically of reduced enamel epithelial origin, consisting in the main of 2–3 cell layers of squamous epithelium with a few foci where

it may be a little thicker. Invariably, however, the epithelial lining is intensely inflamed. Acute inflammatory cells are found in the epithelium which proliferates in response to the inflammatory stimulus, and may form characteristic arcades. Such epithelium is grossly spongiotic. The adjacent corium is hyperaemic and the seat of a chronic inflammatory cell infiltrate (Fig. 5.2).

Treatment

Eruption cysts are most frequently treated by marsupialisation, but in the series of 24 cases reported by Bodner *et al*. (2004), 12 were treated by marsupialisation, 10 resolved without treatment, and in two cases the involved teeth were extracted. The dome of the cyst is excised, exposing the crown of the tooth which is allowed to erupt.

6

Gingival Cyst of Adults, Lateral Periodontal Cyst, Botryoid Odontogenic Cyst

There is a great deal of confusion about the relationship between the gingival cyst of adults and the lateral periodontal cyst, much of which appears to have arisen because both types of cyst have a predilection for occurrence in the canine and premolar area of the mandible and, less frequently, in the maxilla. The pathogenesis of these cysts, particularly with regard to the cells of origin, is also far from clear. This confusion is further complicated by the fact that some cysts in the lateral periodontal position are really keratocysts (OKCs), while others are of inflammatory origin arising adjacent to an accessory root canal in the presence of a necrotic pulp, or by infection through the gingival crevice.

Bhaskar (1965) grouped the gingival and lateral periodontal cysts together as gingival cysts and considered that both arise from extra-osseous odontogenic epithelium, although 13 of his 29 cases showed circumscribed radiolucencies indicative of lateral periodontal cysts. He believed that the radiolucencies were the result of cup-shaped depressions on the periosteal surfaces of the cortical plates produced by enlargement of the gingival cysts. Wysocki *et al.* (1980) postulated, on the basis of the clinical and morphological similarities between the two cysts, that they have a common histogenesis and that they represent the intra-osseous and extra-osseous manifestations of the same lesion. Shear and Pindborg (1975) regarded them as distinct lesions, as did Buchner and Hansen (1979) who suggested, however, that they were probably of the same epithelial origin. Gregg and O'Brien (1982) compared two cases each of the adult gingival cyst and the lateral periodontal cyst. They concluded that the distinguishing clinical feature was the ability to determine the involvement of the periodontal ligament at surgical exploration; while the significant difference histologically was the presence in the lateral periodontal cysts of plaque-like thickenings of the epithelial linings. Westcott *et al.* (1984) believed that their similarities indicated a strong relationship and that the gingival cyst probably represented the extra-osseous counterpart of the intra-osseous lateral periodontal cyst.

The gingival cysts may certainly occur without bone involvement and may produce a gingival swelling, although usually they go unnoticed and most of them have been detected in the course of histological examination of large numbers of gingival biopsies (Moskow, 1966). Ritchey and Orban (1953) discovered six such cysts in 350 gingival biopsies. Occasionally, a cyst originating in the gingival soft tissues may enlarge sufficiently to produce a radiologically obvious bone erosion without producing any gingival swelling. Yet many lateral periodontal cysts are discovered on routine radiological examination in the absence of any clinical symptoms or signs (Moskow *et al.*, 1970; Gold and Sliwkowski, 1973; Fantasia, 1979). These are likely to have arisen within the periodontal ligament and eroded outwards. In the case of lesions that have produced both gingival swelling and a radiolucency, a faint shadow indicates a surface depression and hence a gingival cyst (Fig. 6.1). Where the radiolucency is dark and sharply demarcated then communication with the periodontium is indicated and the lesion is more likely to be a lateral periodontal cyst that has eroded outwards (Fig. 6.9). These assumptions, based on the radiological features, can be confirmed by surgical exploration when the lesion is being removed.

GINGIVAL CYST OF ADULTS

Clinical features

As many published studies have combined gingival and lateral periodontal cysts, meaningful clinical data have been difficult to obtain. Relatively few cases have been recorded in the archives of the Department of Oral Pathology, University of the Witwatersrand, and some publications on the subject have reported only single cases or small series. This suggests that there may, in the past, have been a lack of awareness of the lesion among clinicians, a situation that appears to be changing. Furthermore, many gingival cysts may not enlarge sufficiently to produce symptoms.

Reeve and Levy (1968) reported four cases and Buchner and Hansen (1979) published a series of 33 cases of

Fig. 6.1 Radiograph of a gingival cyst in an adult. There is a faint radiographic shadow (marked with arrows) indicative of superficial bone erosion.

gingival cyst of adults. Only soft tissue lesions of the gingiva with no bony involvement, or only superficial bone erosion on surgical exploration, were included in the latter study. Of their 33 cases, seven were found to be epidermoid cysts or OKCs on histological examination and are best excluded if a critical assessment of the gingival cyst of adults is to be performed. Wysocki *et al.* (1980) have reported another 10 examples. Nxumalo and Shear (1990, 1992) studied a series of 14 cases of their own and pooled their clinical data with those in the cases reported above. Epidermoid cysts of the gingiva and those with typical OKC linings were excluded from their investigation. Shade *et al.* (1987) reported a case of an adult patient with bilateral gingival cysts that developed concurrently; while Bell *et al.* (1997) reported eight cases and reviewed the diagnostic features and treatment of the lesion. Cairo *et al.* (2002) recorded three cases and emphasised the need for radiographic examination to differentiate these lesions from the lateral periodontal cyst. Daley *et al.* (1994) recorded 33 examples in a series of 6879 odontogenic cysts. Tolson *et al.* (1996) described the development of both a gingival cyst and a lateral periodontal cyst in the same patient.

More recently, Giunta (2002) reported a series of 22 adult gingival cysts in 21 patients observed over a period of 10 years and provided an analysis of age, gender and site of a series of 94 cases from the literature, including his own.

Frequency

In the University of the Witwatersrand material presented in this edition, only 21 of the series of 3498 cysts of the jaws (0.6%) were gingival cysts of adults (see Table 1.1). The true frequency may be higher than this as some cases are probably not submitted to the pathologist because of paucity of tissue retrieved at surgery. In the study of Buchner and Hansen (1979), the 33 cases were identified among 21 503 surgical specimens (0.15%) over an 11-year period. In the large Canadian series of 6879 odontogenic cysts accessioned over a 26-year period (Daley *et al.*, 1994), there were 33 examples (0.48%), while in Giunta's 2002 study, the percentage of these cysts in his biopsy service was 0.08% over a 10-year period. In their study of 7121 odontogenic cysts over a period of 30 years, 16 (0.2%) gingival cysts of adults were registered (Jones *et al.*, 2006).

Age

The age distribution of 69 cases including 16 of the University of the Witwatersrand material, four reported by Reeve and Levy (1968) and 26 by Buchner and Hansen (1979) is shown in Fig. 6.2. This number excludes the seven cases of Buchner and Hansen that showed the histological features of epidermoid cysts or OKCs. Drs Amos Buchner and John Giunta kindly provided the additional information. The histogram illustrated in Fig. 6.2 shows only two cases occurring before the age of 30 and a peak frequency in the sixth decade, with 72% of the patients in the fifth and sixth decades. In the series of 10 cases reported by Wysocki *et al.* (1980), the patients ranged in age from 41 to 75 with a mean of 50.7 and a median of 47 years. The review by Giunta (2002) of 94 cases, including his own sample of 22, showed that very few occurred in the first decade, while 77% were in the fourth, fifth and sixth decades. Two patients in his series were 80 years old at the time of diagnosis and the youngest documented patient was 7 years old. In the Sheffield study (Jones *et al.*, 2006) the patients ranged in age from 23 to 70, with a mean of 52.9±12.2 years.

Gender

Three of the four patients in the sample of Reeve and Levy (1968) were females and of the 26 histologically con-

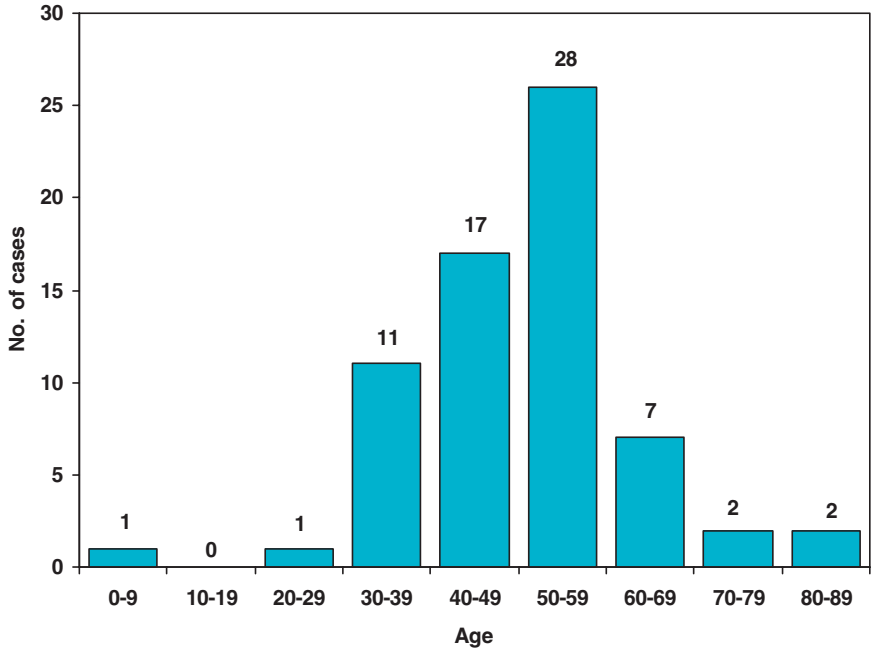


Fig. 6.2 Age distribution of 69 patients with gingival cyst of the adult.

firmed cases reported by Buchner and Hansen (1979), 17 (65%) involved females and nine (35%) were males. Five of the 10 patients in the series of Wysocki *et al.* (1980) were males, four were females and the gender of one was not known. Of 20 patients in the University of the Witwatersrand material for whom the gender was known, 11 were males and nine were females. Bell *et al.* (1997) recorded that seven of eight patients were females and only one was a male. In the study by Giunta (2002) of 21 patients with 22 cysts, 15 were females and six were males. Of the 16 patients in the study of Jones *et al.* (2006), 12 were females and four were males. The data above indicate that of the cases of 104 gingival cysts of the adult among disparate populations, there were 67 females (66.4%) and 37 males (35.6%).

Site

Gingival cysts of adults occur much more frequently in the mandible than in the maxilla, and particularly in the premolar–canine region of the mandible. Of the four cases of Reeve and Levy (1968), three were between the mandibular canine and premolar teeth, while one was between a mandibular lateral and canine. In the report of Buchner and Hansen (1979) 19 of 26 cases (73%) were in the mandible and 17 of these were adjacent to a premolar or canine. Of their seven maxillary cases, six were associated with the premolars or canines. Seven of the series of Wysocki *et al.* (1980) were in the premolar–canine–incisor area of the mandible, one in the lateral incisor area of the maxilla, and the location of two was unknown. Twelve of the University of the Witwatersrand cases involved the mandible and seven the maxilla, and most were adjacent to a premolar or canine tooth. One maxillary case was associated with a molar. Seven of the eight cases in the sample of Bell *et al.* (1997) were in the mandible, as were 16 of 18 of Giunta's own cases. In the latter's literature review, 69 of the cysts occurred in the mandible and 19 in the maxilla (Giunta, 2002).

Clinical presentation

The patient may give a history of a slowly enlarging, painless swelling. The cysts are round to oval, well-circumscribed swellings, usually less then 1 cm in diameter and may occur in the attached gingiva or the interdental papilla, invariably on the facial aspect. The surface is smooth and may be the colour of normal gingiva or bluish (Fig. 6.3). One personally observed case, however, was red clinically and on histological examination was filled with blood, presumably as a result of recent trauma. The lesions are soft and fluctuant and the adjacent teeth are usually vital. During surgical exploration, slight erosion of the surface of the bone may be observed without extension into the periodontium. Rarely, more than one gingival cyst may be found in a patient (Shade *et al.*, 1987; Giunta, 2002).

Radiological features

There may be no radiographic change or only a faint round shadow indicative of superficial bone erosion (Fig. 6.1). Of 46 cases diagnosed as gingival cysts in the study of Moskow *et al.* (1970), 19 showed radiolucencies

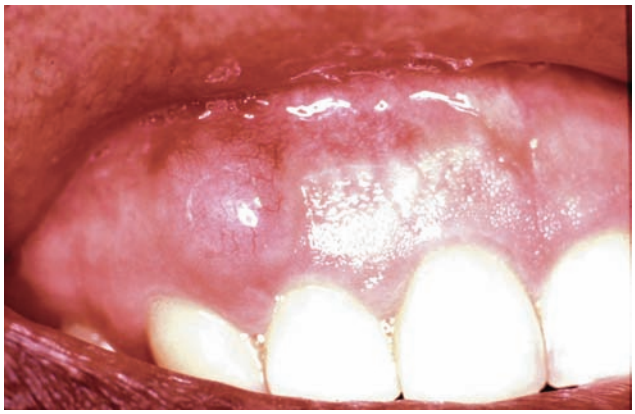


Fig. 6.3 Clinical photograph of a gingival cyst of an adult.

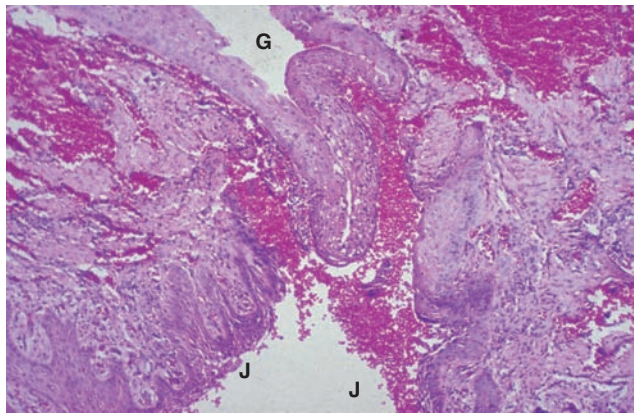


Fig. 6.4 The epithelial lining of a gingival cyst of the adult (G) lying contiguous to the junctional epithelium (J) of an adjacent tooth.

but only two of 33 cases showed this change in the report of Buchner and Hansen (1979). None of the cysts in Giunta's series showed evidence of radiolucency.

Pathogenesis

A number of suggestions have been made about the pathogenesis of the gingival cyst in adults. It was originally proposed that they may arise from odontogenic epithelial cell rests; or by traumatic implantation of surface epithelium; or by cystic degeneration of deep projections of surface epithelium (Ritchey and Orban, 1953). It has also been postulated that, very rarely, they may be derived from glandular elements (Traeger, 1961).

The most favoured theory of origin is from odontogenic epithelial cell rests derived from the dental lamina, although Shafer *et al.* (1983) felt that cysts arising from traumatic implantation of surface epithelium may occur. Reference has already been made to the frequency with which remnants of the dental lamina, many of them forming microcysts, are found in the gingiva of infants. In a study of 266 specimens of adult human gingiva, Stout *et al.* (1968) demonstrated epithelial rests in 90 and a true cyst in one. They found no evidence of traumatic implantation or heterotopic glandular tissue. Many of the epithelial remnants that they observed resembled the cell rests of Malassez.

Hodson (1962) found epithelial residues in the anterior incisor areas in 58% of 26 autopsies and in 14% of 58 edentulous third molar regions. In a number of cases, cell rests were found in the connective tissue of the gingiva without any specific relation to the surface epithelium. Unfortunately, for purposes of the present discussion, Hodson did not examine mandibular premolar regions. There is no clear explanation as to what the stimulus for the proliferation of these rests and their subsequent cystic breakdown might be, but it is certainly not an inflammatory stimulus, which produces well-recognised effects on odontogenic epithelium in radicular cysts, as described later. Wysocki *et al.* (1980), who favoured origin of these cysts from the dental lamina, have suggested that either unicystic or polycystic forms may develop depending on whether single or multiple enlarged epithelial cell rests of the dental lamina break down.

With the publication of evidence that some gingival cysts of adults were lined by epithelium similar to that seen in lateral periodontal cysts (Moskow and Weinstein, 1975; Buchner and Hansen, 1979; Wysocki *et al.*, 1980), it is necessary to try to reconcile their respective histogeneses. In material studied by Nxumalo and Shear (1990, 1992), some cases were observed in which the epithelial cyst lining extended to the deep aspect of the specimen where it lay close to, and was even possibly in continuity with, the junctional epithelium (Fig. 6.4). This same phenomenon can be seen in Fig. 1 of the paper by Buchner and Hansen (1979). This has suggested the possibility that at least some examples of gingival cyst of the adult may have arisen from junctional epithelium which in its turn is derived from reduced enamel epithelium (Schroeder, 1976). This view is reinforced by the frequent occurrence of lining epithelium in these cysts that closely resembles the reduced enamel epithelium found in dentigerous cysts (Fig. 6.5). Furthermore, the regular observation of epithelial atrophy, the tenuous attachment of the epithelium to the connective tissue wall of the cyst (Fig. 6.6), and the occasional presence of low columnar cells on the surface of the epithelium suggesting derivation from ameloblasts led to the conclusion that the epithelial lining may originate from postfunctional reduced enamel epithelium.

Of the remaining theories, origin from basal cell extensions of overlying epithelium, or from remnants of the dental lamina, or from the cell rests of Malassez are the-

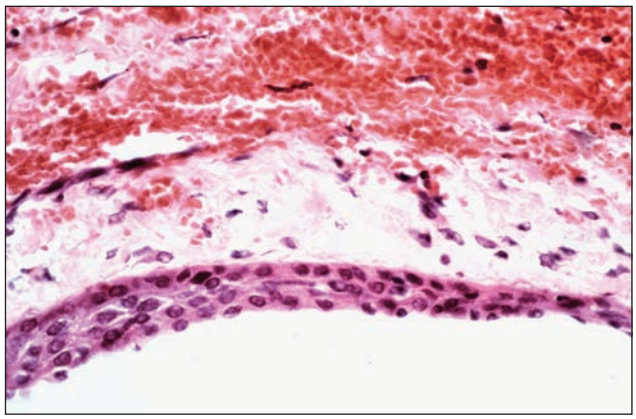


Fig. 6.5 Narrow epithelial lining of a gingival cyst of the adult. It resembles the reduced enamel epithelium found in dentigerous cysts.

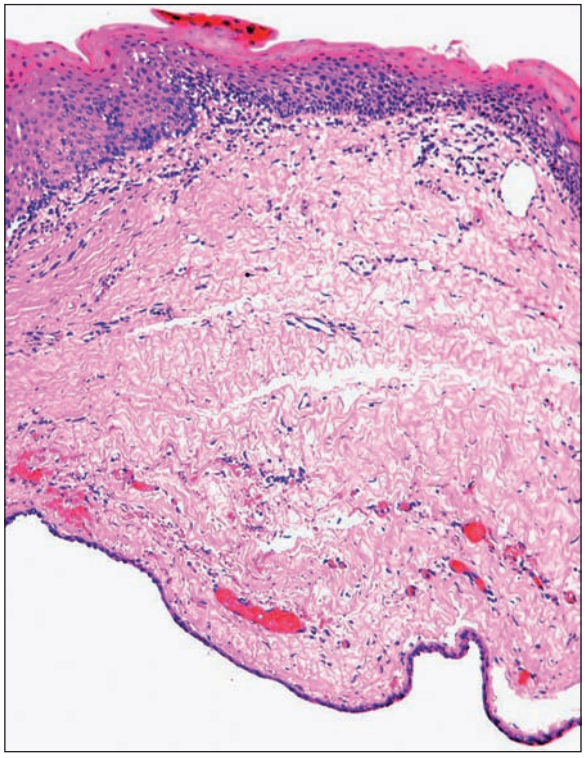


Fig. 6.6 Low-power photomicrograph of a gingival cyst of the adult, showing a very narrow epithelial cyst lining (bottom) deep to the gingival epithelium. Part of the epithelial lining has become detached. (Courtesy of Professor M. Altini and Dr S. Meer.)

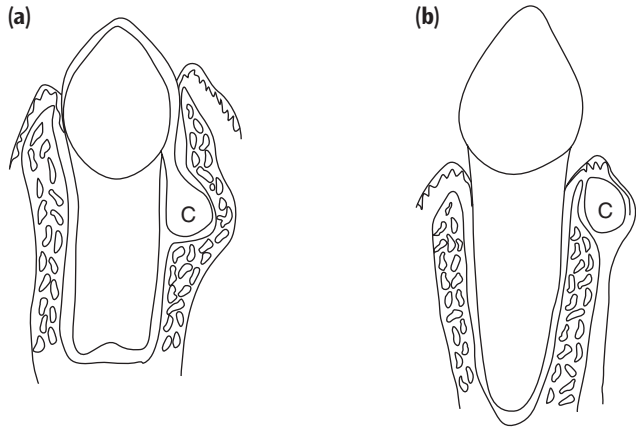


Fig. 6.7 Diagram illustrating the possible histogenesis of the developmental lateral periodontal cyst (a) and the gingival cyst of adults (b). The lateral periodontal cyst is formed from the reduced enamel epithelium by dilatation of the follicle before eruption of the tooth, whereas the gingival cyst of adults is derived from reduced enamel epithelium after eruption of the tooth.

oretical possibilities. The similarities between the gingival cyst of adults and the lateral periodontal cyst, both clinically and histologically, are impressive, as other authors have shown (Buchner and Hansen, 1979; Wysocki *et al.*, 1980). This accords with the view that what are now recognised as the typical gingival cyst of adults on the one hand, and the lateral periodontal cyst on the other, may arise from the same source. This theory postulates that the lateral periodontal cyst develops from reduced enamel epithelium before eruption of the tooth and the gingival cyst of adults from junctional epithelium (reduced enamel epithelium) after eruption of the tooth (Fig. 6.7). Origin from postfunctional epithelium, such as reduced enamel epithelium, would help to explain the unaggressive nature of the gingival cyst of adults and the lateral periodontal cyst compared with the OKC.

The multicystic form that is occasionally found in the gingival cyst of adults (Nxumalo and Shear, 1992) and more frequently in the lateral periodontal cyst, as well as the rarer botryoid form of the lateral periodontal cyst (see pp. 89–93), may arise from epithelial plaques that are pinched off from the mother cyst (see Figs 16.4 and 16.5), a suggestion first proposed by Weathers and Waldron (1973). If, however, the dental lamina theory is correct, then the satellite cysts would undoubtedly be derived from these remnants. The stimulus that leads to the development of these cysts is clearly not inflammatory, and further work at a molecular level is required in order to postulate a genetic origin.

This hypothesis refers to those gingival cysts that are lined predominantly by a thin, non-keratinised epithelium which resembles reduced enamel epithelium. The epidermoid and OKC varieties described by Buchner and Hansen (1979) have different pathogeneses. The epidermoid variety appears to be derived from cell remnants of the dental lamina that have survived into adult life and has developed in a manner similar to that of the gingival

cyst of infants. The pathogenesis of the OKC has been discussed in Chapter 3.

Histology

Gingival cysts in the adult have a variable histological pattern. They are usually small. Some have an extremely thin epithelium, closely resembling reduced enamel epithelium, with 1–3 layers of flat to cuboidal cells containing darkly staining nuclei. In others, the epithelial lining may be of a rather thicker, stratified, squamous nature without rete ridges (Figs 6.5 and 6.6). Many of the epithelial cells have pyknotic nuclei and show perinuclear cytoplasmic vacuolation. Others are atrophic and only 'ghost' outlines remain. Localised areas of thicker epithelium may occur in some cysts and are not the same as those found in the lateral periodontal cyst (Shear and Pindborg, 1975; Altini and Shear, 1992) (see pp. 88–89).

Nevertheless, there are similarities that have led to the commonly held view that the two cysts originate from the same epithelium (Buchner and Hansen, 1979; Wysocki *et al*., 1980).

The attachment of the epithelium to the underlying connective tissue is tenuous and easily peels off, leaving epithelial discontinuities. Occasionally, low columnar cells have been observed on the surface of the epithelium, suggesting origin from ameloblasts and reinforcing the impression that the lining may be derived from reduced enamel epithelium. In a number of instances, the epithelial lining could be traced to, or close to, the junctional epithelium in serial sections (Fig. 6.4).

The fibrous connective tissue wall is usually relatively uninflamed except close to the junctional epithelium where a chronic inflammatory cell infiltrate may occur; and rarely may contain small epithelial islands. The lesion is usually unicystic, but occasional multicystic variants are encountered. We found only one such example in our series of 21 cases.

The histological variant described by Buchner and Hansen (1979), in which the cyst is lined by a keratinised stratified squamous epithelium and the lumen contains keratin, closely resembles the gingival cyst of infants histologically. It appears to be of dental lamina origin and to have followed a similar histogenesis. Two other specimens in their series were lined by epithelium identical to OKC epithelium and should be diagnosed as such despite having an apparently classical gingival cyst picture clinically.

Treatment

The gingival cyst is removed by local surgical excision and in the majority of cases there is no tendency for recurrence. However, caution must be observed if the pathologist reports a multicystic or botryoid variety of cyst. This may signal that one is dealing with a lateral periodontal rather than an adult gingival cyst. This is referred to again later in this chapter.

LATERAL PERIODONTAL CYST

The designation 'lateral periodontal cyst' is confined to those cysts that occur in the lateral periodontal position and in which an inflammatory aetiology and a diagnosis of collateral OKC have been excluded on clinical and histological grounds (Shear and Pindborg, 1975). Many publications on the subject have not distinguished between the lateral periodontal cyst and the gingival cyst of adults. Others have pooled data relating to the lateral periodontal cyst with cysts in that position of inflammatory origin and with collateral OKCs (Fantasia, 1979; Eliasson *et al*., 1989). The first five well-documented cases were reported by Standish and Shafer (1958). Most of the publications on the subject, since the previous edition, have been case reports and there is still no consensus on the pathogenesis of the lesion. A comprehensive list of pre-1990 case reports was documented by Angelopoulou and Angelopoulos (1990).

Clinical features

Frequency

Twenty-four cases of lateral periodontal cyst have been registered in the University of the Witwatersrand Department of Oral Pathology over a 46-year period 1958–2004, representing 0.7% of the 3496 cysts of the jaws seen during that period (see Table 1.1). Of some significance, however, is the fact these were recorded during the 31-year period 1973–2004, indicating that prior to this a number of cases probably went unrecognised.

Age

The ages of 21 of the University of the Witwatersrand series of 24 patients ranged from 19 to 71 years. All but two of these patients were in the 40–71 age group. In the series of 39 cases studied by Wysocki *et al*. (1980), the patients ranged in age from 22 to 85 years with a mean of 50.0 and a median of 53 years. In the sample of 37 cases reported by Cohen *et al*. (1984), the ages of the patients ranged from 21 to 82 years with a mean of 54 years. There was a prominent peak distribution in the sixth decade. Rasmusson *et al*. (1991) included 32 examples in 31 patients in their study. Their patients ranged in

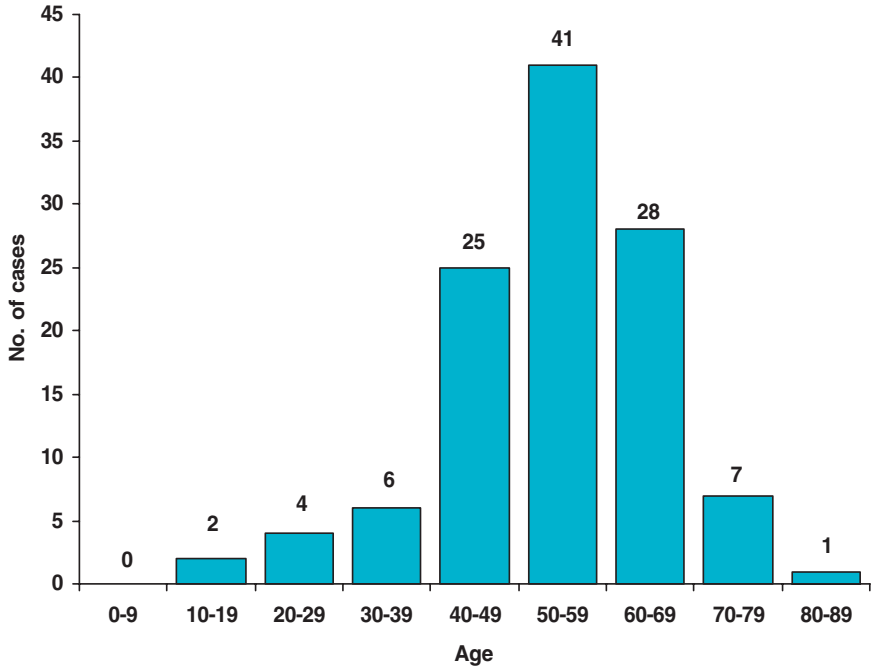


Fig. 6.8 Age distribution of 114 patients with developmental lateral periodontal cysts.

age from 26 to 77 with a mean of 55 years and a peak in the sixth decade. Carter *et al.* (1996) published a comprehensive analysis of 23 cases in patients who ranged in age from 14 to 78 years. Of the 28 cases in the study by Jones *et al.* (2006), the patients ranged in age from 21 to 81, with a mean of 48.2±14.3 years.

The age distribution of 114 patients, including the 24 from the University of the Witwatersrand series, pooled with those of Cohen *et al.*, Rasmusson *et al.* and Carter *et al.*, is shown in Fig. 6.8.

Gender

Wysocki *et al.* observed a preponderance of 26 males to 11 females. There was an equal gender distribution in the sample reported by Cohen *et al.* (1984) and of 24 University of the Witwatersrand patients, 12 were males and 12 were females. There was also an equal gender distribution noted in the study by Carter *et al.* (1996): 12 females and 13 males, but they noted that the cysts in their series occurred at a significantly younger age in the females (mean 40.5 years) than in the males (mean 58.4 years). Rasmusson *et al.* (1991) found 22 lesions in males (69%) and 10 in females (31%) and in the recent study by Jones *et al.* (2006), 16 (57%) were males and 12 (43%) were females. No definite conclusion can be reached on any gender bias from these variable data.

Site

The most frequent location of lateral periodontal cysts reported in the literature is the mandibular premolar area, followed by the anterior region of the maxilla. In the study by Wysocki *et al.* (1980), 26 of the 39 cases (67%) occurred in the premolar–canine–incisor region of the mandible and seven of these were located between the first and second premolars. In Fantasia's (1979) series, all 12 cases that fulfilled the criteria for diagnosis as developmental lateral periodontal cysts occurred adjacent to the premolar or canine teeth of the mandible. In the study of Cohen *et al.* (1984), 78% of cases occurred in the mandible, all of which were anterior to the first permanent molar and most were between the premolars. In the sample of Rasmusson *et al.* (1991), 28 of the cysts (88%) were found in the mandible and four in the maxilla (12%). All were in the premolar–cuspid–incisor area. Carter *et al.* (1996) found that 21 of 24 cases occurred in the mandible (88%) and three in the maxilla. Nineteen occurred in the premolar region and five in the anterior region. In the University of the Witwatersrand material, a higher proportion occurred in the maxilla. Ten of 24 cases (42%) were found in the maxilla and 14 (58%) in the mandible, all of which were clustered anterior to the first premolar teeth.

Clinical presentation

Lateral periodontal cysts may be symptomless and only discovered fortuitously during routine radiological examination of the teeth. Sometimes, a gingival swelling may occur on the facial aspect and it is this type of case that must be differentiated from a gingival cyst, particularly as some lesions are described as blue fluctuant swellings. Pain was a symptom in a number of the University of the

Witwatersrand cases and in those of Cohen *et al*. (1984), as was tenderness on palpation (Eliasson *et al*., 1989). One of the University of the Witwatersrand cases produced a swelling 3 cm in diameter which was depicted as 'springy with egg shell crackling' while another was described as having a gelatinous feel. The associated teeth will be vital unless they happen to have been otherwise involved. In the study of Carter *et al*. (1996), the presence or absence of symptoms was mentioned in 15 of the 25 cases, and six of these patients reported either pain or periodic swelling with drainage. Four of their cases exhibited cortical expansion and one of these perforated the buccal cortex.

Radiological features

Altini and Shear (1992) reported that radiographs of the lateral periodontal cyst showed a round or oval well-circumscribed radiolucent area, usually with a sclerotic margin. The cysts lay somewhere between the apex and the cervical margin of the tooth (Fig. 6.9). Resorption of the adjacent root has not been reported. Most of them are less than 1 cm in diameter except the botryoid variety which may be larger and multilocular and may extend into the periapical areas (Kaugars, 1986; Greer and Johnson, 1988; Altini and Shear, 1992). Rasmusson *et al*. (1991) provided some useful data about the sizes of the lesions in their sample. At the time of treatment, they ranged from 2.5 to 15 mm in diameter but most were in the range 3–7 mm. In only four cysts did the diameter exceed 10 mm. In some of their cases, radiographs from previous examinations were available. The longest follow-up was 14 years during which the diameter of the cyst increased from 9 to 17 mm. From the four cysts in which such data were available, they estimated that the mean growth was 0.7 mm per year.

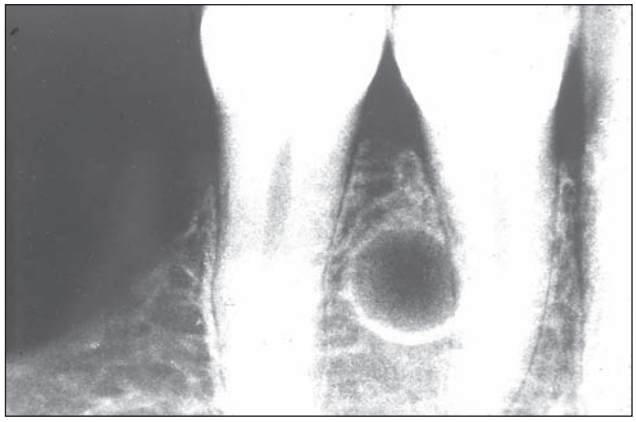


Fig. 6.9 Radiograph of a lateral periodontal cyst lying between the mandibular premolar teeth. The margins are well corticated, indicative of slow enlargement. (Courtesy of the late Professor J.J. Pindborg.)

The collateral variety of OKC may have a very similar radiological appearance and the distinction may not be made until the histological examination (Altini and Shear, 1992).

Pathogenesis

Standish and Shafer (1958) commented that the lateral periodontal cyst was of varied aetiology but that the term 'lateral periodontal cyst' should be used to indicate all cysts developing in the anatomical region of the lateral periodontium. In view of this varied aetiology, they suggested that the term should be qualified to indicate whether the cyst's origin was pulp infection, infection through the gingival crevice or idiopathic stimulation of cell rests. It is now widely accepted that the term 'lateral periodontal cyst' should be confined to cysts in the lateral periodontal position in which an inflammatory aetiology and a diagnosis of gingival cyst of the adult and collateral keratocyst have been excluded on clinical and histological grounds (Shear and Pindborg, 1975; Wysocki *et al*., 1980; Cohen *et al*., 1984; Altini and Shear, 1992).

Although there can be little doubt that lateral periodontal cysts are of odontogenic origin, there is, as with many other odontogenic lesions, considerable debate about which odontogenic epithelium they arise from. Proof of origin from any particular source is lacking and any hypotheses must therefore be based on presumptive evidence. Histological studies show that they are usually devoid of inflammatory cell infiltration except at a distance from the lining and it is reasonable therefore to regard them as being of developmental origin.

Assuming then that the lateral periodontal cyst is a distinct entity of developmental odontogenic origin, from which epithelium does it arise? There seem to be three possibilities: reduced enamel epithelium; remnants of dental lamina; and cell rests of Malassez. As will be seen from a description of the histological features, the cyst is lined for the most part by a narrow non-keratinised epithelium which resembles reduced enamel epithelium. As such, the proposal that it arises initially as a dentigerous cyst developing by expansion of the follicle along the lateral surface of the crown (Shafer *et al*., 1983) is an attractive, albeit not a definitive one. Figure 4.7 is a radiograph of such a phenomenon, which is usually referred to as a lateral dentigerous cyst. If tooth eruption is normal, the expanded follicle may finally lie on the lateral aspect of the root, as illustrated diagrammatically in Fig. 6.10.

This hypothesis is supported by the fact that lateral periodontal cysts tend to occur in areas where dentigerous cysts are likely to be associated with vertically

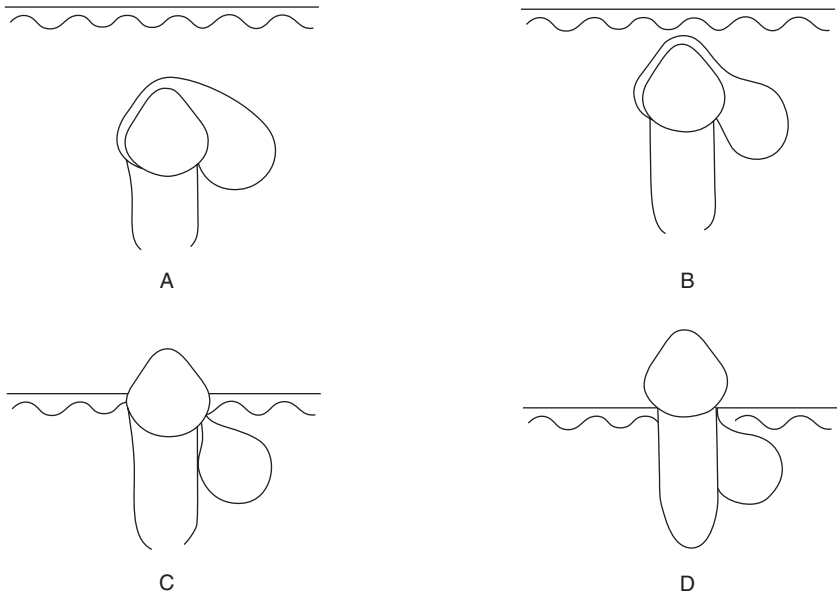


Fig. 6.10 Diagram illustrating the possible pathogenesis of the lateral periodontal cyst. (a) There is expansion of the follicle on the lateral surface of the crown of the unerupted tooth. At this stage a radiograph would show what appeared to be a lateral dentigerous cyst. (b–d) The tooth erupts leaving the expanded follicle behind. (Previously published in *Scand J Dent Res*, 1975, **83** 103–10, and reproduced in earlier editions of this book by courtesy of the editor at the time.)

impacted teeth such as mandibular premolars and maxillary incisors and canines. In this respect it is of interest that epithelial plaques similar to those seen in the lateral periodontal cyst are occasionally found in dentigerous cysts.

It seems also not unreasonable to postulate that it requires only a limited focus of separation of reduced enamel epithelium from a surface of an unerupted tooth to trigger the formation of a microcyst that may, subsequent to the eruption of the tooth, remain in the periodontium in the same way as suggested in Fig. 6.10.

Wysocki *et al.* (1980) have proposed that the lateral periodontal cyst, like the gingival cyst of adults, arises from clear cell rests of dental lamina. They suggested that unicystic forms arise through cystic change in a single dental lamina rest and polycystic lesions develop if concomitant changes occur in several adjacent cell rests. They postulated that the limited growth potential of the lateral periodontal cyst compared with the OKC, which is also of dental lamina origin, is that the former arises from postfunctional cells of the dental lamina whereas the latter presumably arises from that part of the dental lamina still possessing marked growth potential. In support of their hypothesis, Wysocki *et al.* placed much emphasis on the fact that glycogen-containing clear cell rests of the dental lamina may sometimes be demonstrated, and that similar cells also occur in parts of the lining of lateral periodontal cysts, as well as in the epithelial plaques which are a feature of their linings. They also pointed to the occasional presence of glycogen-rich clear cell rests of what they interpreted as dental lamina remnants in the walls of the cysts.

As is pointed out later in this chapter, the epithelial plaques are not comprised of clear cells *de novo*, but start rather as fusiform cells with scanty cytoplasm arising by localised proliferation of basal cells. It has also been suggested, in the discussion of the pathogenesis of the gingival cyst of adults, that what were described by Wysocki *et al.* as rests of dental lamina in these cyst walls, may in fact be 'pinched-off' epithelial plaques. However, there is no dispute with Wysocki *et al.* (1980) on the view that the lateral periodontal cyst and the gingival cyst of adults have a common ancestry and the argument on this point has been pursued earlier in this chapter.

The third possibility suggested is origin from the cell rests of Malassez. The rests of Malassez occur in the periodontium and they are well positioned for a lateral periodontal cyst but the support for this theory of origin is scanty. Buckley *et al.* (1989) reported a case in which two separate developmental odontogenic cysts were associated with an unerupted lower third molar tooth. Radiological and histological examination showed that these were a lateral periodontal cyst and a dentigerous cyst. The authors contended that this provided evidence that the periodontal cyst may have an origin from the cell rests of Malassez. This view has been supported by Bascones and Llanes (2005) on the basis of finding several apparently inactive epithelial nests composed of clear cells in a periapical lesion.

Altini and Shear (1992) have made the point that the lateral periodontal cyst occurs predominantly in the fifth and sixth decades, particularly the sixth, and hence is probably a slowly developing and growing lesion. If the postulate is correct that the reduced enamel epithelium from which the cyst appears to develop is derived from a portion of the covering of the tooth crown, this epithelium must lie dormant for many decades before the cyst manifests. They suggested therefore that the development of the lateral periodontal cysts, particular the multicystic and botryoid varieties, may be stimulated by some genetic

factor, as are some other jaw cysts, later in life. The formation of the epithelial plaques, their budding off to form epithelial islands which in turn become cystic and the repetition of this process through numbers of generations, are indicative of an active process of proliferation of the odontogenic epithelium in their genesis.

Histology

Most commonly, the lateral periodontal cysts were lined by a thin, non-keratinising layer of squamous or cuboidal epithelium usually ranging from 1 to 5 cell layers wide, which resembled the reduced enamel epithelium (Fig. 6.11). The epithelial cells were sometimes separated by intercellular fluid. Their nuclei were small and pyknotic.

Wysocki *et al.* (1980) also described the occasional presence of conspicuous, sometimes numerous, glycogen-rich clear cells in the epithelial linings. In their study of 20 cases, Altini and Shear (1992) confirmed the presence of glycogen in about two-thirds of them, either in the lining epithelium or in the plaques, or both. It was not found exclusively in the clear cells, many of which showed no positivity, but also occurred in the superficial layers of the squamous and cuboidal cells of the lining epithelium.

Sometimes the epithelial lining was of a more distinctly stratified nature, but when the characteristic features of an OKC are observed this should be the diagnosis rather than lateral periodontal cyst. Indeed, Gold and Sliwkowski (1973) have shown in their study that such collateral OKCs have, as one would expect, a definite tendency to recur following surgical removal.

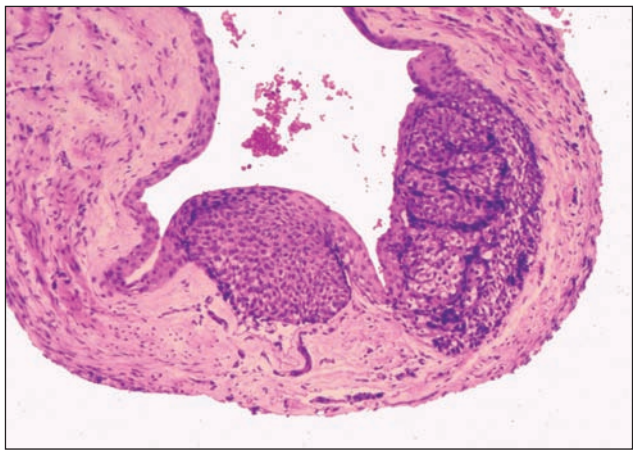


Fig. 6.11 Lateral periodontal cyst which in part has a thin, non-keratinised stratified squamous epithelial lining resembling reduced enamel epithelium. Two epithelial plaques are seen. The one on the right is convoluted as in stage (f) in Fig. 6.12. (Previously published in *Scand J Dent Res*, 1975, **83**, 103–10, and reproduced in earlier editions of this book by courtesy of the editor at the time.)

An interesting feature seen in many of the lateral periodontal cysts was the presence of what appear to be localised plaques or thickenings of the epithelial lining (Figs 6.11 and 6.12). Some of these were small whereas others were larger and extended into the surrounding cyst wall and also produced mural bulges which protruded into the cyst cavity. Some cysts contained a number of these plaques. The cells of the plaque were sometimes fusiform with their long axes parallel to the basement membrane; frequently they were large and clear, with small pyknotic nuclei. Wysocki *et al.* (1980) have shown that these also contain glycogen.

Examination of histological material at the light microscope level, and particularly study of serial sections, indicates the possible mode of formation of these plaques (Shear and Pindborg, 1975). The usual sequence (Fig. 6.12) is that there appears to be proliferation of the flat basal cells which produces a slight localised thickening of the epithelium.

At this stage, the thickened epithelium consists predominantly of darkly staining fusiform basal cells. This early plaque may extend into the fibrous wall of the cyst or bulge into the lumen. The plaque increases in size both by further basal cell proliferation and by swelling of these epithelial cells. At this stage there is a more pronounced bulging into the lumen and also into the wall. The bulbous nature of the thickening into the wall sometimes leads to undermining of the adjacent cyst lining. Complex convolutions of the epithelium may be seen in the larger plaques. Occasionally, the cells of the plaque may differentiate and take on a distinctly spinous appearance.

What produces these localised epithelial proliferations is not known. However, they do seem to be a spontaneous process which tend to occur in reduced enamel epithelium and probably also in other lesions of odontogenic epithelium. It is possible that the thickenings represent another of the many examples of odontogenic epithelium recapitulating ontogeny under pathological conditions. In this instance, the process seems to be similar to that which takes place during the early stages of tooth development, when there is thickening of stomadeal ectoderm to form the dental lamina.

A detailed description of the histopathology of 20 cases was reported by Altini and Shear (1992). They pointed out that in their study of 20 cases, two groups were recognised. Nine lesions were unicystic and 11 were multicystic. Six of the multicytic group comprised two or more cystic spaces contained within a single round or ovoid fibrous capsule; whereas five were larger and less regular. The latter had a distinctly botryoid appearance, consisting of several cystic spaces of varying size, separated by fibrous tissue (Figs 6.13 and 6.14). Most of the lesions were small, varying from 5 to 15 mm in diameter, whereas the botryoid variety were substantially larger, one of the cases having measured 50 mm.

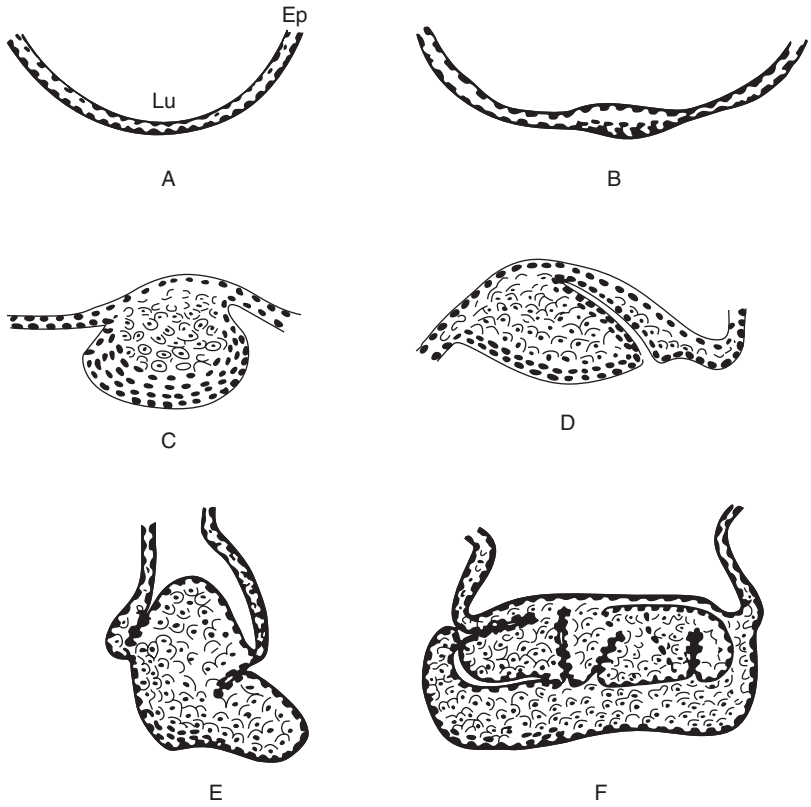


Fig. 6.12 Diagram illustrating the possible mode of formation of epithelial plaques by localised proliferation of cells. (a) Cyst lined by thin epithelium resembling reduced enamel epithelium. (b) Early epithelial thickening by basal cell proliferation. (c) Basal cells continue to proliferate. Superficial cells swell by accumulation of intracellular fluid. (d) and (e) Basal proliferation ceases or slows down. Superficial cells are waterlogged and swollen. Plaque protrudes into cyst cavity and cyst wall where it can undermine and raise adjacent cyst lining. (f) Epithelial plaque can form convolutions. Protrusions into cyst wall as in (c–f) may be 'pinched off' and develop into daughter cysts, leading to the formation of the botryoid variety of lateral periodontal cyst.

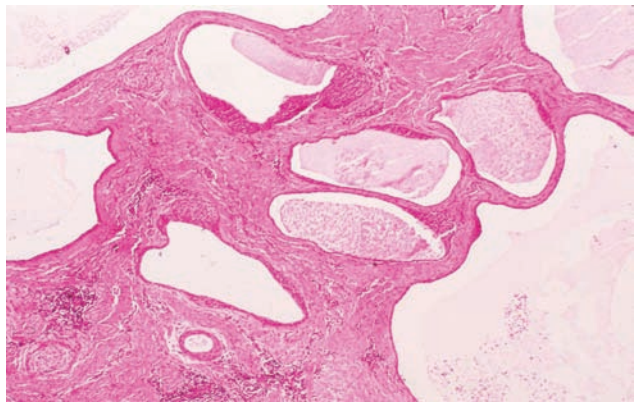


Fig. 6.13 Botryoid odontogenic cyst developing from a lateral periodontal cyst. There are numerous daughter microcysts, many of which also show epithelial plaques. These plaques may be 'pinched off' to form granddaughter cysts.

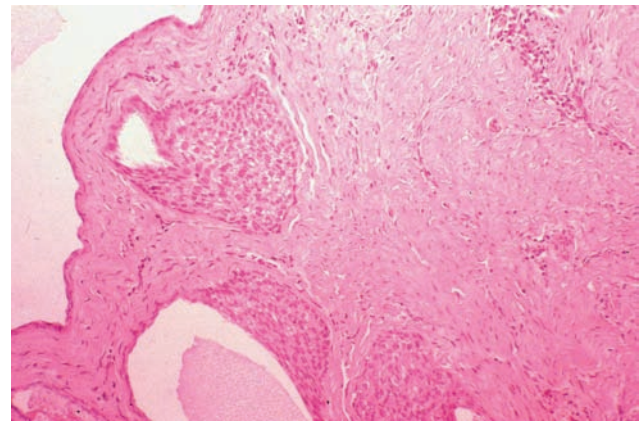


Fig. 6.14 'Pinched off' plaques forming further microcysts.

While the unicystic and multicystic varieties share similar histological features, the botryoid type may occasionally show somewhat different characteristics and these will be described in a separate section later in this chapter. All varieties of lateral periodontal cyst may have small epithelial nests or follicles in the fibrous wall. These are often closely associated with the epithelial plaques and there is some histological evidence to suggest that they may arise from them (Fig. 6.15). These nests may in turn enlarge and be the source of further microcysts. The epithelial linings may be tenuous and separate to differing degrees from the fibrous cyst wall and there are occasional areas of juxta-epithelial hyalinised collagen. The fibrous cyst wall shows a variable chronic inflammatory cell infiltrate but is usually remarkably free of inflammation.

In a histochemical study on the linings of their sample, Rasmusson *et al.* (1991) demonstrated positive reactions for $NADH_2$ and $NADPH_2$-diaphorase, glutamate dehydrogenase and lactate dehydrogenase in the epithelium,

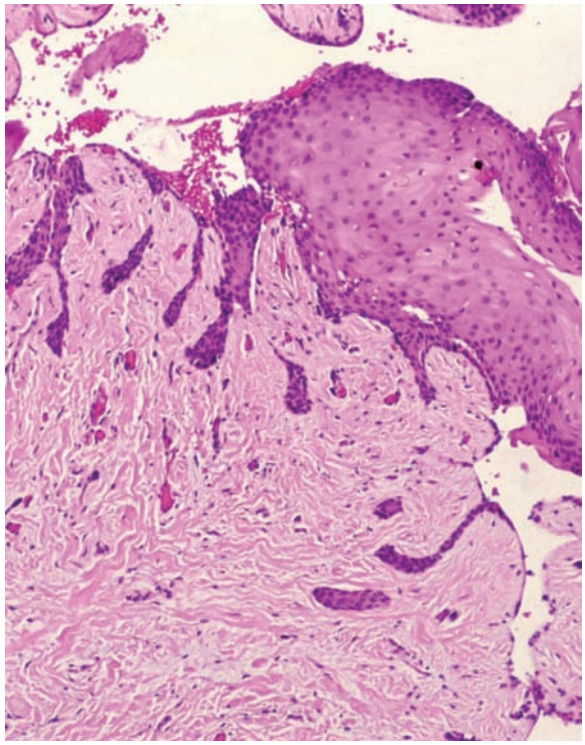


Fig. 6.15 Part of the wall of a lateral periodontal cyst showing multiple epithelial extensions 'raining down' from the cyst lining.

while the reactions for acid and alkaline phosphatase were very weak. They observed the same reactions in the epithelial islands in the cyst walls. They pointed out that these reactions differed from those in OKCs, which exhibited high levels of acid phosphatase activity in the epithelium.

Grand and Marwah (1964) and Buchner *et al.* (1996) have each reported a case of lateral periodontal cyst in the epithelial lining of which were melanin-containing cells. In the latter paper, the lesions were also examined ultrastructurally. The epithelial cells contained mature (stage IV) melanosomes, and macrophages containing aggregates of melanosomes were identified in the fibrous cyst wall. The authors suggested that ethnic pigmentation had a role in this and other odontogenic lesions in which melanin pigment had been identified. One of the cases in the University of the Witwatersrand sample also showed melanin pigmentation.

Gold and Christ (1970) have described what they referred to as a granular-cell odontogenic cyst which had the clinical and radiological features of a lateral periodontal cyst. Histologically, the epithelial lining cells had undergone extensive granular cell change, as had some of the odontogenic epithelial islands in the cyst wall. They commented on the similarity between these cells and those found in the granular-cell ameloblasoma. Buchner (1973) reported another example of a granular-cell odontogenic cyst and his specimen had features that suggested the diagnosis of unicystic granular-cell ameloblastoma. The case of Gold and Christ recurred 18 years later as a follicular ameloblastoma, with no histological evidence of granular cells (Abaza *et al.*, 1989), and the latter authors concluded that the original lesion was probably a unicystic granular-cell ameloblastoma.

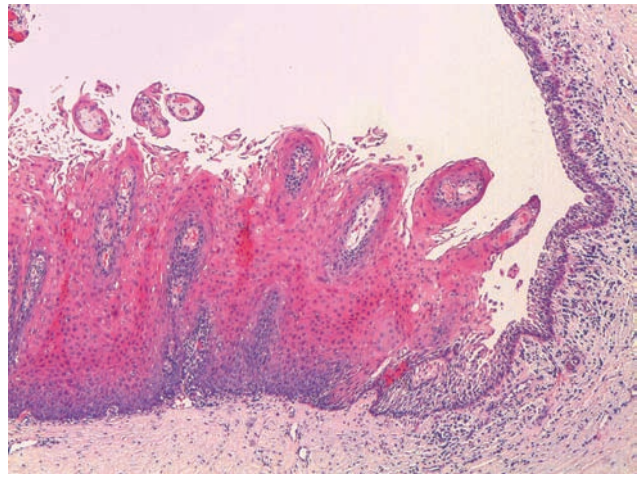


Fig. 6.16 Photomicrograph of this unusual odontogenic cyst showing transition of the epithelial lining to a verrucous hyperplasia, with no infiltration into the fibrous wall of the cyst.

Recently, there has been a case in a 13 year old girl, reported as an odontogenic cyst with verrucous proliferation, that radiologically and histologically showed features suggestive of origin from a developmental lateral periodontal cyst (Aldred *et al.*, 2002). Microscopically, part of the lining comprised a thin layer of stratified squamous epithelium resembling reduced enamel epithelium undergoing a mild degree of hyperplasia in some areas. Elsewhere, the cyst was lined by markedly hyperplastic stratified squamous epithelium that was thrown up into a series of verrucous projections shedding keratin into the lumen (Fig. 6.16). The microscopic resemblance to a verrucous hyperplasia of the oral mucosa was remarkable. Although the presence of hypergranulosis and cells resembling koilocytes suggested the possiblity of human papillomavirus (HPV) involvement, this was not supported by immunocytochemical staining and polymerase chain reaction (PCR) amplification for viral DNA.

Enriquez *et al.* (1980) and Pomatto *et al.* (2001) have reported the occurrence of verrucous carcinoma arising from odontogenic cysts. The verrucous projections in the case of Aldred *et al.* (2002) were superficial to the surrounding epithelium and did not invade the deeper tissues; there was no evidence of any residual or recurrent pathology at the site of the cyst. Although tempted

to name the lesion a 'verrucous odontogenic cyst', the authors indicated that it might be appropriate that this should await the documentation of further similar cases.

Treatment

Provided that the lesion is unilocular on radiological examination, the lateral periodontal cyst is treated by surgical enucleation. Attempts should be made to avoid sacrificing the associated tooth, but this may not always be possible. A number of reports have been published that indicate that the botryoid variety has a predilection for recurrence, and this feature is dealt with in the next section of this chapter. It is not yet clear from the literature whether the encapsulated multicystic lateral periodontal cyst has the same tendency to recur following simple enucleation. Eight of 10 recurrent cases reported by Greer and Johnson (1988) were unilocular radiologically but multicystic histologically. Until we have further information about the behaviour of the encapsulated multilocular variety, clinicians are advised to follow these cases for a number of years.

BOTRYOID ODONTOGENIC CYST

In the previous section of this chapter frequent reference has been made to the 'botryoid variety' of the lateral periodontal cyst. Essentially, this is a cystic lesion with clinical and radiological features of a lateral periodontal cyst, but which shows macroscopic and microscopic features of a botryoid dontogenic cyst. Van der Waal (1992) has argued that 'if one defines a lateral periodontal cyst as (one) that occurs in the lateral periodontal position it becomes difficult to accept the botryoid odontogenic cyst as a variant of the lateral periodontal cyst when the lesion is extending well beyond the lateral area of a tooth.' He suggested that the term 'botryoid odontogenic cyst' should be abandoned.

This begs the question: is the lesion referred to as a 'botryoid odontogenic cyst' merely a botryoid variety of a lateral periodontal cyst, or is it an entity with a tendency to recurrence if not completely removed at operation? The evidence is that it is a variant of lateral odontogenic cyst, but that the term 'botryoid odontogenic cyst' should be retained because of the tendency of this variant to recur if inadequately removed. Even small lateral periodontal cysts may be bicystic or polycystic, and with further growth can take on a botryoid (grape-like) appearance (Altini and Shear, 1992). As concluded by Machado de Sousa *et al*. (1990) and Ramer and Valauri (2005), it is important to separate the two lesions because the multicystic nature of the botryoid odontogenic cyst makes the lesion more expansive and increases the possibility of recurrence when surgical curettage is inadequate.

It was Weathers and Waldron (1973) who first suggested the term. They reported two examples of a multilocular cystic lesion of the jaws for which they proposed the term 'botryoid odontogenic cyst' because the gross specimen resembled a cluster of grapes. Some years elapsed after the publication of the article by Weathers and Waldron before any further papers appeared on this variety of lateral periodontal cyst. Since their original description, botryoid odontogenic cysts have been widely regarded as variants of the lateral periodontal cyst and publications on the subject have not distinguished them from the multicystic lateral periodontal cysts.

Clinical features

Frequency

Age

The extensive literature review published by Ramer and Valauri (2005) identified 60 cases of botryoid odontogenic cyst, including the large series of 33 cases of Gurol *et al*. (1995), to which they have added six of their own. The age distribution of these 66 patients is shown in Fig. 6.17. As with the lateral periodontal cysts, most of the patients were in their fifth, sixth and seventh decades at diagnosis.

Site

Of the three cases reported by Kaugars (1986), one occurred in the midline of the mandible, one between the mandibular premolars and one in an edentulous mandible. Eight of the 10 lesions documented by Greer and Johnston (1988) involved the mandible, predominantly the anterior region. In the review paper by Ramer and Valauri (2005), nine of 65 cases (14%) were located in the maxilla, while 56 (86%) occurred in the mandible. All but one of this series were intra-osseous and the one extra-osseous case involved the gingiva. Eleven cases involved the mandible bilaterally.

Clinical presentation

Gurol *et al*. (1995) listed the presenting symptoms of their 33 patients. Eight were asymptomatic, while 13 had developed swellings. Two complained of pain, one experienced paraesthesia and two reported that there had been drainage. There was no record of symptomatology for eight patients. The more recent review of Ramer and Valauri (2005) that included the data of Gurol *et al*. and their own six cases, comprised 59 cases with information as to clinical presentation. Thirty-eight had symptoms or signs and 21 not. These were swellings (30), paraesthesia

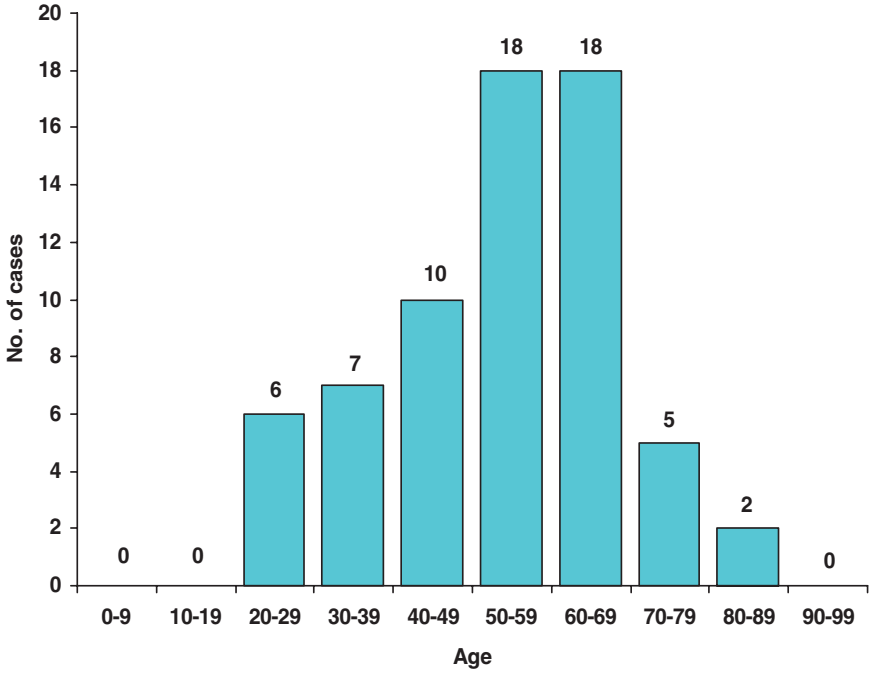


Fig. 6.17 Age distribution of 66 patients with botyroid odontogenic cysts.

(2), pain (3) and discharge (2). In one, the positive responses were ill-defined. There were five reports of positive vitality responses of involved teeth.

Two of the lesions reported by Kaugars (1986) enucleated easily. All showed the same histological features, as described below. They suggested that a lesion that was radiologically or histologically multilocular would have an increased risk of recurrence or persistence and recommended that patients treated for a botryoid odontogenic cyst should be followed periodically. Three of the 10 cases documented by Greer and Johnston (1988) represented recurrences, 8, 10 and 10 years, respectively, after previous surgery, and the authors supported Kaugar's concern that patients must be followed up. Follow-up information on recurrences was available for 11 cases of the 33 reported by Gurol *et al.* (1995). Two of these had recurred once and nine had not recurred: two after 12 months, one after 2 years and one after 14 years, while the follow-up periods for the other five were not specified.

Further documentation of the tendency for the botryoid odontogenic cyst to recur has been provided in papers by Phelan *et al.* (1988), Heikinheimo *et al.* (1989) and Ramer and Valauri (2005). Other papers, such as those by Machado de Sousa *et al.* (1990), Redman *et al.* (1990), Weibrich *et al.* (2000) and Öçok *et al.* (2005) reported on the large size, multilocularity or multicystic nature of botryoid odontogenic cysts they had examined.

Radiological features

All three lesions reported by Kaugars (1986) showed multilocular radiolucencies on radiological examination. Of the series of Greer and Johnston (1988), eight of 10 showed unilocular radiolucencies and two were multilocular, ranging in size from 0.4 to 4.5 cm. In the large series of 33 cases documented by Gurol *et al.* (1995), radiographs were available for 16, Of these, 15 were unilocular and only one was multilocular. Ramer and Valauri (2005) examined radiographs of six cases, and two of these were multilocular.

Altini and Shear (1992) commented that one of their botryoid cases measured 50 mm in diameter.

Pathogenesis and histopathology

Microscopically (Figs 6.13–6.15), the lesion is similar to the lateral periodontal cyst but exhibits some differences. The lesion is multicystic with thin fibrous connective tissue septa. The cyst cavities are of varying size, with the smaller ones tending to be orientated towards the larger ones. The cyst cavities are sometimes lined by a thin non-keratinised epithelium comprising, for the most part, 1–2 layers of flat cells but occasionally are lined in some areas by a somewhat thicker stratified squamous epithelium. In many of the cysts there are foci of plaque-like thickenings, most of them consisting of flat fusiform cells (Fig. 6.13). Weathers and Waldron suggested that these plaques may possibly be the source of new cyst locules, an opinion with which we concur (Fig. 6.14). Clear cells are unusual both in the lining epithelium and in the plaques. There is an increase in the nucleo-cytoplasmic ratio in much of the epithelium with resultant crowding of the cells, the nuclei of which are pyknotic.

All cases of Greer and Johnston (1988) showed the same histological features already described, and all 10 were multicystic. Light and electron microscopic comparison of the plaques with the convoluted zones seen in three adenomatoid odontogenic tumours found remarkable similarities in two of them. This observation is of interest because early adenomatoid odontogenic tumours can be shown to arise in the epithelial linings of dentigerous cysts, particularly those related to maxillary canine teeth. In view of this finding, and their opinion that the botryoid odontogenic cyst may arise from the stratum intermedium, it is surprising that Greer and Johnson rejected the possibility of origin from reduced enamel epithelium. Where does stratum intermedium go if not into reduced enamel epithelium?

In their 1992 paper, Altini and Shear described in some detail, by means of diagrams supported by photomicrographs, a hypothesis of how a unicystic lateral periodontal cyst may progress to a multicystic, yet encapsulated lesion, and then by progressive enlargement of the many microcysts, develop into an irregular thin-walled multicystic structure, which is identified now as a botryoid odontogenic cyst. It is not unusual to see epithelial cells from one or more plaques apparently budding off from the mother cyst, later apparently becoming detached and sometimes breaking down centrally to form a daughter cyst (Fig. 6.14). There is also microscopic evidence that basal cells of the mother cyst may rain down into the wall (Fig. 6.15). Unless removed intact, the lesion seems to have the potential to extend in the bone and become multilocular.

It is difficult to envisage this type of active growth occurring without some genetic influence, and work along these lines is awaited with interest.

Heikinheimo *et al.* (1989) undertook an immunocytochemical comparison of the cytokeratin expression of the cyst epithelium from their case with that of the overlying epithelium. Simple cytokeratin 18 was strongly expressed. Cytokeratin No. 19, which is a major component of odontogenic epithelia, was distinctly expressed in all epithelial cells of their cyst. The cyst lining also showed features of non-keratinising epithelia, as seen in some odontogenic cysts as well as in tooth germs.

Three of the cases of the botryoid variety reported by Altini and Shear (1992) also share some features with the glandular odontogenic cyst, in that they have epithelial crypts and superficial low columnar cells, although no mucous cells were demonstrated. This raised the question of whether the glandular odontogenic cyst formed part of the clinicopathological spectrum of the lateral periodontal cyst.

Treatment

It is clear from the numerous reports of recurrences that the botryoid odontogenic cyst requires careful excision and that attempts at conservative enucleation have not been successful. It has yet to be determined whether the smaller, apparently encapsulated multicystic variety has the same tendency to recurrence. Until there is clarification on this point, cases must be carefully followed for a number of years.

7

Glandular Odontogenic Cyst (Sialo-Odontogenic Cyst)

A cyst with fairly typical histological features, which has some characteristics in common with the lateral periodontal cyst and the botryoid odontogenic cyst, was discussed at the meeting of the International Association of Oral Pathologists in 1984, but was first documented as 'sialo-odontogenic cyst' by Padayachee and Van Wyk (1987) and then by Gardner *et al.* (1988) as 'glandular odontogenic cyst' (GOC). The latter term was used by Kramer *et al.* (1992) in the World Health Organization (WHO) *Histological Typing of Odontogenic Tumours* and this name has since been in general use in scientific publications.

The original defining article by Padayachee and Van Wyk (1987) described two cases that resembled both the botryoid odontogenic cyst and the central mucoepidermoid tumour of the jaws but, after careful analysis, they concluded that the lesions differed sufficiently to warrant separation as an entity. They indicated that the typical features of the cyst were that it was intrabony and multilocular radiologically; that it could recur if not adequately excised; and that it was multicystic, with the cystic spaces lined by a non-keratinised epithelium akin to that of reduced enamel epithelium. Epithelial thickenings or plaques were present in the cyst linings and mucous and cylindrical cells formed an integral part of the epithelial component. Mucinous material within the cystic spaces was a prominent feature.

Gardner *et al.* (1988) also believed that its histological features and biological behaviour were sufficiently distinct for it to be regarded as an entity. They reported eight cases, from which they felt that they could draw certain conclusions about its biological behaviour. It apparently occurred over a wide age range, in either jaw, and had the propensity to grow to a large size and to recur. One of their cases, however, grew very slowly and remained small. Radiologically, some of their cases showed unilocular radiolucencies with either smooth or scalloped margins, while others were distinctly multilocular. They also gave a detailed account of the histological features of their series. Among the early cases to be reported were those by Waldron and Koh (1990), who discussed it in the context of a possible relationship with the central mucoepidermoid tumour of the jaws, and Ficarra *et al.* (1990), who reported a case in which a diagnosis of low-grade mucoepidermoid carcinoma had been made. Patron *et al.* (1991) reported three new cases and summarised the data from 13 cases which indicated that three of 10 cases that had been followed up had recurred.

The lesion has evoked a considerable amount of interest in the years since these publications because of accumulating evidence of its aggressive growth potential, its frequent multilocular radiographic presentation, and its unusual but diagnostic microscopic features. Its possible relationship to the central mucoepidermoid carcinoma of the jaws has also exercised the minds of pathologists. Numerous reports of single or of relatively few cases have been published since the third edition of this book in 1992 (van Heerden *et al.*, 1992; Semba *et al.*, 1994; Economopoulou and Patrikiou, 1995; Savage *et al.*, 1996; de Sousa *et al.*, 1997; Magnusson *et al.*, 1997; Ramer *et al.*, 1997; Koppang *et al.*, 1998; Manojlović *et al.*, 1998; Chavez and Richter, 1999; Lin *et al.*, 2000; Jose *et al.*, 2000; Tosios *et al.*, 2000; Barreto *et al.*, 2001; Noffke and Raubenheimer, 2002; Ertaş *et al.*, 2003; Osny *et al.*, 2004; Pires *et al.*, 2004; Tran *et al.*, 2004; Abu-Id *et al.*, 2005; Qin *et al.*, 2005; Shen *et al.*, 2006). Many of these authors have ascribed aggressive growth or extensive bone involvement to their examples. The documentation of these cases has made it possible over the years for accumulation of data on the GOC, and pooling of material has led to reviews of increasing numbers of cases.

Ramer *et al.* (1997) reviewed 38 cases from the world literature and Koppang *et al.* (1998) extended this number to 47, including two of their own cases. The latter paper by Koppang *et al.* included a table that has meticulously documented the details of the 47 cases including age, gender, location, radiological features, initial therapy, duration of follow-up, the period between initial operation and recurrences and a column listing the reference numbers of the cases cited.

The most recent reviews at the time of writing are those by Qin *et al.* (2005), who described the clinicopathologic

features and treatment of 14 cases; Kaplan *et al.* (2005b) who reported on the treatment and recurrences of this lesion; Kaplan *et al.* (2005a) in a paper on the use of molecular markers in the diagnosis of the GOC; and Shen *et al.* (2006) who added 12 cases in China. The first of the two papers by Kaplan *et al.* analysed 56 cases, 49 from the literature and seven new cases. In the 2005a paper, the authors recorded that 71 cases, including their own, had been published in the English language literature since the first description in 1987.

High *et al.* (1996) reported five cases that had the radiological and histological features of the glandular odontogenic cyst and an aggressive growth pattern. They proposed the term 'polymorphous odontogenic cyst' for the lesion.

Clinical features

Frequency

The glandular odontogenic cyst is a rare lesion. Data from the archives of the Department of Oral Pathology of the University of the Witwatersrand for the period 1992–2004 indicated only six cases in a series of 3498 jaw cysts (0.2%) as shown in Table 1.1. This diagnosis had not been made in the previous 32 years but that does not necessarily mean, of course, that none had occurred during that period. Shen *et al.* (2006) found a similar frequency of 12 cases in a series of 7023 jaw cysts (0.17%) over a 37-year period; and Jones *et al.* (2006) listed 11 cases (0.2%) in their sample of 7121 odontogenic cysts over a 30-year period.

Age

Koppang *et al.* (1998) recorded the ages and genders of 47 patients with GOCs, including two of their own. We have added, from publications subsequent to theirs, the ages and genders, when recorded, of a further 48 cases, including six of our own (Economopoulou and Patrikiou, 1995; Savage *et al.*, 1996; Ramer *et al.*, 1997; Magnusson *et al.*, 1997; de Sousa *et al.*, 1997; Manojlović *et al.*, 1998; Chavez and Richter, 1999; Lin *et al.*, 2000; Tosios *et al.*, 2000; Barreto *et al.*, 2001; Noffke and Raubenheimer, 2002; Ertaş *et al.*, 2003; Abu-Id *et al.*, 2005; Kaplan *et al.*, 2005b; Qin *et al.*, 2005). The age distribution of the 95 patients is shown in Fig. 7.1. No cases have been reported in the first decade and only two patients were over the age of 79. There was a distinct peak frequency in the sixth decade, particularly in men. In the Sheffield review by Jones *et al.* (2006), the youngest patient in their series of 11 cases was 31 years and the oldest was 81, with a mean of 48.5±17.6.

Gender

In addition to the documented ages and genders of 95 patients with GOCs, another 17 reports recorded only the genders of patients. Of the total 112 patients, 62 were males (55.4%) and 50 were females (44.6%). These gender differences are not statistically significant. Jones *et al.* also recorded a male predilection.

Site

In addition to our six University of the Witwatersrand cases, six publications in which the locations of the GOCs

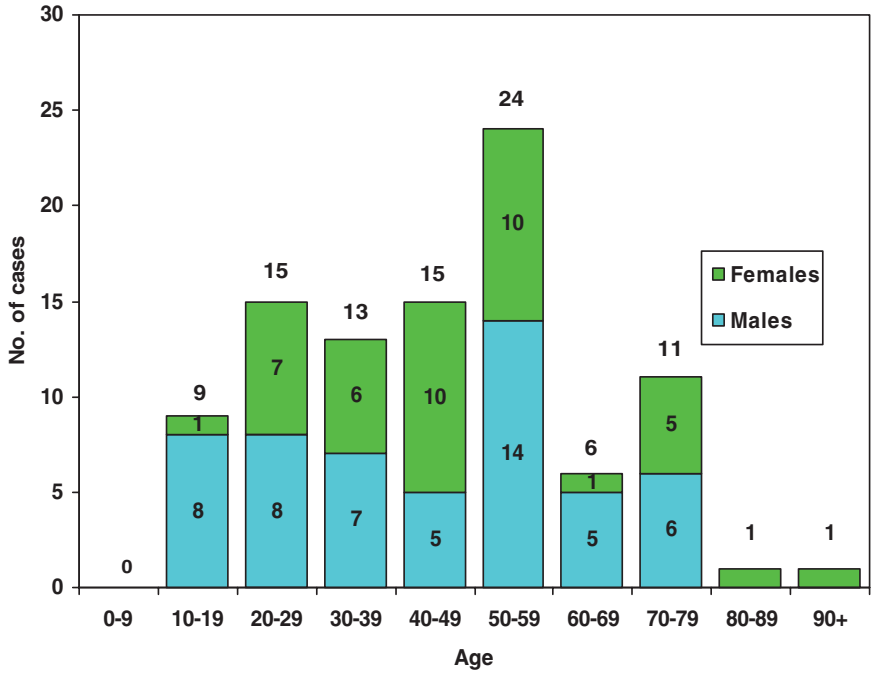


Fig. 7.1 Age distribution of 95 patients with glandular odontogenic cysts.

were reported provided appropriate details for 98 patients (Hussain *et al*., 1995; Magnusson *et al*., 1997; Koppang *et al*., 1998; Noffke and Raubenheimer, 2002; Kaplan *et al*., 2005b; Qin *et al*., 2005; Shen *et al*., 2006). Sixty-five were in the mandible (66.3%) and 33 in the maxilla (33.6%), a difference that was statistically significant (P <0.1%). The cysts involved each of the jaws to a varying extent. The Koppang group have listed the individual locations of 40 cases in both mandible and maxilla. Most of these (34) were in the anterior mandible and six were in the maxilla. Some involved the mandible from incisor or canine to the molar regions. One was described as involving the entire mandible. In the series of Noffke and Raubenheimer, six of nine cases involved the mandible and four of the these were bilateral. Of the seven cases reported in the study by Kaplan *et al*. (2005b), four were in the maxilla, three with extensive involvement including the maxillary sinus. Ertaş *et al*. (2003) described an example in the mandible that extended from the right first premolar to the left second premolar.

Clinical presentation

From the data presented in the four paragraphs above, the GOC might be described as a relatively rare cystic lesion of the jaws that occurs over a wide age range from the second to the ninth decades, with a peak frequency in the sixth decade, more frequently in men than in women and more commonly found in the mandible, particularly anteriorly, than in the maxilla. Of the 14 patients documented by Qin *et al*. (2005), 11 complained of painless swelling of the jaw or face, one complained of painful swelling of the maxilla and two reported 'pain in the teeth'. The involved teeth reacted negatively to sensitivity testing. All nine patients of Noffke and Raubenheimer (2002) presented with swelling of the jaws, as did the seven patients reported by Kaplan *et al*. (2005b). Six of the latter seven were painless swellings, three of which were on the buccal aspect, one buccal and lingual, one palatal, one was in the retromolar area and one of the maxillary cases showed facial and nasal swelling with infra-orbital paraesthesia.

Considerable evidence has accumulated from numerous publications that the GOC is an aggressive or potentially aggressive cystic lesion that has a history of recurrence if not adequately excised. In their analysis of recurrences after treatment, Kaplan *et al*. (2005b) included a sample of 48 patients including seven treated in their own department. Details of the selection of their sample are outlined in the 'treatment section' of this chapter following a description of the radiological features. Pooling together patient data that recorded location, size, radiographic features, different modalities of primary treatment of the lesions, and length of follow-up, they found that recurrences occurred in 13 cases (27.1%). Two patients had three recurrences each within 2 years. Citing a series of publications, they found recurrence rates ranging from 21 to 55%. About two-thirds of the recurrences were initially treated by conservative surgical procedures. Of 34 patients without a recurrence, 25 had been treated conservatively (enucleation or curettage) and the other nine by peripheral ostectomy, marginal resection, partial jaw resection and one by marsupialisation. In the series of Shen *et al*. (2006), with follow-up periods of 10 of their cases ranging from 2 to 40 years, only one cyst recurred and this was in the third year postoperatively, a relatively low recurrence rate because nine of their cases were treated either by enucleation or curettage.

Radiological features

In the six cases from the University of the Witwatersrand series, three were described as showing well-defined multilocular radiolucencies and two as well-defined unilocular radiolucencies.

In the literature survey of Koppang *et al*. (1998), eight GOCs had been described radiologically as unilocular and 18 as multilocular radiolucencies. Other cases had merely been reported as radiolucencies. In the later literature survey of 51 cases by Manor *et al*. (2003), in which there was probably some overlap with the Koppang series, 52% of the cases had been described as unilocular and 48% as multilocular. Almost all (95%) had well-defined borders which were sclerotic in 8% and scalloped in 13%. Information on cortical plate integrity was available in only 24 cases, half of which reported perforation and 17% erosion or thinning of the cortical plates. Root resorption was reported in 22% of patients and tooth displacement in 24%.

Noffke and Raubenheimer (2002) reported a radiological study of nine cases. The examination had been performed with panoramic, occlusal, Waters and periapical radiographs. Measurements were made in horizontal and vertical dimensions on standardised panoramic views. All showed cortical expansion and those with a diameter of more than 6 cm had perforated the cortical plate. Seven of the series were unilocular and well circumscribed: five with smooth borders and two with irregular borders. Eight cases showed tooth displacement. Both multilocular lesions showed irregular or scalloped borders and perforations. Their measurements ranged from 3.2×2.0 cm in a 14 year old boy, to a multilocular lesion of 16.5×4.0 cm in a 53 year old woman. Unlike the survey by Manor *et al*. (2003), no significant root resorption of involved teeth had been observed.

These authors suggested that multilocularity might be a size-related phenomenon, and that the GOCs measuring in excess of 6 cm, all of which had shown bone expansion and perforation, supported their aggressive expansile

behaviour. They also pointed out that the GOCs in their sample were not associated with impacted teeth, but rather tended to displace erupted teeth, which indicated that most had probably developed after all the permanent teeth had erupted.

Qin *et al*. (2005) also reported on the radiological features of 14 of their own cases: 11 appeared as unilocular lesions with or without well-defined margins and the other three as multilocular cystic lesions. In five cases a tooth was present in the cyst cavity and tooth displacement and root resorption was also seen in five cases.

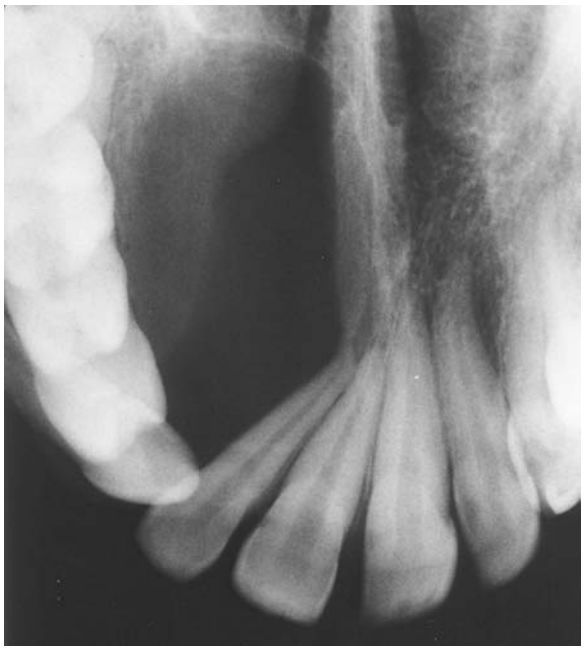


Fig. 7.2 Radiograph of a glandular odontogenic cyst in the maxilla. There is a large unilocular radiolucent area with a smooth corticated margin. These features are non-specific. (Courtesy of Professor E.J. Raubenheimer.)

The radiograph illustrated in Fig. 7.2 shows a unilocular radiolucent area with a smooth corticated margin between the maxillary lateral and canine teeth, the roots of which are displaced. Figure 7.3 shows an expansile multilocular GOC of the mandible, extending from molar to molar.

Histological features

The microscopic features are variable. The cyst may be lined in parts by a non-keratinised stratified squamous epithelium of variable thickness, with a chronic inflammatory infiltration of the connective tissue wall. The diagnosis is made when the superficial layer of the epithelial lining consists of columnar or cuboidal cells (Figs 7.4a, b), sometimes referred to as 'hobnail', occasionally with cilia or filiform extensions of the cytoplasm (Fig. 7.5). Furthermore, the epithelium has a glandular or pseudoglandular structure, with intra-epithelial crypts or microcysts or pools lined by cells similar to those on the surface (Figs 7.4a, b and 7.5). In certain planes of section, these microcysts may be seen to open onto the surface of the epithelium through openings or crypts, giving the epithelium a papillary or corrugated surface (Figs 7.4a, b). They are sometimes empty and sometimes contain a structureless eosinophilic material which gives a positive mucicarmine reaction. Numerous goblet cells may be present, mainly in the superficial part of the epithelium (Fig. 7.5). Occasionally, the epithelium is thinner, similar to reduced enamel epithelium. Epithelial thickenings or plaques may be present either in this thin epithelium or in the stratified squamous epithelium. The plaques, when present, are identical morphologically to those in the gingival cyst of adults, the lateral periodontal cyst and the botryoid odontogenic cyst, and may either protrude into the cyst cavity or extend into the connective tissue wall. Intra-epithelial spherules often occur. Islands of

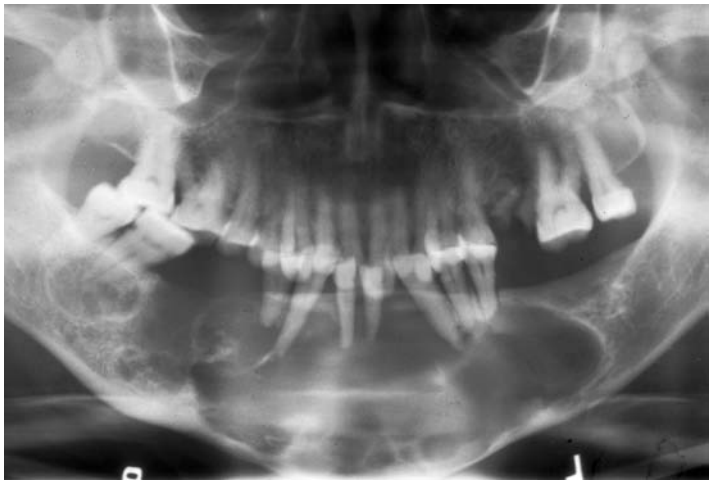


Fig. 7.3 Radiograph of an extensive multilocular glandular odontogenic cyst. (Courtesy of Professor C. Nortjé.)

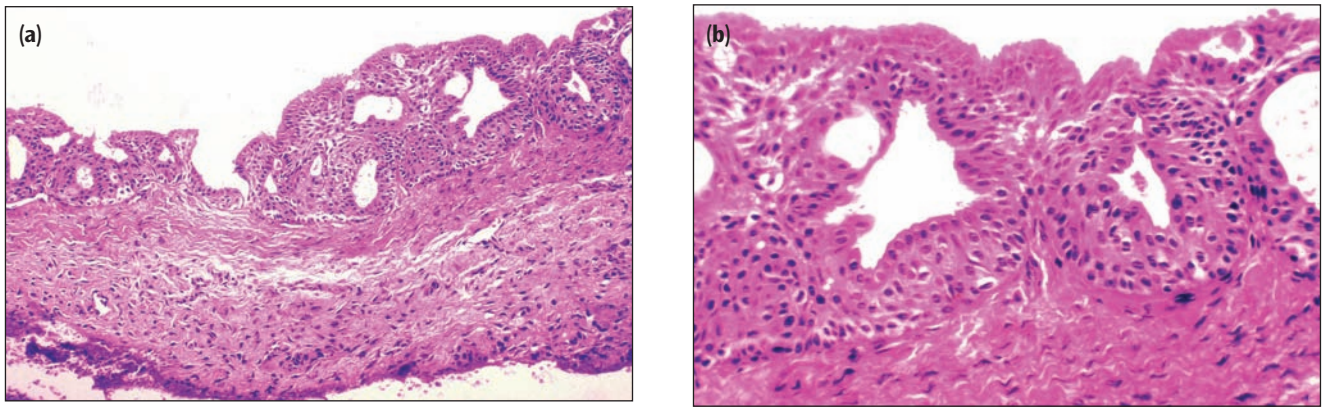


Fig. 7.4 (a) Histopatholgy of the glandular odontogenic cyst. In this photomicrograph, columnar and cuboidal cells lie on the surface of the epithelium and extend into, and line, the intra-epithelial crypts. The openings onto the surface give the epithelium a corrugated appearance. (Histological section kindly lent by Dr R. Morency.) (b) Higher magnification of part of (a).

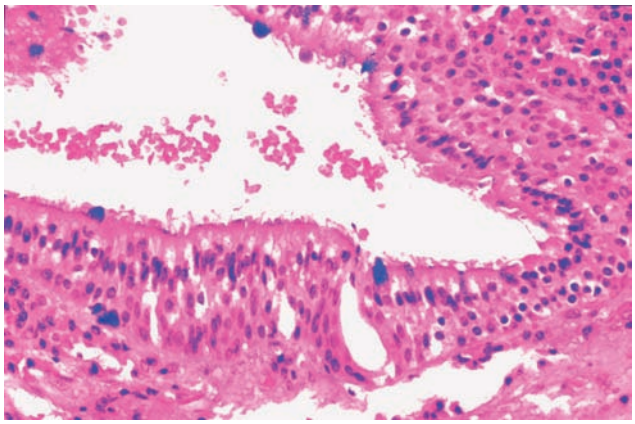


Fig. 7.5 Glandular odontogenic cyst showing columnar or pseudostratified columnar epithelium with mucus-secreting goblet cells and filiform extensions of the cytoplasm. Alcian blue stain.

odontogenic epithelium and even microcysts may be present in the connective tissue wall of the cyst. Irregular calcifications may also be present in the connective tissue wall.

An unusual feature for a GOC was the presence of hyaline bodies in the thickened epithelium and in the lumen of an otherwise typical specimen (Ide *et al*., 1996). Takeda (1991) observed similar epithelial microcysts, which he called duct-like structures, in the odontogenic epithelium of a compound odontoma.

Immunocytochemistry

Most (if not all) histopathologists, faced with histological sections of a GOC, will have been struck by some of its similarities with the central mucoepidermoid carcinoma (MEC), which is occasionally found in the jaws. So striking is this resemblance that it has been suggested that an appropriate name for the lesion might be mucoepidermoid odontogenic cyst (Sadeghi *et al*., 1991). Understandably, this designation has not found favour, for fear of aggravating the confusion between the GOC and the salivary gland tumour.

Günzl *et al*. (1993), Semba *et al*. (1994), de Sousa *et al*. (1997), Koppang *et al*. (1998) and Pires (2004) have addressed this question, with some variations, by comparing the cytokeratin expression in the two lesions. In the latter and most recent paper on the subject, six cases of central MEC, selected using strict criteria for inclusion, and 10 cases of GOC were compared immunohistochemically using a range of 11 monoclonal antibodies. These results were compared with cytokeratin (CK) profiles in salivary gland MECs and a range of odontogenic tumours and cysts.

Without going into the details of the different permutations and combinations comparing the 11 cytokeratins and the four lesions – GOC, other odontogenic lesions, central MEC and salivary gland MEC – it might be helpful to cite the authors' conclusions:

'It can be difficult to establish the origin and pathogenetic relationship of odontogenic and glandular lesions based solely on CK expression. However, CK profiles can be useful adjunctive tools to the histological and morphological features to establish a definitive diagnosis. Our results suggest that the central MEC and the GOC are distinct entities with different CK profiles, and that expression of CKs 18 and 19 could be useful adjunctive tools in differentiating these two entities. Our data also indicate that the central MEC has a CK profile similar to that of the MEC of glandular origin (CKs 7, 8 and 18) and the GOC shows a profile overlapping that of odontogenic lesions (CK19) and that of MECs (CKs 7, 8 and 18).'

Shen *et al*. (2006) also reported on the CK histochemistry of their 12 cases and believed that their findings supported the odontogenic origin of the GOC.

Tosios *et al.* (2000) investigated the expression of bcl-2 protein, Ki-67 antigen and p53 protein in three GOCs. The GOCs showed homogeneous reactivity for bcl-2 protein, either in the entire thickness of the epithelium or in the basal and suprabasal layers with a tendency to diminish towards the surface. Bcl protein facilitates cell survival by regulating apoptosis and has been identified in many human tumours. Most mucous cells and the superficial cuboidal cells were negative, while the cell membranes of the vacuolated cells gave a positive reaction. Ki-67 and p53 protein were demonstrable in a few cells, mainly in the basal layer.

The authors speculated, in conclusion, that the increased expression of the anti-apoptotic bcl-2 may be associated with deregulation of cell death in the lining epithelium of the GOCs, while cell proliferation and p53 status did not seem to play a significant part.

Kaplan *et al.* (2005a) performed a more extensive study of p53, Ki-67 and proliferating cell nuclear antigen (PCNA) markers on a series of 11 GOCs, nine MECs of salivary gland and 15 radicular cysts showing mucous metaplasia. Counts of positive cells were carried out in 10 random microscopic fields and a labelling index calculated by dividing the numbers of positive cells by the total number of cells. Their results showed some differences (Kruskal–Wallis) in the labelling indices for p53 ($P=0.048$) and Ki-67 ($P=0.03$) but no significant difference in PCNA readings. Leaving out the results for radicular cysts with mucous metaplasia, which should not pose difficulties in differentiation from the GOC, only the Ki-67 results show a difference between the readings for the GOC and the mucoepidermoid carcinoma of salivary gland. Given that the paper by Tosios *et al.* (2000) found only a few Ki-67-positive cells, these molecular markers do not seem promising as diagnostic aids in differentiating the GOC from the central MEC.

In their study of p63 expression in the epithelium of odontogenic cysts, Lo Muzio *et al.* (2005) included only one glandular odontogenic cyst, and this showed positivity in the basal and parabasal layers but not in the intermediate or superficial layers.

PTCH gene

In Chapter 3 the role of the *PTCH* gene, a tumour suppressor gene, was considered in some detail. The similarities between the behaviour of the GOC and the keratocyst led Barreto *et al.* (2001) to hypothesis that *PTCH* gene mutations may underlie the 'tumorigenesis' of the GOC.

Their sample was only one specimen of a GOC. Each of the 23 exons of the *PTCH* gene was amplified and direct sequencing of all exons was performed. All demonstrated absence of mutations in the coding region of the *PTCH* gene. The authors pointed out that despite the small sample, the technique of direct DNA sequencing of PCR products is very sensitive and had been applied successfully to detect mutations in odontogenic keratocysts.

They concluded therefore that the *PTCH* gene seems not to be involved in the pathogenesis of the GOC.

Treatment

Kaplan *et al.* (2005a) carried out an extensive survey of the treatment and follow-up of a sample of 56 patients with GOCs, including three of their own cases. The mandible was involved in 41 cases (73%) and the maxilla in 15 (27%). Eleven lesions were located in the anterior region, nine in the posterior and 36 overlapped both.

Based on the results of their survey, Kaplan *et al.* (2005b) suggested that the protocol for the treatment of the GOC should take into account that the small unilocular lesions are usually enucleated before a definitive histological diagnosis has been made. If these lesions are completely enucleated, further surgery is not indicated because recurrence is unlikely. They recommend, however, that these patients should be followed for at least 3 years and preferably as long as 7 years.

Large unilocular or multilocular lesions should be biopsied before treatment is planned. The authors recommended that as unilocular lesions had a lower risk of recurrence than the multilocular ones, the treatment for the large lesions should be enucleation with preservation of vital structures. Peripheral ostectomy in conjunction with enucleation can reduce recurrences and should be performed whenever possible. Marsupialisation is recommended as an option if the lesions approach vital structures. If marsupialisation is performed, curettage and peripheral ostectomy is advised for second-phase surgery.

For large multilocular lesions, major treatment modalities are indicated. These include peripheral ostectomy, marginal resection or partial jaw resection, depending on the size of the lesion, integrity of the jaw borders and proximity to vital structures. They recommend that if the lesion lies close to the sinus, pterygoid or nasal cavity, marsupialisation with second-phase enucleation after reduction of the lesion should be undertaken.

8

Calcifying Odontogenic Cyst (Calcifying Cystic Odontogenic Tumour)

Over the years since its first description, it has become clear that the calcifying odontogenic cyst (COC) has a number of variants, including features of a benign odontogenic tumour. It was classified as such, with SNOMED code 9301/0, in the World Health Organization's (WHO) publication *Histological Typing of Odontogenic Tumours* (Kramer *et al*., 1992). The studies of Prætorius *et al*. (1981) led them to conclude that what had previously been regarded as a calcifying odontogenic cyst actually comprised two entities: a cyst and a neoplasm. In the latest WHO publication on odontogenic tumours (Prætorius and Ledesma-Montes, 2005) it was classified as a benign odontogenic tumour and was renamed calcifying cystic odontogenic tumour (CCOT).

Li and Yu (2003) have drawn attention to the dilemma regarding the nature of these 'ghost cell lesions' as cysts, neoplasms and even malignancies. They have therefore proposed what they have called a more concise terminology and classification based on the likely differences in biological behaviour of the COC and its related lesions. They divided the lesions into three groups – cysts, benign tumours and malignant tumours – and suggested that the term COC should be used specifically to designate the unicystic lesions with or without an associated odontoma.

They believed that the unicystic lesions, with or without an associated odontoma, were mostly localised and well circumscribed with little, if any, tendency to recur after enucleation. These fulfilled the diagnostic histological criteria described in the 1992 WHO classification and were best classified as developmental odontogenic cysts. As such, they believed that this group should retain the term COC. They have argued that the reason for inclusion of odontoma-associated COCs in this group is that these odontomas are hamartomatous and unlikely to modify their behaviour. They believed that other ghost cell lesions identified as benign or malignant tumours, should be classified separately and named accordingly.

Prætorius (personal communication, 2006), who was one of the authors of the first description of the lesion (Gorlin *et al*., 1962) and who has had extensive experience of the range and variations of ghost cell lesions of the jaws in general, disagrees in some respects with the classification proposed by Li and Yu (2003). He argues that the COC is not just a developmental cyst like the dentigerous cyst because it often forms islands of epithelium and dentinoid in the wall; while in some of them, an odontoma forms in the wall. Accordingly, he believes that cystectomy is mandatory and that cystotomy is not indicated. In a case he has personally observed in which a cystotomy was performed, the entire lumen became filled with COC tissue within a short time and protruded through the surgical window. He has proposed a classification of the odontogenic ghost cell lesions, shown in Table 8.1, and reproduced in this chapter with his kind permission.

The calcifying odontogenic cyst (COC) was first described by Gorlin *et al*. (1962, 1964) who were impressed by the significant presence of so-called 'ghost cells' and its histological resemblance to the cutaneous calcifying epithelioma of Malherbe. The eponym of 'Gorlin cyst' is frequently used. Since its early description, the lesion has been widely recognised, occurring both peripherally and centrally in the jaws, while its origins, pathogenesis and histopathological variations have evoked considerable discussion in the literature. Earlier publications cited in the previous edition of this book, were papers by Abrams and Howell (1968), Ulmansky *et al*. (1969), Fejerskov and Krogh (1972), Altini and Farman (1975), Freedman *et al*. (1975), Prætorius *et al*. (1981), Nagao *et al*. (1983), Shamaskin *et al*. (1989), Takeda *et al*. (1990), Buchner (1991) and Hong *et al*. (1991). Subsequent literature will be referred to in the course of this chapter.

Other lesions in which 'ghost cells' are a feature, have been dealt with in separate sections of the 2005 WHO publication under the headings 'dentinogenic ghost cell tumour' (Prætorius and Ledesma-Montes, p. 314) and 'ghost cell odontogenic carcinoma' (Takata and Lu, 2005, p. 293). Synonyms for the dentinogenic ghost cell tumour have been listed as 'calcifying ghost cell odontogenic tumour', 'odontogenic ghost cell tumour' and 'dentinoameloblastoma', while the dentinogenic ghost cell tumour is considered a solid variant of the calcifying odontogenic cyst (Prætorius and Ledesma-Montes,

Table 8.1 Suggested classification of the odontogenic ghost cell lesions. (From Prætorius, 2006, personal commmunication.)

Group 1	'Simple' cysts
	Calcifying odontogenic cyst (COC)
Group 2	Cysts associated with odontogenic hamartomas or benign neoplasms: *calcifying cystic odontogenic tumours* (CCOT). The following combinations have been published:
	CCOT associated with an odontome
	CCOT associated with adenomatoid odontogenic tumor
	CCOT associated with ameloblastoma
	CCOT associated with ameloblastic fibroma
	CCOT associated with ameloblastic fibro-odontoma
	CCOT associated with odonto-ameloblastoma
	CCOT associated with odontogenic myxofibroma
Group 3	Solid benign odontogenic neoplasms with similar cell morphology to that in the COC, and with dentinoid formation
	Dentinogenic ghost cell tumour
Group 4	Malignant odontogenic neoplasms with features similar to those of the dentinogenic ghost cell tumour
	Ghost cell odontogenic carcinoma

p. 314). A detailed study of the histology, immunohistochemistry, lectin-binding profiles and biophysical aspects, has been published by Mori *et al.* (2000).

Hirshberg *et al.* (1994) have identified a range of reported cases of odontogenic tumours and odontomas associated with a unicystic COC, and these have been listed as Group 2 lesions in Table 8.1.

Clinical features

Frequency

Despite the fact that the range of COC/CCOTs are now well-recognised lesions, they are not very commonly encountered. Over the 46-year period 1958–2004, only 30 examples accessioned as COCs were recorded in the archives of the University of the Witwatersrand Department of Oral Pathology, representing 0.9% of 3498 jaw cysts documented during that period (see Table 1.1). Shamaskin *et al.* (1989) reported 20 cases that had been recorded in their department over an 18-year period. Of these, 15 were central lesions and five peripheral. The age and gender distributions referred to below are derived mainly from a literature review, including 12 cases presented by Prætorius *et al.* (1981), 10 by Fregnani *et al.* (2003), 16 by Yoshida *et al.* (2001), seven by Moleri *et al.* (2002) and 16 by Li and Yu (2003), combined with 18 cases from the University of the Witwatersrand department, eight of which were previously reported by Altini and Farman (1975).

Buchner (1991) pointed out that there were about five times as many central lesions reported in the literature as peripheral lesions.

Age

The age distribution of 141 cases from a range of sources as referred to above, including both central and peripheral lesions, is shown in Fig. 8.1. The lesion occurs over a wide age range. The youngest recorded patient was 1 year old, the oldest 82 years, and there is an impressively high peak in the second decade, a feature confirmed in reports by many groups. Prætorius *et al.* (1981) have drawn attention to a bimodal age distribution in support of their contention that different entities may be involved, and numbers of papers have referred to this feature. While the relatively large pooled sample illustrated in Fig. 8.1 does show a bimodal distribution, the second peak is not particularly impressive given the large numbers (38%) in the second decade.

In a survey of 23 cases in the Japanese literature, Nagao *et al.* (1983) reported that with the exception of two patients, all were under 39 years, with a peak in the second decade. Shamaskin *et al.* (1989) found that of five extra-osseous lesions, four were in patients over 50 years. In their literature review of 29 extra-osseous cases, Kaugars *et al.* (1989) established that 16 patients were in their sixth decade or older. In their study of the peripheral lesions, Buchner *et al.* (1991) observed a bimodal age distribution with peaks in the second and sixth decades.

Gender

There is a negligible difference in gender distribution, so that of 88 cases documented for earlier editions of this book, 44 were in men and 44 in women. In Buchner's survey, 105 patients were men and 110 women. Of the 49 cases reported by Yoshida *et al.* (2001), Moleri *et al.* (2002), Fregnani *et al.* (2003) and Li and Yu (2003), 27 involved men and 22 were women. Combining the two sets of figures, of 137 documented cases, 71 involved men (52%) and 66 occurred in women (48%). There was also an equal gender distribution in the series of extra-osseous cases reported by Kaugars *et al.* (1989).

Race

No race predilection has been identified.

Site

Of 50 cases reviewed by Fejerskov and Krogh (1972), the mandible (23 cases) and maxilla (27 cases) were involved with almost equal frequency. The majority of cysts (36

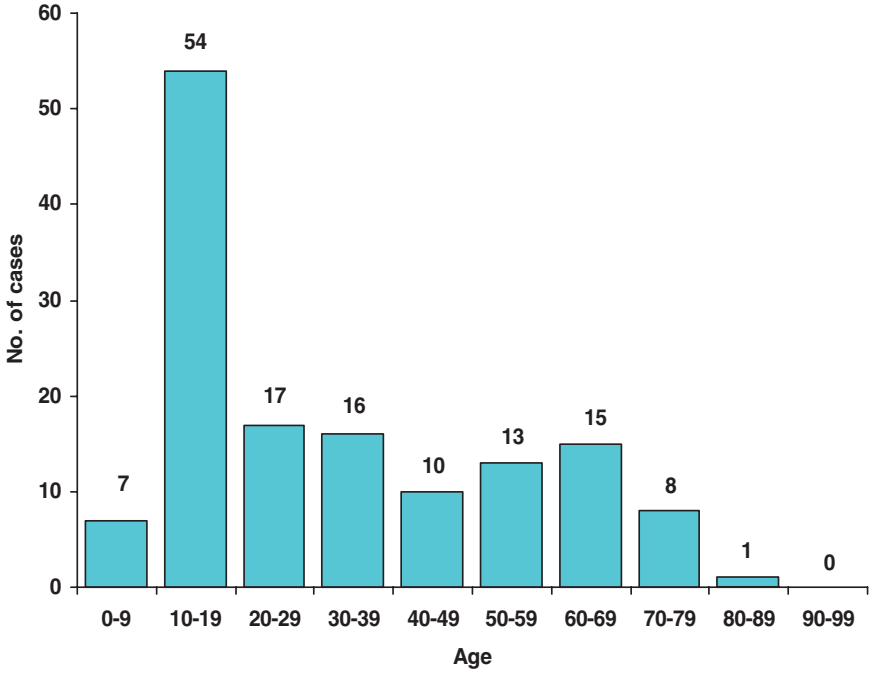


Fig. 8.1 Age distribution of 141 patients with calcifying odontogenic cysts.

cases) occurred within the jaws and 15 were found outside bone in the soft tissues related to the jaws. Of the series of 29 extra-osseous cases documented by Kaugars *et al*. (1989), about half developed between the canines and none was posterior to the first molar. One case, recorded by Gorlin *et al*. (1964), was found in the parotid salivary gland. Freedman *et al*. (1975) pointed out that 70% of their sample occurring in patients before the age of 41 were in the maxilla whereas 80% in patients older than 41 were in the mandible. In the Japanese study (Nagao *et al*., 1983), the maxilla was involved in 17 cases and the mandible in six. Li and Yu (2003) reported that in their sample, the maxilla was more frequently involved (69%) than the mandible and that there was a predilection for the canine–premolar region of the maxilla. Daniels (2004) recorded a recurrent case that involved the maxillary sinus and eroded the floor of the orbit and body of the zygoma. The histopathology of the recurrent and the original lesion 8 years before, were reported as COCs.

The most common site of occurrence has been the anterior part of the jaws. In the mandible, several cases have crossed the midline but this is less usual in the maxilla.

Most of the peripheral lesions were located in the maxillary or mandibular gingiva or alveolar mucosa anterior to the first molar (Buchner *et al*., 1991).

Clinical presentation

Swelling is the most frequent complaint and has occurred in about half of the reported cases. Only rarely has there been pain. Intra-osseous lesions may produce a hard bony expansion and may be fairly extensive. Lingual expansion may sometimes be observed. Occasionally, the calcifying odontogenic cyst may perforate the cortical plate and extend into the soft tissues. In a few cases, displacement of the teeth has been described. Some cases have been completely symptomless and have been discovered fortuitously during routine radiological examination. Extra-osseous lesions tend to be pink to red, circumscribed elevated masses measuring up to 4 cm in diameter (Prætorius and Ledesma-Montes, 2005, p. 313).

Occasional recurrences have occurred, as in the case reported by Daniels (2004), who also cited other examples.

Radiological features

The calcifying odontogenic cyst that occurs as an intra-osseous lesion appears as an essentially radiolucent area. Some have a regular outline with well-demarcated margins. Others may be quite irregular and may have poorly defined margins. They are usually unilocular but a few have been multilocular. Irregular calcified bodies of varying size and opacity may be seen in the radiolucent area (Figs 8.2 and 8.3) and in some cases the calcification may be substantial and occupy the greater part of the lesion. Denser opacities are likely to be present if the cyst is associated with a complex odontome, as it sometimes is. Prætorius and Ledesma-Montes (2005, p. 313) described the intra-osseous lesions as generally being unilocular radiolucencies with well-circumscribed borders and variable amounts of radiopaque material being present in about 50% of them; and Yoshida *et al*. (2000) have listed the radiological features of all 16 of their cases as radiolucencies with radiopaque material. Some cases

have been reported as being associated with an unerupted tooth. Displacement of teeth is often seen. Resorption of the roots of adjacent teeth is a frequent finding, and is regarded as an important radiological feature by Tanimoto *et al.* (1988). Local expansion sometimes occurs and perforation of the cortical plate, when present, may be radiologically demonstrable.

The extra-osseous lesions show localised superficial bone resorption, or saucer-shaped radiolucencies and sometimes displacement of adjacent teeth (Prætorius and Ledesma-Montes, 2005).

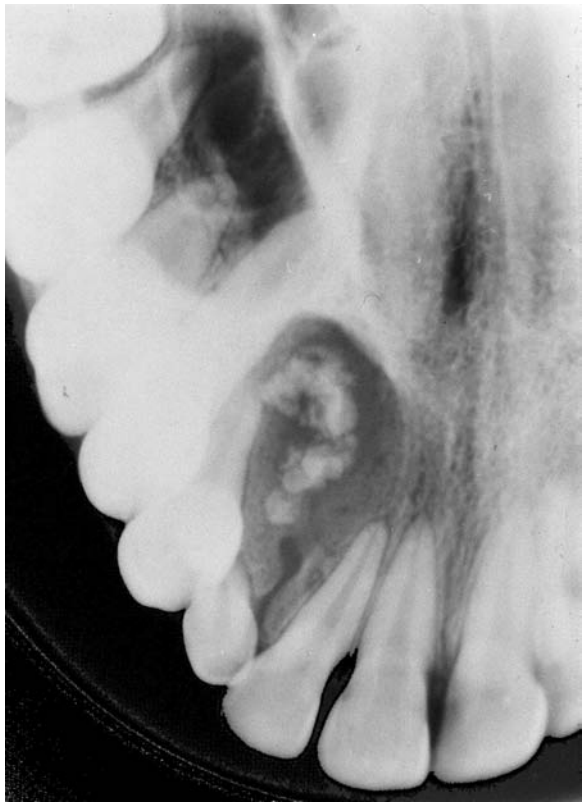


Fig. 8.2 Radiograph of a calcifying odontogenic cyst of the maxilla. There is a well-demarcated margin and calcifications suggestive of tooth material. (Courtesy of Professor J.E. Seeliger.)

Pathogenesis and pathology

The histological features of a classic calcifying odontogenic cyst are characteristic and present few diagnostic problems. As defined in the WHO classification of 1992, it is:

> 'A cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer that is often many cells thick and that may resemble stellate reticulum, and masses of "ghost" epithelial cell that may be in in the epithelial lining or in the fibrous capsule (Fig. 8.4). The "ghost" epithelial cells may become calcified. Dysplastic dentine may be laid down adjacent to the basal layer of the epithelium (Figs 8.5 and 8.6), and in some instances the cyst is associated with an area of more extensive dental hard tissue formation resembling that of a complex or compound odontoma.'

However, elucidation of the pathogenesis is considerably complicated by the fact that the epithelial lining of a calcifying odontogenic cyst appears to have the ability to induce the formation of dental tissues in the adjacent connective tissue wall; and that other odontogenic tumours such as the ameloblastoma, the odontoameloblastoma, the ameloblastic fibroma and the ameloblastic fibro-odontome may sometimes be associated with it (Prætorius, 1975; Hirshberg *et al.*, 1994; Aithal *et al.*, 2003; Lin *et al.*, 2004; Iida *et al.*, 2004). Prætorius pointed out that the ghost cells that are so characteristic a feature of the calcifying odontogenic cyst also occur in other odontogenic cysts, the craniopharyngioma and the calcifying epithelioma of Malherbe, as well as in the other odontogenic tumours already mentioned. The mere presence of ghost cells in a lesion does not, therefore, justify the diagnosis of calcifying odontogenic cyst.

In the first edition of this book, the question was posed as to whether those calcifying odontogenic cysts

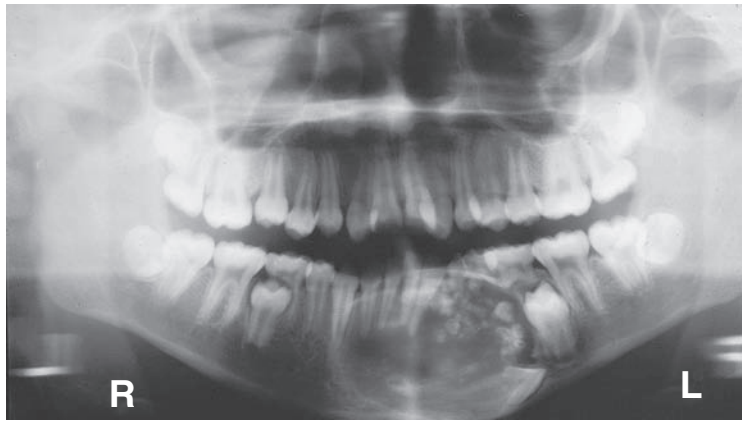


Fig. 8.3 Radiograph of a calcifying odontogenic cyst with well-demarcated margins extending from the right to the left premolar regions of the mandible. Numerous calcifications are present, some suggestive of small denticles.

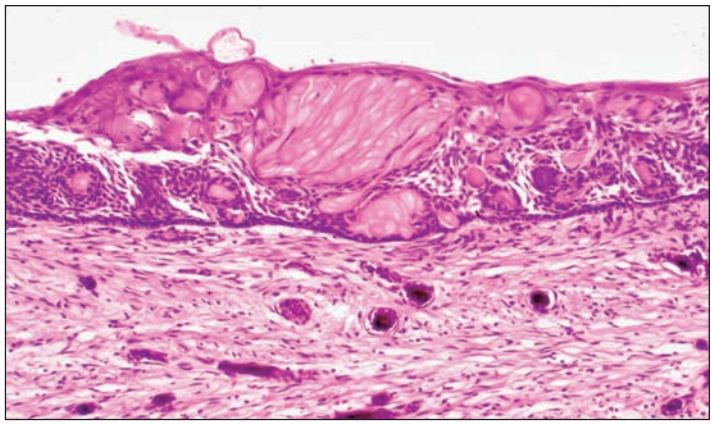


Fig. 8.4 Histological features of a calcifying odontogenic cyst with clusters of fusiform ghost cells and focal calcifications, lying in a stratified squamous epithelium.

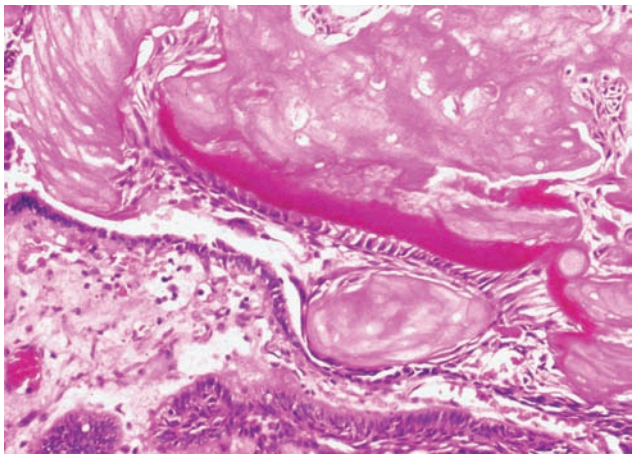


Fig. 8.5 In this calcifying odontogenic cyst, there are sheets of ghost cells and a focal area in which there has been induction of a strip of dysplastic dentine (dentinoid).

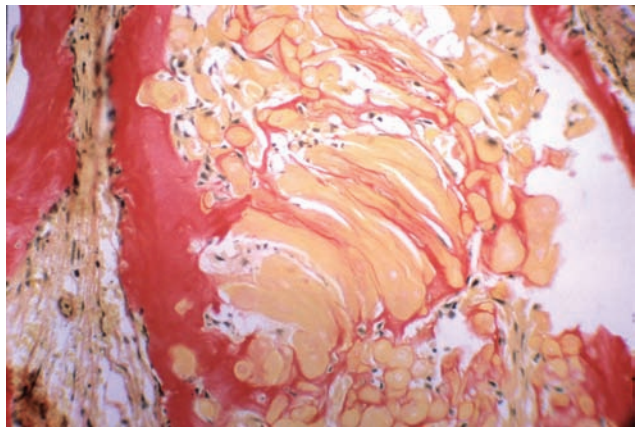


Fig. 8.6 A van Gieson stain distinguishes the red-staining dentinoid from the yellow-staining ghost cells.

that have other features of odontogenic tumours develop these secondarily, or whether the cysts themselves were secondary phenomena in pre-existing odontogenic tumours. Takeda *et al.* (1990) were convinced that the cysts arose *de novo,* as were Prætorius *et al.* (1981), who concluded from their study that substantial evidence existed that the tumour developed from the wall of the cyst. They suggested that the calcifying odontogenic cyst was a unicystic process that developed from reduced enamel epithelium or remnants of odontogenic epithelium in the follicle, gingival tissue or bone. Dentinoid alone, or an odontome, may be found in the cyst wall, induced by the lining epithelium. Wang *et al.* (2003) identified juxta-epithelial dentinoid in all 10 of their Taiwanese sample. The subclassification suggested by Prætorius *et al.* (1981) has been modified, as indicated earlier in this chapter (F. Prætorius, 2006, personal communication). Prætorius believes that the dentinogenic ghost cell tumour is a neoplasm *de novo*, but the COC plus benign neoplasm or hamartoma is a cyst from the beginning. This latter view is reinforced by the observation that COCs occur in which various stages in the development of an odontome are found in the wall. Hirshberg *et al.* (1987) reviewed the literature and identified six cases reported as calcifying odontogenic cysts that were solid masses with or without ameloblastomatous proliferation and without any association with other odontogenic tumours. In their review of 'odontogenic ghost cell tumours', Colmenero *et al.* (1990) observed two different entities: one with infiltrating odontogenic epithelium and ghost cells that was locally aggressive like the ameloblastoma; and the other which was malignant with potential to metastasise. The latter entity is best described as a 'ghost cell odontogenic carcinoma' (Grodjest *et al.*, 1987).

Lu *et al.* (1999) published a literature review of 12 ghost cell odontogenic carcinomas and added another four cases. The numbers were too few to allow for meaningful clinical analysis but, histologically, elements of a benign COC could be identified in all the malignant variants. It seemed that the tumour arose most often from malignant transformation of a pre-exisiting benign COC, but that it may also have developed from other odonto-

genic tumours. Goldenberg *et al*. (2004) have documented another case.

Scott and Wood (1989) reported a case with ameloblastomatous and basaloid features that behaved aggressively and believed that as such a tumour had more in common with an ameloblastoma than a calcifying odontogenic cyst, its diagnostic designation should adequately reflect this. They proposed the term 'dentinogenic ghost-cell ameloblastoma'. In terms of the proposed Prætorius classification of 2006, it would be a Group 2 lesion and its appropriate terminology would be 'CCOT associated with ameloblastoma'. The classic COC is most frequently a unilocular lesion but multicystic lesions have been reported (Buchner, 1991; Hong *et al*., 1991). Satellite cysts may develop from odontogenic epithelial islands in the wall (Takeda *et al*., 1990). In the study of the peripheral lesions by Buchner *et al*. (1991), two-thirds were cystic and one-third were solid.

The epithelial lining has characteristic odontogenic features with a prominent basal layer consisting of palisaded columnar or cuboidal cells and hyperchromatic nuclei which are polarised away from the basement membrane (Figs 8.4 and 8.5). The epithelium may be a regular 6–8 cells thick over part of its length and be continuous with parts that may be very thin and others that are considerably thickened. Budding from the basal layer into the adjacent connective tissue and epithelial proliferations into the lumen are frequently seen.

Melanin deposits are sometimes present in the epithelial linings.

The most remarkable feature of the COC is the presence of ghost cells which have been compared with those found in the calcifying epithelioma of Malherbe in the skin. The ghost cells are found in groups, particularly in the thicker areas of the epithelial lining. The spinous cells in such situations may be widely separated by intercellular oedema and the epithelium around the ghost cells is often convoluted (Figs 8.4 and 8.5).

The ghost cells are enlarged, ballooned, ovoid or elongated elliptoid epithelial cells. They are eosinophilic and although the cell outlines are usually well-defined, they may sometimes be blurred so that groups of them appear fused. A few ghost cells may contain nuclear remnants but these are in various stages of degeneration and in the majority all traces of chromatin have disappeared leaving only a faint outline of the original nucleus. The ghost cells represent an abnormal type of keratinisation and have an affinity for calcification. They have the same histological reactions as keratin, giving a yellow fluorescence with rhodamine B (Prætorius, 1975) (Fig. 8.7). Hong *et al*. (1991) showed that in formalin-fixed tissue the ghost cells expressed little or no cytokeratin reactivity and suggested that this, in association with their histological features, may represent the product of coagulative necrosis of odontogenic epithelium. Sapp and Gardner (1977) found that calcification may occur in some of the ghost cells, initially as fine powdery or coarse basophilic granules and later as small spherical bodies that ultrastructural studies have shown to represent dystrophic calcification.

The ghost cells may be in contact with the connective tissue wall of the cyst where they may then evoke a foreign body reaction with the formation of multinucleate giant cells. In the fibrous wall there are usually strands and islands of odontogenic epithelium, either in direct contact with the epithelium or separately in the connective tissue. These vary from a few strands to extensive proliferations. Takeda *et al*. (1990) have performed a histological study of satellite cysts and odontogenic epithelial islands in the connective tissue walls of these lesions. The satellite cysts could be grouped into the same three histological types described by Prætorius *et al*. (1981), but these did not always coincide with the typing of the mother cyst.

An atubular dentinoid is often found in the wall close to the epithelial lining and often in relation to the epithelial proliferations. It is frequently described as being

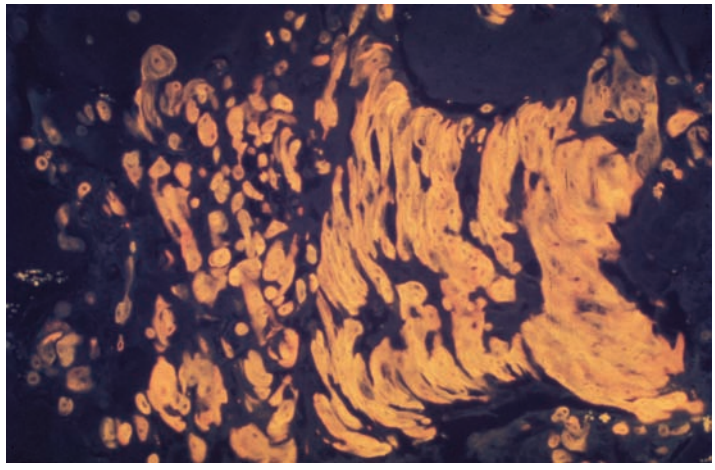


Fig. 8.7 The ghost cells have the same histological reactions as keratin, giving a yellow fluorescence with rhodamine B.

found particularly in contact with masses of ghost cells (Fig. 8.5). As pointed out in the classification of Prætorius (2006, personal communication), there are many variations of odontogenic lesions characterised by the presence of these 'ghost cells'. Numbers of these are solid tumours and not cysts at all. Others are cysts but are associated with odontogenic hamartomas or benign neoplasms, for which the term 'calcifying cystic odontogenic tumour' is thought to be more appropriate than 'calcifying odontogenic cyst' (Prætorius and Ledesma, 2005, p. 313; Prætorius, 2006, personal communication). Figure 8.8(a) shows a calcifying odontogenic cyst associated with the ameloblastic fibroma component an ameloblastic fibro-odontoma. Figure 8.8(b) shows ghost cells and plentiful dentinoid in the same lesion. In other parts of this lesion enamel spaces are present. In terms of the Prætorius classification outlined in Table 8.1, this lesion would be classified as a Group 2 odontogenic ghost cell lesion and would more appropriately be termed a calcifying cystic odontogenic tumour (CCOT).

Immunohistochemistry

Recent immunohistochemical studies on the COC have been published by Takata *et al.* (2000a–c), Abiko *et al.* (2001), Yoshida *et al.* (2001), Fregnani *et al.* (2003) and Kusama *et al.* (2005). The Takata group was interested in determining the nature of the ghost cells by examining their immunoreactivity with antibodies against amelogenin, enamelin, enamelysin (MMP-20) and sheathlin (prism sheath protein). They showed that the cytoplasm of the ghost cells in COCs demonstrated distinct immunolocalisation of the enamel-related proteins, but were negative in the ghost cells of the calcifying epitheliomas (Malherbe) in the skin. Monoclonal antibody 203-IC7 was found to be useful as an enamel-specific marker in the late stage of enamel matrix development and calcification, including the immature enamel matrix of ameloblastic fibro-odontomas and odontomas. Enamelysin was detected in a portion of the ghost cells in COCs tested.

Kusama *et al.* (2005) investigated the immunoreactivity of the ghost cells in 14 COCs to three kinds of antibodies raised against human hair proteins. These antibodies reacted only with ghost cells, not with other epithelial cells. The authors speculated that the ghost cells might represent differentiation into hair. Immunoreactivity for phosphothreonine, detected in hard alpha-keratins, was also found in the ghost cells.

In an immunohistochemical study to determine the localisation of amelogenin in human odontogenic tumours, Abiko *et al.* (2001) confirmed that some ghost cells in the linings of COCs were strongly stained. In a range of ghost cell odontogenic lesions, Yoshida *et al.* (2001) confirmed the presence of amelogenin protein in the cytoplasm of the ghost cells in all 16 of their cases, and also the epithelial linings of five of these specimens. Cytokeratin 19 protein was expressed in the epithelial lining cells in all cases, while ghost cells were devoid of staining. Bcl-2 protein was expressed in the epithelial linings of 12 cases, but ghost cells in only two. They found that the epithelial lining cells showed only sporadic Ki-67-positive reactions in nuclei. While their material included lesions exhibiting various histological features including 'proliferative type lining epithelium, ameloblastomatous appearance, and combined odontoma', they also observed transitional features. However, they found no difference in amelogenin or cytokeratin (CK) 19 expression among the lesions with various histological features, and only a slight difference in bcl-2 and Ki-67

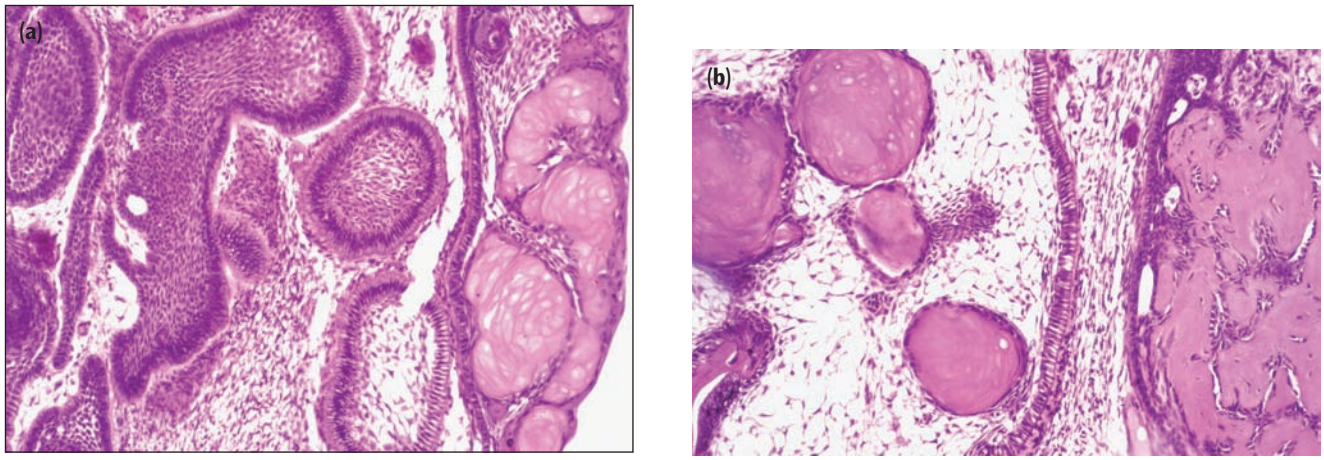


Fig. 8.8 (a) A calcifying odontogenic cyst associated with the ameloblastic fibroma component of an ameloblastic fibro-odontoma. (b) The same case as (a) in which ghost cells and plentiful dentinoid are present. In other parts of the lesion (not shown), enamel spaces are present. (Figs 8a and b, courtesy of Professor F. Prætorius, would be classified as a Group 2 odontogenic ghost cell lesion and more appropriately called a calcifying cystic odontogenic tumor in terms of the 2005 WHO classification.)

expression. They concluded that COCs with varying histological features have neoplastic potential and may not be separate entities.

Fregnani *et al.* (2003) have shown that CK 8, 4, 19, AE1/AE3 and 34βE12 were expressed in the suprabasal cells of all 10 of their cases, and cytokeratins 14 and AE1/AE3 were expressed in the basal cells of the epithelial linings of all cases. Ghost cells expressed only cytokeratins AE1/AE3 and 34βE12. Of the 10 cases, only six were classifiable as Group 1 cases (Table 8.1). All cases expressed bcl-2 in the basal and suprabasal cells, but ghost cells were negative in all cases. Proliferating cell nuclear antigen (PCNA) and Ki-67 expression was higher in the proliferative than in the non-proliferative lining epithelium, and the highest proliferative activity was found in a case that also showed ameloblastomatous proliferation.

Genetic studies

Two concurrent publications have reported beta-catenin mutations in the cytoplasm and nuclei of a series of COCs, and the authors believe that these mutations may have a critical role in the pathogenesis of these lesions (Hassanein *et al.*, 2003; Sekine *et al.*, 2003). Of 20 ameloblastomas in the paper of Sekine *et al.*, only one, a follicular variety, showed moderate nuclear and cytoplasmic accumulation of beta-catenin.

Ultrastructure

Ultrastructurally, the ghost cells do not show the same features as keratin in epidermis and oral epithelia which are characterised by evenly distributed fine tonofilaments embedded in a matrix (Fejerskov and Krogh, 1972). The cytoplasm of some ghost cells in the study of Fejerskov and Krogh contained fine tonofilaments separated by small empty spaces. Most of the cells showed very thick electron-dense fibre bundles of relatively uniform size which were sharply defined against the large empty spaces in the cytoplasm. Endoplasmic reticulum, mitochondria, Golgi apparatus and ribosomes could not be identified. The cell membranes were intact with junctional complexes of various types.

In their study, Mimura *et al.* (2002) found that on transmission electron microscopy, many calcifications showed a distinctive ring formation around the periphery of an amorphous central core. The calcifications were associated with necrotic remnants of nuclear material and identifiable epithelial cells, mitochondria and thin fibres. The cytoplasm of the ghost cells comprised numerous short electron-dense tonofilament bundles in which needle-like structures were observed and these were shown by X-ray diffraction analysis to be hydroxyapatite.

In an ultrastructural study of a COC associated with an odontoma, Satomura *et al.* (1999) identified four types of cell in the epithelial layer of the COC. There were low columnar basal cells containing some intracellular organelles. They were attached, with a few desmosomes, to cells of the adjacent layer that resembled internal enamel epithelium of the enamel organ. The polygonal stellate reticulum-like cells possessed desmosomes and many cytoplasmic projections, while the cytoplasm contained some intracellular organelles and a few bundles of tonofilaments. The ghost cells contained many haphazardly arranged bundles of tonofilaments 60–240 nm in diameter. No intact intracellular organelles were observed in their cytoplasm. They were attached to neighbouring ghost cells with scanty desmosomes and their cell membranes were discontinuous in parts. A variety of vesicles, 90–450 nm in diameter, were scattered among the tonofilaments and some contained needle-like crystals that were thought to be the initial calcification sites in ghost cells. These vesicles resembled matrix vesicles and the authors suggested that matrix vesicle-like structures might be involved in the initiation of calcification of the ghost cells. The fourth cell types the authors identified were scattered in the vicinity of the focal accumulations of ghost cells. Their cell membranes were discontinuous in part and contained dilated membranous organelles and evenly distributed tonofilaments.

Treatment

The COC is treated by surgical enucleation unless it is associated with another odontogenic tumour, in which case wider excision may be required. In the presence of a complex odontome, conservative removal will still be adequate. An ameloblastoma or one of its variants with foci of ghost cells must be treated as would be an ameloblastoma without ghost cells. Although classic uncomplicated cases of COCs may grow to a large size, reported recurrences are rare.

9

Nasopalatine Duct (Incisive Canal) Cyst

The epithelial-lined cysts of non-odontogenic origin had been thought to be derived from embryonic epithelial residues in the nasopalatine canal and, in the opinion of many workers, from epithelium included in lines of fusion of embryonic facial processes. The latter view has been extremely controversial, as many embryologists and pathologists discount the possibility of such an origin, stating that the grooves between the processes are smoothed out by proliferation of the underlying mesenchymal growth centres, a process referred to as 'merging'. An exception is in the case of the palatal shelves where developmental processes do make ectoderm to ectoderm contact with subsequent ectodermal degeneration (Allard *et al.* 1981a; Allard, 1982; Daley and Wysocki, 1997). An account of the embryology and anatomy of the anterior region of the palate will be found in the latter publications.

It is generally agreed that the nasopalatine duct cyst is an entity. It may occur within the nasopalatine canal or in the soft tissues of the palate, at the opening of the canal, where it is called the 'cyst of the palatine papilla'. The term 'nasopalatine duct cyst' is preferred to the synonymous 'incisive canal cyst'.

In recent years, doubt has been expressed as to whether the so-called 'median palatine cyst' is an entity or whether cysts in that region are merely posterior extensions of nasopalatine duct cysts. This point is discussed again later. Our policy, therefore, has been to report all developmental midline cysts of the maxilla as nasopalatine duct cysts.

Clinical features

Frequency

The nasopalatine duct cyst is the most common of the non-odontogenic cysts and comprises, in the University of the Witwatersrand, Department of Oral Pathology, 404 of the 3498 jaw cysts registered over a 46-year period (11.6%) (see Table 1.1). These include the cysts that were originally diagnosed as median palatine cysts and those that were predominantly in the soft tissues and were called cysts of the palatine papilla. Some indication of the frequency of nasopalatine duct cysts in the general population may be determined from studies on cadaver and dry skull material. Meyer (1931) examined 600 cadavers and observed a frequency of 1.5%. This was similar to the frequency of 1.3% reported by Chamda and Shear (1980) who found 13 cysts in 970 dry skulls in the Raymond Dart collection of the Department of Anatomy, University of the Witwatersrand. Killey *et al.* (1977), however, reported detecting only two nasopalatine duct cysts in a series of 2394 dry skulls (0.08%).

In a series of 403 non-odontogenic cysts identified by Daley *et al.* (1994) in 40 000 consecutively accessioned oral biopsies, the nasopalatine duct cyst was the most frequently diagnosed, comprising 295 (73.4%).

Age

The age distribution of 227 of the University of the Witwatersrand cases is shown in Fig. 9.1. There was only one case in the first decade and the majority occurred in the third to the sixth decades. Another rare case has been reported of a nasopalatine duct cyst in an 8 year old girl (Velasquez-Smith *et al.*, 1999).

Gender

In our material there has been a significantly higher ($P < 0.001$) frequency of nasopalatine duct cysts in men (71%) than women (29%) and a somewhat higher ratio of men to women in the sample of black patients (2.7:1) than in white (2.0:1). In a series of 256 patients, 182 were men (71%) and 74 were women (29%): a ratio of men to women of 2.5:1. Of these, 128 were black men and 47 black women (2.7:1); 54 were white men and 27 white women (2.0:1) (Table 9.1).

Killey *et al.* (1977), Hedin *et al.* (1978), Bodin *et al.* (1986), Swanson *et al.* (1991), Vasconcelos (1999) and Elliott *et al.* (2004) also recorded a male preponderance, but in the series of Abrams *et al.* (1963) there was an equal gender frequency.

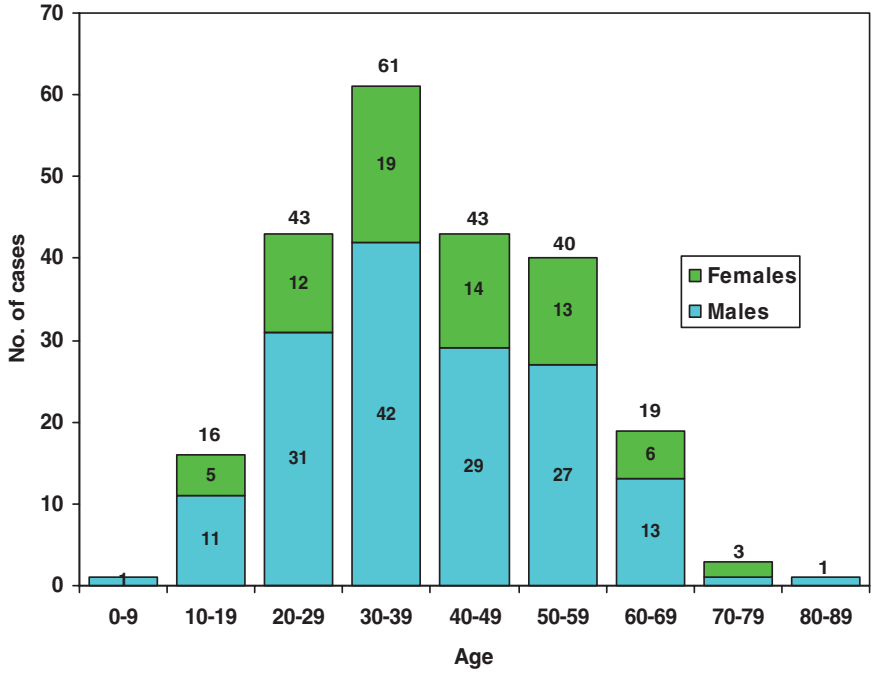


Fig. 9.1 Age distribution of 227 patients with nasopalatine duct cysts.

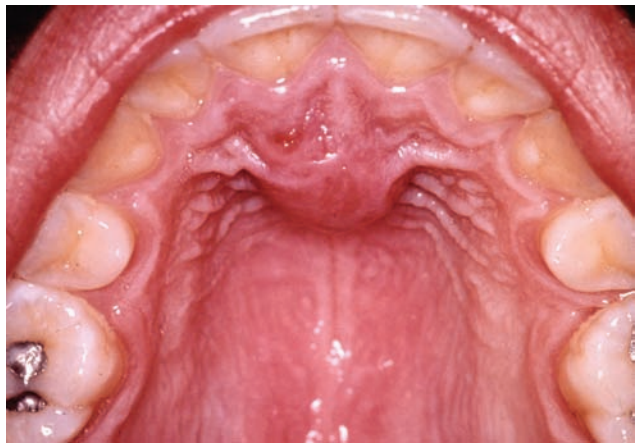


Fig. 9.2 Small nasopalatine cyst presenting as a soft ovoid swelling in the midline of the maxilla, posterior to the central incisor teeth. (Courtesy of the late Professor J.J. Pindborg.)

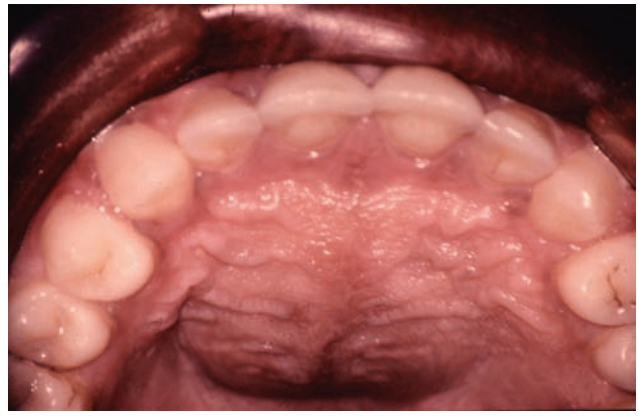


Fig. 9.3 Large nasopalatine duct cyst extending laterally and posteriorly to involve much of the hard palate.

Table 9.1 Gender distribution of 256 black and white patients with nasopalatine duct cysts.

	Men	Women	Row Total	Ratio of M : F
Black	128	47	175	2.7 : 1
White	54	27	81	2.0 : 1
Column total	182 (71%)	74 (29%)	256	2.5 : 1
B : W ratio	2.4 : 1	1.7 : 1	2.2 : 1	

Clinical presentation

The most common symptom is swelling, usually in the anterior region of the midline of palate (Figs 9.2 and 9.3). Swelling also occurs in the midline on the labial aspect of the alveolar ridge (Fig. 9.4) and in some cases 'through and through' fluctuation may be elicited between the labial and palatal swellings. The cyst may produce bulging of the floor of the nose. In the series of 35 cases reported by Anneroth *et al.* (1986), almost all varied between 1.0 and 2.5 cm and the majority were seen as ovoid or round swellings. It is when midline swellings of the palate occur further posteriorly that diagnoses with the erroneous terminology of 'median palatine cyst' tend to be made. In a number of cases, the swelling is associated with pain through pressure on the nasopalatine nerves; as well as discharge, but sometimes discharge is the only complaint and in a few cases pain is the only symptom. Various combinations of swelling, discharge and pain may occur. The discharge may be mucoid, in which case patients sometimes describe a salty taste, or it may be purulent and patients complain of a foul taste. In patients with cysts of the palatine papilla, there may be a

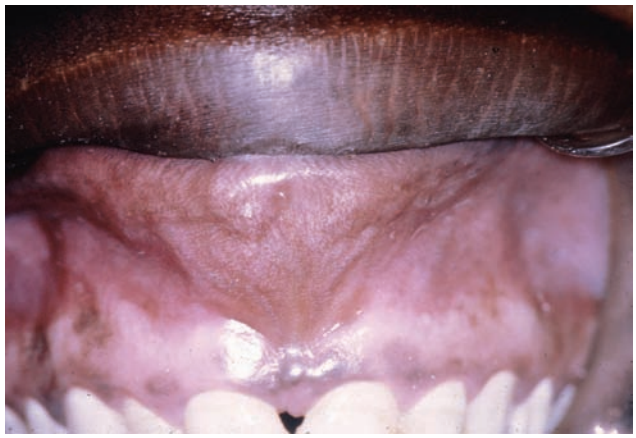


Fig. 9.4 Nasopalatine duct cyst producing a midline swelling of the labial aspect of the alveolar ridge.

history of recurrent swellings that periodically discharge and then 'go down'. Displacement of teeth is observed fairly often.

In general, symptoms are not severe and patients often disregard them for many years. They may also be completely symptomless and be discovered fortuitously by the dentist during routine radiological examination, and occasionally the presence of a cyst may become apparent after dentures are placed.

Nortjé and Farman (1978) and Hertzanu *et al.* (1985) have suggested that this lesion may produce more severe symptoms and be more aggressive and larger in black South African patients. From a sample of 114 nasopalatine duct cysts, the latter authors selected all cases with a transverse diameter of greater than 30 mm. All of these occurred in black patients. They did point out, however, that late clinical presentation may be responsible for the large size at the time of diagnosis.

In establishing a diagnosis of nasopalatine duct cyst it is important to attempt to exclude the possibility of a periapical lesion by testing the pulp vitality of the incisor teeth. It has also been pointed out (Neville *et al.*, 1997) that the odontogenic keratocyst must be included in the differential diagnosis of anterior midline radiolucencies of the maxilla. They reviewed 18 such cases and reported that 16 of these patients were older than 60 years of age.

Radiological features

The nasopalatine duct cyst occurs in the incisive canal and it may be difficult to decide whether a radiolucency in that area is a cyst or a large incisive fossa. In attempting to distinguish between the two, the study carried out by Roper-Hall (1938) has frequently been quoted. In an investigation of 2162 skulls selected at random from a series of over 6000, he found that the incisive fossae of 2154 were absent or small. Five were of medium size, one was enlarged but shallow and two were large and cystic. The shapes of the fossae were round, oval, diamond or triangular and sometimes funnel-shaped. Their anteroposterior measurements were usually greater than the widths although the average measurements were 3 mm wide, 3 mm anteroposteriorly and 2–3 mm deep. The largest fossa that was at all frequent was 5 mm wide and 7 mm anteroposteriorly. Of the seven that were larger than this, four were 6 mm wide and 8 mm anteroposteriorly; and one was 6 mm wide and 10 mm anteroposteriorly. The two cavities which were large and cystic were 7 ×15 mm and 7×14 mm respectively. Roper-Hall concluded that any radiograph of the fossa that showed a shadow less than 6 mm wide may be considered to be within normal limits, provided the patients have no other symptoms. Similar observations made by Killey *et al.* (1977) on 2394 fossae confirmed Roper-Hall's views.

In our own study, however, in which the dimensions were measured of the incisive fossae of 970 skulls from the Raymond Dart Collection in the Department of Anatomy, University of the Witwatersrand, the mean anteroposterior dimensions and the widths were both substantially greater than those in the previous reports (Chamda and Shear, 1980). The mean anteroposterior dimension and standard deviation in our sample was 10.19±3.24 mm and the mean width 4.79±1.33. Incisive fossa widths of greater than 6 mm were found in 148 specimens (15.3%) of which 13 were associated with cysts. The greatest width in the non-cystic category was 8.05 mm. Anteroposterior dimensions of greater than 7 mm were found in 799 specimens (82.4%) including the 13 cysts. The greatest anteroposterior dimension in the non-cystic category was 17.5 mm.

Radiographs, using a standardised technique, were taken of 164 of the skulls, selected at random (Fig. 9.5). The mean anteroposterior dimensions of the incisive fossae on these radiographs was 11.67±3.27 mm and the mean widths 4.50±1.61 mm. The difference between these measurements and the actual measurements on the same 164 skulls was statistically significant. In some instances, the ratio of skull : radiograph dimensions was greater than unity and in others less than unity. Although the two sets of measurements correlated strongly with each other, the range of variation around unity indicated that it was invalid to extrapolate skull dimensions from radiographic measurements even if a multiplication factor was used.

It would appear from this latter study that a radiographic shadow with anteroposterior dimensions of as much as 10 mm in the incisive fossa region may be within normal limits. In the absence of any other symptoms or signs, such patients should be observed and re-radiographed at intervals rather than be subjected to immediate surgery. Bodin *et al.* (1986) proposed that if the width of the radiolucency exceeded 8 mm, was pronounced and had a thin cortical border on the periphery,

exploratory surgery should be considered especially if the lesion was asymmetrically bulging; and that radiolucencies exceeding 14 mm in diameter were always cysts.

Incisive canal cysts are found in the midline of the palate, above or between the roots of the central incisor teeth (Fig. 9.6). In the latter case, the incisor roots may diverge. The lesions are round or ovoid and some may appear heart-shaped, either because they become notched by the nasal septum during their expansion or because the nasal spine is superimposed on the radiolucent area, or if there are bilateral cysts. Cysts may develop bilaterally in both Stenson canals and in some instances the radiolucency may be seen laterally if a single cyst develops in one of the major lateral canals of Stenson (Stafne, 1969).

Very large cysts extend posteriorly and superiorly and it is these that may have given rise to the diagnosis of median palatine cyst (Fig. 9.7). Cysts close to the floor of the nose may be more clearly demonstrated on panoramic than on occlusal films (Nortjé and Farman, 1978). The margins of nasopalatine duct cysts are well demarcated but exhibit varying degrees of cortication (Bodin *et al.*, 1986; Nortjé and Wood, 1988). In the sample of 46 cases reported by the latter authors, the radiolucencies ranged from 9 to 52 mm in greatest diameter. Tooth displacement was common with their roots directed distally. Amorphous intraluminal calcifications were seen in a few cases. In the study of Bodin *et al.* (1986), the great majority of radiolucent areas had lateral dimensions in the

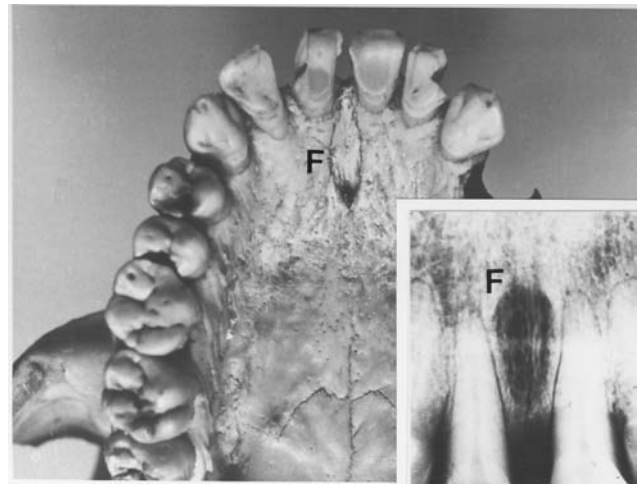


Fig. 9.5 Incisive fossa (F) on a dry skull. Inset: radiograph of an incisive fossa (F) on a different dry skull. (Courtesy of Dr R. Chamda.)

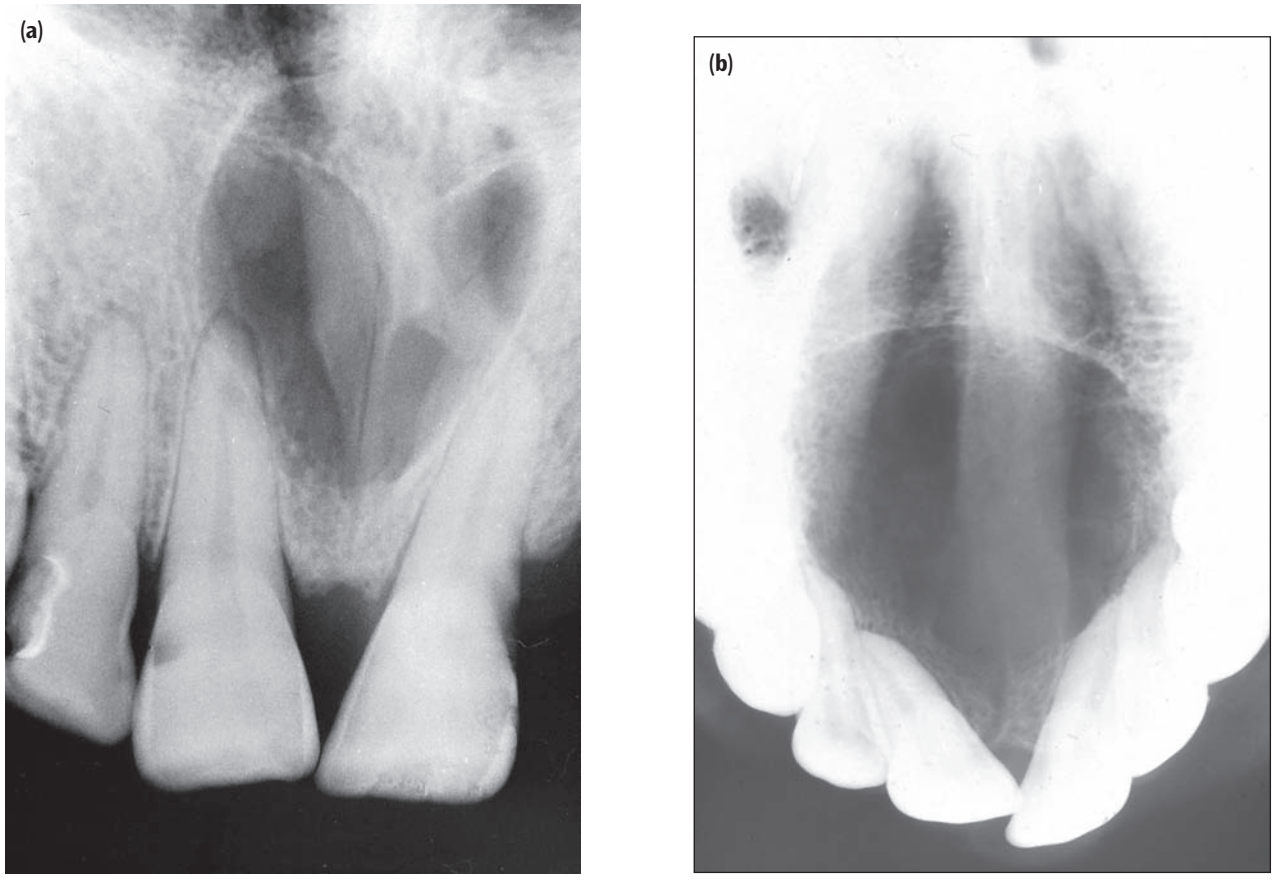


Fig. 9.6 (a) Radiograph of a nasopalatine duct cyst showing a pear-shaped radiolucency in the anterior maxilla. The lamina dura on the left is intact although the apex appears to be in the cyst. (b) Shows a large round radiolucency. The roots of the maxillary incisor teeth are displaced laterally.

range 7–12 mm. In a sample of 116 cases reported by Swanson *et al.* (1991), 6.4% were 6 mm or less in diameter. Struthers and Shear (1976) observed some degree of root resorption with four of 11 nasopalatine duct cysts which were contiguous with tooth roots.

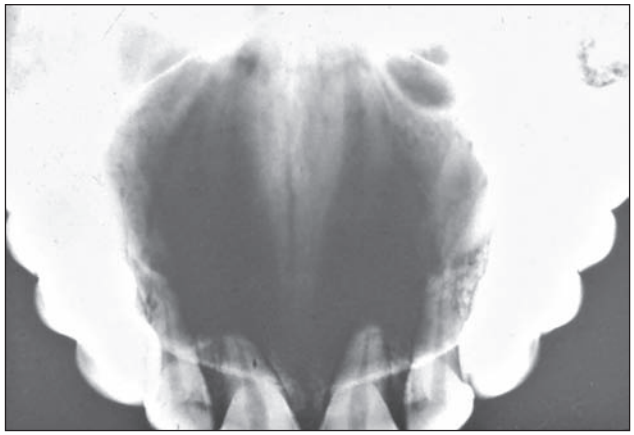


Fig. 9.7 Radiograph of a large nasopalatine duct cyst producing separation of the incisor roots. Lesions like this would, in the past, have been diagnosed as median palatine cysts.

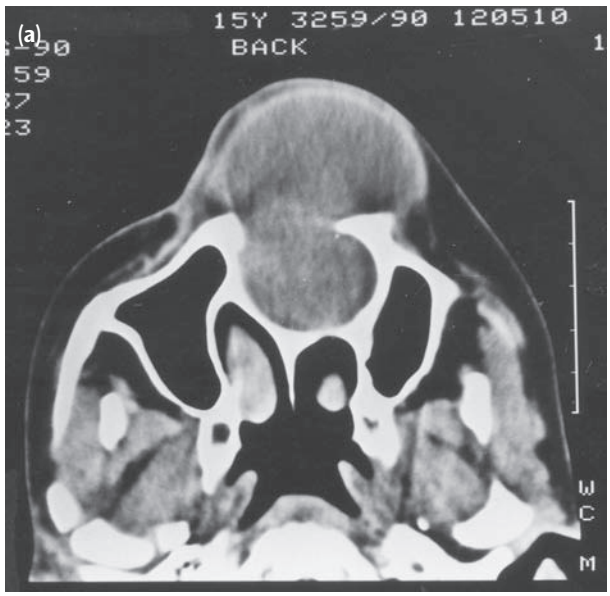
If the radiolucent area appears on a dental radiograph to be related to the apex of an incisor tooth, an occlusal view will usually demonstrate that the cyst and the apex are separated. In addition to the demonstration of pulp vitality, it may also be possible to see an intact lamina dura around the tooth apices (Fig. 9.6).

The radiological investigation of nasopalatine duct cysts by tomography has been described by Lysell and Molin (1972). Hertzanu *et al.* (1985) suggested that computed tomography appeared to be of value in the investigation of large lesions with destruction of bone and posterior and intranasal extension (Fig. 9.8). Spinelli *et al.* (1994) and Hisatomi *et al.* (2003) have referred to the value of magnetic resonance imaging in the diagnosis of the nasopalatine duct cysts.

Woo *et al.* (1987) reported a case of a keratocyst that occurred in the anterior midline of the maxilla, simulating a nasopalatine cyst, and reference has been made above to similar findings by Neville *et al.* (1997).

Pathogenesis

Nasopalatine duct cysts are thought to arise from the nasopalatine ducts in the incisive canal, but the aetiolog-



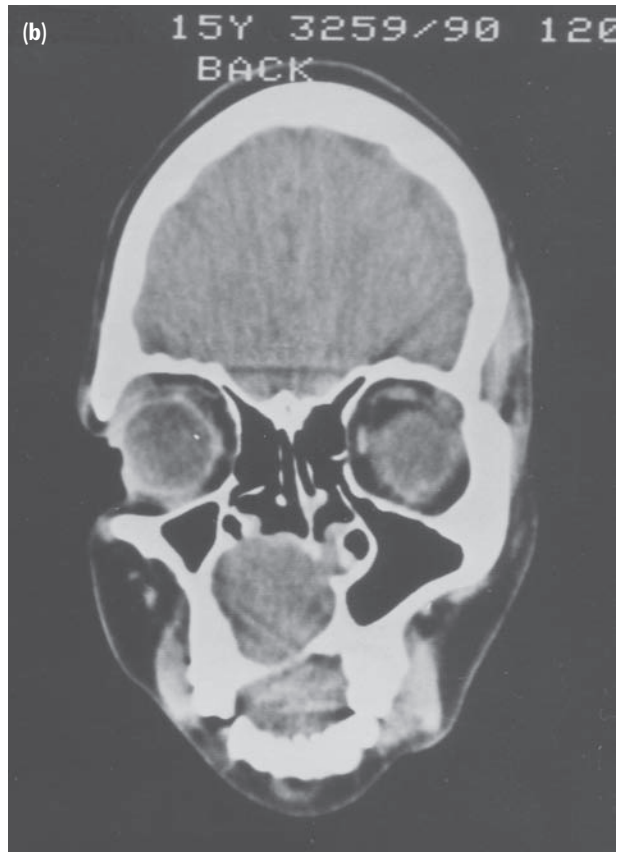


Fig. 9.8 Nasopalatine duct cyst. (a) Axial CT scan showing a well-defined mass extending through the palatal ridge. (b) Coronal scan showing bowing of the hard palate and extension of the mass into the nasal cavity. (Courtesy of Professor J. Lownie.)

ical factors associated with their formation and their pathogenesis are largely speculative.

In lower animals, the nasopalatine ducts are concerned in some way with the sense of smell. In humans, vestigial remnants of this primitive organ of smell may be found in the incisive canals in the form of epithelial-lined ducts, epithelial cords, epithelial rests or combinations of these. Epithelial rests may show central degeneration. The frequency with which a continuous patent nasopalatine duct between the nasal and oral cavities occurs in humans is uncertain, as various authors have reported different findings. These were summarised by Abrams *et al.* (1963) who carried out similar studies on 24 fetuses. In none of these was there either a continuous patent duct or epithelial cords. In no instance did they find a patent oral opening of a nasopalatine duct, although nine patent nasal openings were identified. Sixteen fetuses had portions of nasopalatine duct with central lumina and three of these had an appearance suggestive of cystic degeneration. In their investigation the ducts were lined most frequently by squamous epithelium (82% of cases) and most of these were in the oral and middle thirds of the incisive canals. A primitive or cuboidal lining was present in 41% of cases, and these were predominantly in the nasal third. Although squamous epithelium lined some nasopalatine ducts in the nasal third of the canal, in no case was pseudostratified columnar epithelium found in the oral third.

The vomer–nasal organs of Jacobson are sometimes mentioned as a possible source of cysts in the incisive canal but this is most unlikely. They are bilateral structures that lie at the base of the nasal septum just above the nasal extremity of the incisive canals. They are believed to be associated with the nasopalatine ducts as olfactory organs in many animals, and have been demonstrated in human embryos (Abrams *et al.*, 1963).

As far as aetiology is concerned, it has been suggested that trauma or bacterial infection could stimulate the nasopalatine duct remnants to proliferate. There is, however, very little evidence to support such hypotheses. On the contrary, a number of factors tend to preclude these possibilities. If trauma to the area during mastication is the cause, why are the cysts found so infrequently when such trauma is very common? Why are the cysts so much more frequent in males than females? Some nasopalatine duct cysts, particularly those higher up in the canal away from the mouth, are relatively free of inflammatory infiltrate. Nor does one see arcading of proliferating stratified squamous epithelium as in inflamed radicular cysts. These latter two points do not of course definitely exclude the possibility of an inflammatory origin, as the inflammatory process could have subsided before the cyst was removed. They do, however, suggest that more evidence is required to support such a theory of onset. The fact that there may be an intense inflammatory cell infiltrate in the walls of cysts of the palatine papilla is not really adequate evidence to support an inflammatory origin, as cysts of this region are more than likely to be traumatised and thereby show a secondary inflammatory reaction.

The fact that mucous glands develop in association with nasopalatine ducts and are sometimes seen in the walls of the cysts has led to the suggestion that the cysts may be caused by secretion of mucin from the glands into the duct lumina, particularly when the duct is blocked. Factors against such an origin are that only very infrequently have connections between the mucous glands and the duct lumina been demonstrated and that the secretory pressure that would exist is unlikely to be adequate to produce bone resorption and form an intra-osseous cyst.

Main (1970a) has postulated that nasopalatine duct cysts, like keratocysts, develop spontaneously. Although there is no proof for such an hypothesis, the concept is in accord with some of the facts. First, there is the observation that small cystic dilatations of portions of the nasopalatine ducts are occasionally seen in fetal material. It would explain the absence of inflammatory cell infiltrates from so many cases as well as the relative infrequency of the cysts in relation to the frequency of trauma in the nasopalatine area. Main (1970a) has shown that nasopalatine duct cysts display a lesser tendency than keratocysts for epithelial proliferation, which partly explains their slow growth and moderate size. Main (1970b) believed that fluid accumulation was likely to be responsible for the enlargement of nasopalatine duct cysts but what leads to the initial collection of fluid in the cyst cavity is uncertain. Osmotic attraction of serum through normal capillary walls may occur and in the absence of drainage of this fluid (Toller, 1966b) the hydrostatic pressure would increase. Osmotically active particles would be supplied by the breakdown of cells shed into the cyst cavity.

The mechanism that might initially trigger the spontaneous development of nasopalatine duct cysts, if this is indeed what happens, has yet to be identified. It seems possible that the occurrence of these cysts, as with other jaw cysts, may have some genetic determinant.

Histological features (Figs 9.9–9.11; Table 9.2)

The microscopic features of the epithelial linings of nasopalatine duct cysts are extremely variable. Stratified squamous, pseudostratified columnar, cuboidal, columnar, or primitive flat epithelium may be seen, individually or in combination.

Goblet cells may be found in pseudostratified columnar epithelial linings and cilia, although most frequently seen on the surface of pseudostratified columnar epithelia, may

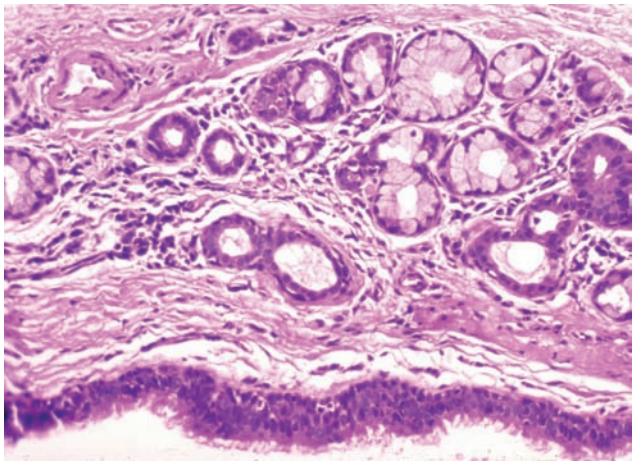


Fig. 9.9 Nasopalatine duct cyst lined in this field by pseudostratified ciliated columnar epithelium. Mucous glands are present in the wall.

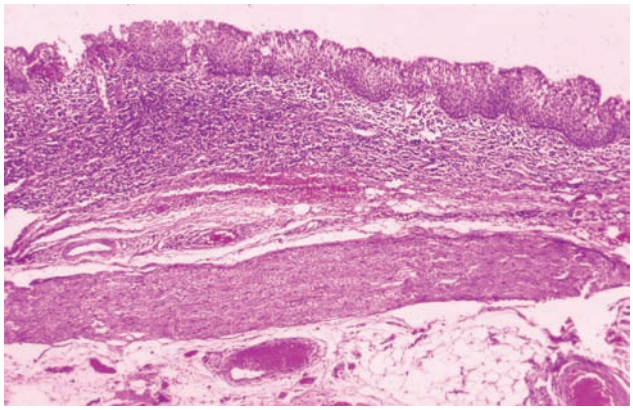


Fig. 9.11 Neurovascular bundle in the wall of a nasopalatine duct cyst.

also be present in association with columnar and, very rarely, with cuboidal epithelium.

Stratified squamous epithelium is found more frequently than any other, followed by pseudostratified columnar. In a series of 86 of our own cases which have been analysed histologically (Table 9.2), 67 (78%) were lined by stratified squamous epithelium; 33 entirely, whereas 22 were lined in part by pseudostratified ciliated columnar epithelium. Thirty-nine cysts (45%) contained pseudostratified ciliated columnar epithelium in part of their linings, but only seven were lined entirely in this way. Four cysts were lined in part by simple columnar and 18 by simple cuboidal epithelium. One was lined entirely by cuboidal epithelium. These distributions are very similar to those of Abrams *et al.* (1963). Similar histological analyses have been done by Allard *et al.* (1981a) and Bodin *et al.* (1986).

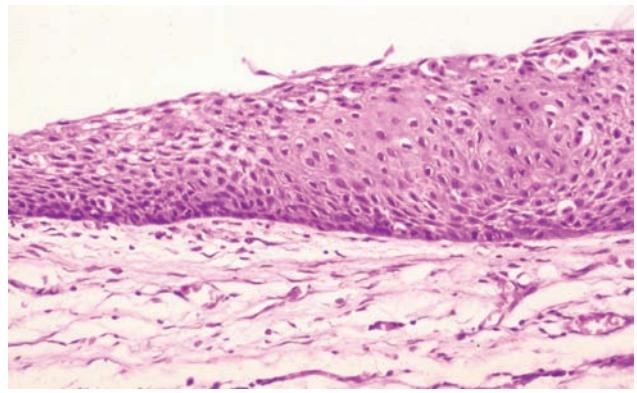


Fig. 9.10 Nasopalatine duct cyst lined in this field by stratified squamous epithelium.

Table 9.2 Histological features in 86 nasopalatine duct cysts.

	Numbers	Percentage
Epithelium		
Stratified squamous	67	78
entirely	33	
partly pseudostratified ciliated	22	
partly cuboidal	10	
partly columnar	2	
Pseudostratified ciliated columnar	39	45
entirely	7	
partly squamous	22	
partly cuboidal	8	
partly columnar	2	
Fibrous cyst wall		
Neurovascular bundle	39	45
Large muscular-walled vessels	62	72
Mucous glands	6	7
Cartilage	6	7
Nasopalatine duct remnants	19	22
Inflammatory infiltrate		
absent	21	24
mild	39	45
moderate	17	20
severe	9	11

Although it has been averred that cysts lined by respiratory epithelium probably originate from nasopalatine duct adjacent to the nasal cavity, whereas those lined by stratified squamous epithelium develop from the lower portion of the duct, this should not be regarded as a rule. For one thing, cysts of the palatine papilla may be lined by pseudostratified ciliated columnar epithelium, and for another, it is rare to find a nasopalatine duct cyst lined entirely by one variety of epithelium (Table 9.2). Furthermore, except for cysts of the palatine papilla, it is

rare for a surgeon to state in the biopsy request what the anatomical level of any particular nasopalatine duct cyst was, so that it is not really possible to correlate position with histology. The fact that the majority of cyst linings have a combination of epithelial varieties is suggestive of their origin from pluripotential epithelium but the possibility that metaplasia occurs must also be considered.

A valuable diagnostic feature of nasopalatine duct cysts is the presence of nerves and blood vessels in the fibrous capsule (Fig. 9.11). Abrams *et al.* (1963) showed that moderate-sized nerves were present in 88% of their series and in the remaining 12% nerves were present, although few and small. In 87% of their cases, muscular arteries and numerous small veins were present. Our own observations support the frequency with which these features are found. In our series of 86 cases, prominent neurovascular bundles were found in 45% and large muscular arteries in 72%. The explanation for this phenomenon is that the long sphenopalatine (nasopalatine) nerve and vessels that pass through the incisive canal are either included in the cyst wall or are removed with the cyst in the course of surgical enucleation.

Small foci of mucous glands (Fig. 9.9) were found in the fibrous capsules of approximately one-third of cases in the series of Abrams *et al.* (1963) and of Allard *et al.* (1981a) but in only 7% of our own. As the foci are small, it is probable that their frequency would be higher if biopsy material were more extensively sampled. It has been suggested that the presence of mucous glands in a cyst wall is strong evidence in favour of the diagnosis of nasopalatine duct cyst, but we have seen them in an undoubted nasolabial cyst (see Fig. 10.6).

One patient in our series had bilateral cysts and in 19 cases (22%) nasopalatine ducts or their remnants were present in the main cyst wall. In the study of Abrams *et al.* (1963), epithelial cell rests were found in the walls of 22 of 61 cysts (36%).

As far as evidence of inflammation is concerned, we found that 21 of our cases (24%) were relatively free of inflammatory cell infiltrate. In 39 (45%) there was a mild chronic inflammatory cell infiltrate. In 17 (20%) the chronic inflammatory process was graded as moderate and in 9 (11%) as severe. In two cases there was a superimposed acute inflammatory cell infiltrate.

Small islands of hyaline cartilage may very rarely be seen in the cyst walls. They were present in six of our cases (7%) and Abrams *et al.* (1963) found cartilage in all four of their palatine papilla cysts. The latter authors pointed out that unlike the incisive canal and surrounding palatal bone, the palatine papilla normally possessed a small accumulation of cartilage in its anterior aspect.

Redman (1974) and Stam *et al.* (1979) have reported the occasional occurrence in nasopalatine duct cysts of an epithelial lining containing granules of pigment which was identified histochemically as melanin and possibly also lipofuscin. These workers were impressed by the resemblance of this lining to olfactory epithelium where olfactory neurons and goblet cells were sparse. Redman suggested that their origin was from nasopalatine duct which had differentiated into olfactory epithelium whereas Stam *et al.* considered that the epithelium developed from remnants of Jacobson's organ. El-Bardaie *et al.* (1989) reported two cases of pigmented nasopalatine duct cysts in which they were able to demonstrate dendritic melanocytes in the basal layer of the epithelium, thereby identifying the pigment as melanin.

Gao *et al.* (1989) reported that nasopalatine duct cysts differed in their cytokeratin pattern from those of odontogenic origin in strongly expressing simple epithelial keratins.

Treatment

Nasopalatine duct cysts are treated by surgical enucleation.

NOTE ON THE SO-CALLED MEDIAN PALATINE, MEDIAN ALVEOLAR, MEDIAN MANDIBULAR AND GLOBULOMAXILLARY CYSTS

In previous editions of this book, a separate chapter was devoted to this group of lesions. In recent years, their existence as separate entities has been questioned and they were excluded from the 1992 WHO Classification of epithelial jaw cysts (Kramer *et al.*, 1992). Previously, it had been thought that these cysts developed from epithelium entrapped in the process of fusion of embryonic processes. It is now believed that they represent posterior extension of an incisive canal cyst in the case of median palatine cyst; anterior extension in the case of median alveolar cyst; and a range of other odontogenic cysts, frequently an odontogenic keratocyst, in the case of the globulomaxillary cysts. Moreover, the so-called median alveolar cyst may also, in a number of instances, be a keratocyst derived from dental lamina in the midline of the maxilla.

The authors of this edition believe that the time has come to lay this group of lesions to rest once and for all. The purpose of this note is to provide an epitaph to support this decision.

Reference has been made elsewhere (see Chapter 2) to the presence of cysts along the midpalatal raphé which arise from epithelial inclusions at the line of fusion of the palatal folds and the nasal processes. After birth, the epithelial inclusions usually atrophy and become resorbed, but some may produce keratin-containing

microcysts (see Fig. 2.4), which extend to the surface and rupture during the first few months after birth. These are not, however, what are usually referred to as median palatine or median posterior palatine cysts, which are described as intrabony cysts in the midline of the palate. If a median posterior palatine cyst indeed existed it would be necessary to postulate its origin as being by enlargement of a midpalatine raphé cyst, or from epithelial inclusions in the region (Courage *et al.*, 1974). The contingency of this occurring must be remote. The midpalatine raphé cysts and the epithelial inclusions lie close to the palatal epithelium. It seems unlikely that a median palatine cyst could develop in this site and produce extensive bone resorption without forming a large palatal swelling at a very much earlier stage of its natural history.

A re-examination was carried out some years ago of the histological sections of 15 cases diagnosed as median palatine cysts before 1968 when we stopped making this diagnosis. Six of these were lined exclusively by stratified squamous epithelium while the remaining nine were lined in part by pseudostratified ciliated columnar, cuboidal or columnar epithelium. Of the six lined exclusively by stratified squamous epithelium, three contained neurovascular bundles in the wall and another two contained large muscular blood vessels. Two of this group also showed remnants of nasopalatine ducts in their walls. There was no evidence of mucous glands in the walls of any of the 15 cases. These histological features would be consistent with a diagnosis of a nasopalatine duct cyst.

As far as the median alveolar cyst of the maxilla was concerned, Sicher (1962) was convinced that there was no embryological basis for assuming that it developed from epithelium enclaved at the site of fusion between the right and left globular processes. 'Such a fusion,' wrote Sicher, 'simply does not occur'.

Median mandibular cyst

A cyst occasionally occurs in the midline of the mandible. It produces a well-defined round, ovoid or irregular radiolucent area and may separate the roots of the lower incisor teeth. In some of the reported cases, the associated teeth have given non-vital pulp responses (Olech, 1957: Case 2; Albers, 1973; Kniha and Gokel, 1985) and in others they have all been vital (Olech, 1957: Case 1; Meyer, 1957; Lucchesi and Topazian, 1961; Blair and Wadsworth, 1968; Buchner and Ramon, 1974; White *et al.*, 1975; Case 1; Killey *et al.*, 1977; Soskolne and Shteyer, 1977; Nanavati and Gandhi, 1979).

The presence of a cyst in the midline of the mandible associated with vital teeth tempted some workers to propose its origin from epithelial inclusions trapped in the area during embryonic development. However, this concept is not tenable as the mandible forms in the mandibular process which develops as a single unit. As no fusion takes place between ectodermal processes it is not possible to postulate that epithelial entrapment occurs. However, there are still those who argue otherwise. Allard (1982) has cited Patten (1961) who stated that if, during the process of merging, the mesenchyme inferior to the dividing groove becomes relatively inactive and the mesenchyme in the protruding eminences continues to grow at a normal or accelerated rate, the ectodermal surfaces could come into contact and form a source of fissural epithelium. Allard added, however, that the rebuilding of the midline portion of the mandible about Meckel's cartilage reduced the chances of survival of any enclaved epithelial rests.

Those cysts associated with teeth that have non-vital pulps are very likely to be radicular, and when these are lined in parts by ciliated pseudostratified columnar epithelium, it may very possibly be the result of secretory metaplasia. Olech's Case 1 and Meyer's case show histological features that resemble but are not identical to those of keratocysts. The two cases reported by Buchner and Ramon appear to be keratocysts. The published photomicrographs of the cases reported by Lucchesi and Topazian (1961) and by Blair and Wadsworth (1968) show a thin epithelial lining resembling reduced enamel epithelium and may possibly be lateral periodontal cysts, as is the case reported by Difiore and Hartwell (1987). The case of Killey *et al.* (1977) was a solitary bone cyst, as was that of Zachariades *et al.* (1982). Craig *et al.* (1980) have described an intra-osseous dermoid cyst in the midline of the mandible and suggested that this possibility should be considered in the differential diagnosis of midline cystic lesions of the mandible. Tanimoto *et al.* (1983) analysed 12 cysts in the median mandibular region and believed that all could be either keratocysts, solitary, lateral periodontal or radicular cysts. Gardner (1988) surveyed 20 reported cases of median mandibular cyst and concluded that all could be odontogenic cysts. Allard (1982) has stated that in a series of about 8000 surgical specimens seen in the oral pathology department of his institution over a 10-year period, a diagnosis of median mandibular cyst could not be made with confidence in a single case. This would probably be the experience of most oral pathology departments.

There is little evidence, therefore, to indicate that the median mandibular cyst is an entity.

Globulomaxillary cyst

The globulomaxillary cyst has traditionally been described as a fissural cyst found within the bone between the maxillary lateral incisor and canine teeth.

Radiologically, they have been well-defined radiolucencies that frequently cause the roots of the adjacent teeth to diverge. While there can be no doubt that cysts do occur in this region and that the pulps of the adjacent teeth may give positive vitality responses, there is now a considerable body of opinion against the idea that they are fissural cysts. The evidence against their being fissural cysts is in fact more substantial than the evidence in favour.

The first description of the globulomaxillary cyst has been ascribed to Thoma (1937). It was believed for many years that they were fissural cysts arising from non-odontogenic epithelium included at the site of fusion of the globular process of the medial (frontonasal) process and the maxillary process. A variation of this concept was proposed by Ferenczy (1958) who considered that these cysts formed at the junction of the premaxilla and maxilla and that they should be called premaxillary maxillary cysts. Sicher (1962) seriously questioned the traditional theory of origin of globulomaxillary cysts, stating that on embryological grounds such an explanation was impossible. He believed that cysts in that region were probably keratocysts. Sicher's views were strongly supported by Kitamura (1976) on the basis of his own extensive embryological studies.

Embryologists have pointed out (Arey, 1965; Sadler, 1995) that the surface bulges seen in the nasomaxillary complex of the embryo and which are called 'facial processes' are not in fact prolongations with free ends which meet in the nasal region. Other than at the median palatal raphé there is no ectoderm–ectoderm contact that requires dissolution of the ectodermal surfaces prior to mesenchymal merging and there is therefore no possibility of enclavement of ectodermal residues. The facial processes are in fact merely elevations or ridges that correspond to centres of growth in the underlying mesenchyme. These are covered by a continuous sheet of folded epithelium. As these growth centres proliferate and develop, the surface furrows between them become more shallow and eventually smooth out.

A critical study of the whole question of globulomaxillary cysts was reported by Christ (1970). In a survey of the literature over the 50-year period 1920–1969, he found very few cases that fulfilled the criteria for acceptance; namely, a radiograph of the lesion, positive vitality of adjacent teeth, and tissue sections or photomicrographs of the histological material. He pointed out that his literature review revealed that a wide variety of other lesions present clinically and radiologically as globulomaxillary cysts. These included adenomatoid odontogenic tumours, myxoma and haemorrhagic bone cyst. Many cases were reported in the literature as globulomaxillary cysts despite the fact that there were non-vital or absent lateral incisors or canines.

He also reviewed 27 cases from his own departmental records and found that only three satisfied the criteria for inclusion in his study. Histologically, two of these appeared to be keratocysts and the other was thought to be of odontogenic origin. He suggested, therefore, that the globulomaxillary cyst was in fact an odontogenic cyst and that its clinical and radiological appearances may fit the diagnosis of lateral periodontal, lateral dentigerous and keratocyst.

Zegarelli and Zegarelli (1973) emphasised also that the globulomaxillary region was a potential site for a wide range of pathological entities and a definitive diagnosis should not be made before histopathological examination.

A review in 1975 of 17 of our own cases accessioned as globulomaxillary cysts tended to support Christ's views. Only six of them showed any semblance of respiratory epithelium. Two of the cases had the classic histological features of keratocysts; four were associated with missing or root-treated teeth and fulfilled the criteria for diagnosis as radicular or residual cysts; four had histological features very much like those seen in lateral periodontal cysts; and in five the clinical information was quite inadequate for a definitive diagnosis. There remained two possible cases, and even in these the clinical information was equivocal and the respiratory epithelium in the cyst linings could be explained on the basis of metaplasia. The 18 so called globulomaxillary cysts included in Table 1.1 are relics of that earlier period.

Wysocki (1981) came to the same conclusion following his analysis of 37 cases that had been diagnosed clinically as globulomaxillary cysts. On histological examination 19 were radicular cysts, six periapical granulomas, four developmental lateral periodontal cysts, three keratocysts, three central giant cell granulomas, one calcifying odontogenic cyst and one odontogenic myxoma. Other lesions such as the adenomatoid odontogenic tumour, ameloblastoma and haemorrhagic bone cyst have also been reported in the globulomaxillary region and misdiagnosed as such on clinical and radiological grounds. Kuntz and Reichart (1986) have reported a case of an adenomatoid odontogenic tumour simulating a globulomaxillary cyst and Vedtofte and Holmstrup (1989) have described a series of inflammatory cysts in the globulomaxillary region which they considered to be paradental cysts.

However, a different point of view on the pathogenesis has been put forward by Little and Jakobsen (1973). They quoted Patten (1961) in support of their belief that processes that join by merging may still entrap epithelium between them if mesenchymal growth is retarded below the groove that separates them. They believed, too, that the 'epithelial wall' that formed by fusion of the medial nasal process and the maxillary process at the inferior margin of the nasal pit was another potential source of epithelial remnants, despite the fact that these have not been found in studies of normal fetal tissues. Although agreeing that the globular process is not involved, they

believed that a developmental cyst could arise from these epithelial residues. They suggested that cysts in this region of the maxilla may therefore be of either odontogenic or non-odontogenic epithelial origin.

While this is clearly an intriguing question, most of the evidence currently available leads to the conclusion that the so-called globulomaxillary cyst is not an entity but that a variety of cysts and tumours can occur as well-demarcated radiolucent lesions in the lateral incisor–canine region of the maxilla.

We would be surprised if many, if any, oral pathology departments continue to make this diagnosis.

10
Nasolabial (Nasoalveolar) Cyst

The nasolabial cyst occurs outside the bone in the nasolabial folds below the alae nasi. It is traditionally regarded as a jaw cyst although strictly speaking it should be classified as a soft tissue cyst. As the alveolus is not involved, the term nasolabial is preferred to nasoalveolar cyst.

Clinical features

Frequency

Nasolabial cysts are rare lesions; only 21 examples have been recorded in the archives of the Department of Oral Pathology of the University of the Witwatersrand over a period of 46 years (see Table 3.1). In an extensive review of the literature, Roed-Petersen (1969) found information relating to 155 patients with nasolabial cysts and has carried out a statistical analysis of the combined data of 111 of these patients plus five of his own cases. A survey of cases reported subsequent to Roed-Petersen's review has been reported from the University of the Witwatersrand (van Bruggen *et al.*, 1985). This identified another 45 examples of which 25 had sufficient documentation for analysis (Brons and Jongebreur, 1967; Crawford *et al.*, 1968; Harada *et al.*, 1968; Fanibunda, 1970; Santora *et al.*, 1970; Stoelinga, 1971b; Karmody and Gallagher, 1972; Brandao *et al.*, 1974; Campbell and Burkes, 1975). The data presented below are based on Roed-Petersen's 116 cases, the 25 examples just referred to, 18 cases from Choi *et al.* (2002), eight from Chinellato and Damante (1984) and 10 from the University of the Witwatersrand files: a total of 177 cases. El-Din and el-Hamd (1999) found eight cases in a population of 500 000 in 1 year; and the 18 cases reported by Choi *et al.* (2002) were seen over a period of 12 years. These are frequencies that appear to be rather less rare than in other reported series. Vasconcelos *et al.* (1999), however, identified only 15 examples among 12 591 biopsy specimens over a 32-year period. A further literature review was that of Wesley *et al.* (1984).

Age

The age distribution of 167 patients for whom this information was available, based on data from a range of publications, is shown in Fig. 10.1. There is a wide age spread ranging from 12 to 75 years, with a peak frequency in the fourth and fifth decades.

Gender

There is a considerable preponderance of women with nasolabial cysts, compared with men (Fig. 10.1). In the sample of van Bruggen *et al.* (1985), 119 patients were women (79%) and 32 were men (21%), a ratio of 3.7:1. This difference is statistically significant ($P < 0.001$). All of the University of the Witwatersrand patients have been women. The series reported by Kuriloff (1987) included 19 women and seven men; Vasconcelos *et al.* (1999) recorded that 13 out of 15 patients were women; and in the literature review by Chinellato and Damante (1984), including their own eight cases, 117 were women and 42 were men.

Clinical presentation

The duration of symptoms in recorded cases has varied from less than 1 month to as many as 40 years. The most frequent symptom is swelling and very often this was the only complaint. Sometimes the patients complained of pain and difficulty in nasal breathing, but pain is generally present when the cysts are infected. In some cases, difficulty with an upper denture has drawn attention to the problem, and occasionally the cysts are diagnosed fortuitously during routine examination. Cohen and Hertzanu (1985) reported a case that reached a huge size, causing severe facial deformity. In most cases the cysts are unilateral, but in the study of van Bruggen *et al.*, 16 patients had bilateral lesions (10.6%). Bilateral occurrence has been documented by other authors whose papers have been cited above.

The cysts grow slowly, producing a swelling of the lip. They fill out the nasolabial fold and often lift the ala nasi,

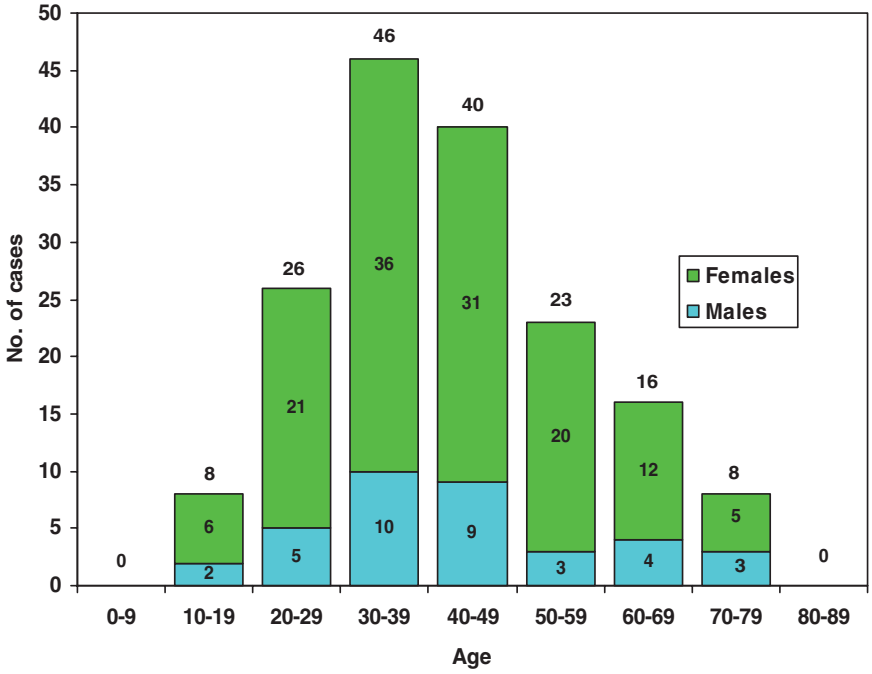


Fig. 10.1 Age distribution of 167 patients with nasolabial cysts.

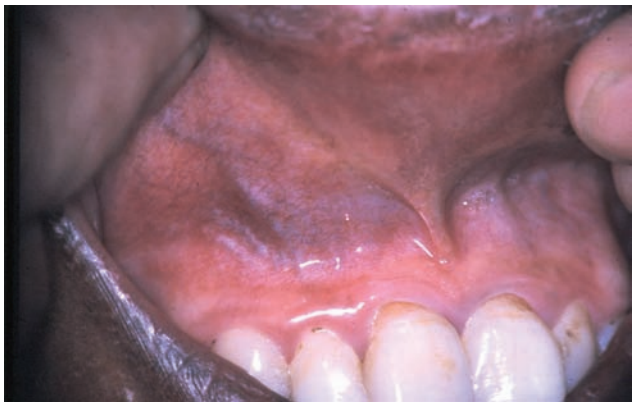


Fig. 10.2 Nasolabial cyst producing a swelling of of the right upper lip, forming a bulge in the labial sulcus.

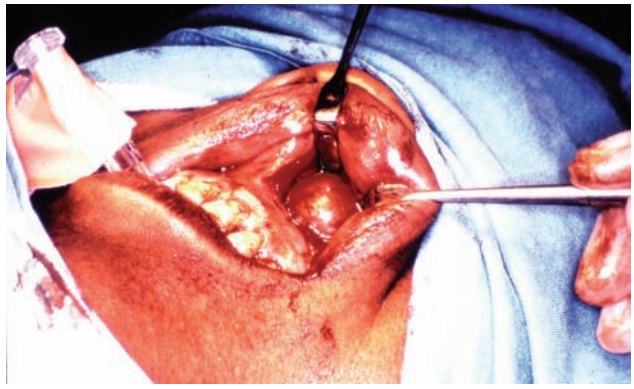


Fig. 10.3 This photograph of the operation site shows exposure of the nasolabial cyst after reflection of the overlying muco-periosteum.

distort the nostril and produce a swelling of the floor of the nose. Intra-orally they form a bulge in the labial sulcus (Fig. 10.2). The cysts are fluctuant and, on bimanual palpation, fluctuation may be elicited between the swelling on the floor of the nose and that in the labial sulcus. Infected cysts may discharge into the nose. In a detailed description of the clinical features of eight cases, Chinellato and Damante (1984) observed elevation of the ala of the nose in all the patients. Figure 10.3, a photograph taken at operation, shows a nasolabial cyst exposed after reflection of the mucoperiosteal flap.

Radiological features

A detailed description of the radiological features has been provided by Seward (1962a). He pointed out that there was a localised increase in radiolucency of the alveolar process above the apices of the incisor teeth. This radiolucency resulted from a depression on the labial surface of the maxilla which may be detectable in a tangential view. When the depression extended to the lateral margin of the anterior bony aperture of the nose, there was resorption of the lower part of the nasal notch. The inferior margin of the anterior bony aperture of the nose was distorted by the lesion. As a result, standard occlusal radio-graphs showed a pronounced posterior convexity in half of the bracket-shaped radiopaque line which formed the bony border of the nasal aperture, instead of the usual double curve (Fig. 10.4). Chinellato and Damante (1984) confirmed from their own studies that this landmark feature was stable and could be identified in 90% of the

occlusal radiographs taken of control individuals. Alterations in it by lesions can be readily observed.

The cyst may be aspirated and a radiopaque liquid introduced, after which it may be viewed in tangential and posteroanterior views of the jaws or in vertex occlusal views (Fig. 10.5). It is normally a spherical or kidney-shaped lesion lying against the inferior and lateral borders of the anterior bony aperture of the nose, extending from the midline to the canine fossa. Chinellato and Damante (1984) believed that injection of radiographic contrast medium was more of academic than of routine clinical importance and that aspiration of cystic fluid was sufficient to establish the diagnosis.

Choi *et al.* (2002) reported their findings of computed tomography (CT) on 11 patients. They found that generally the scans showed a well-demarcated, low-density cystic lesion lateral to the pyriform fossa. They observed no invasion of bone in any of their patients.

In reporting on magnetic resonance imaging (MRI) of two cases of nasolabial cysts, Curé *et al.* (1996) confirmed that the lesions were extra-osseous but that scalloping of the underlying bone may be seen. Sedimentation levels, when present, confirmed the cystic nature of the lesions. Contents of uncomplicated lesions may be slightly hyperintense relative to cerebrospinal fluid (CSF) on T1-weighted MRI and isointense with CSF on T2-weighted MRI. They found no enhancement of the cyst walls or contents. They concluded that CT was preferable to MRI in the evaluation of a suspected nasolabial cyst because of its lower cost.

Pathogenesis

There is general agreement that nasolabial cysts are of developmental origin, and this is reinforced by the finding of a 10.6% frequency of bilateral cysts in the review carried out by van Bruggen *et al.* (1985). Roed-Petersen's survey referred to a report of nasolabial cysts occurring in father and daughter. Another remarkable feature is the high frequency in women, the only cyst of the oral regions other than the aneurysmal bone cyst to show a female preponderance. The reason for this is unknown.

The traditional concept of the pathogenesis of the nasolabial cyst, as described in many textbooks, was that the nasolabial cyst was the soft tissue equivalent of the globulomaxillary cyst. It was therefore suggested that it arose from epithelium enclaved at the site of fusion of the globular, lateral nasal and maxillary processes. This concept, however, is not tenable as the embryological basis for it has been seriously disputed (see Chapter 9, p. 115). Flöe-Möller and Philipsen (1958), Seward (1962a), Roed-Petersen (1969), Kitamura (1976), Allard (1982) and David and O'Connell (1986) have reviewed the various hypotheses proposed to explain the origin of nasolabial cysts, and there is considerable support for the proposal first put forward by Brüggemann (1920) that they developed from the lower anterior part of the nasolacrimal

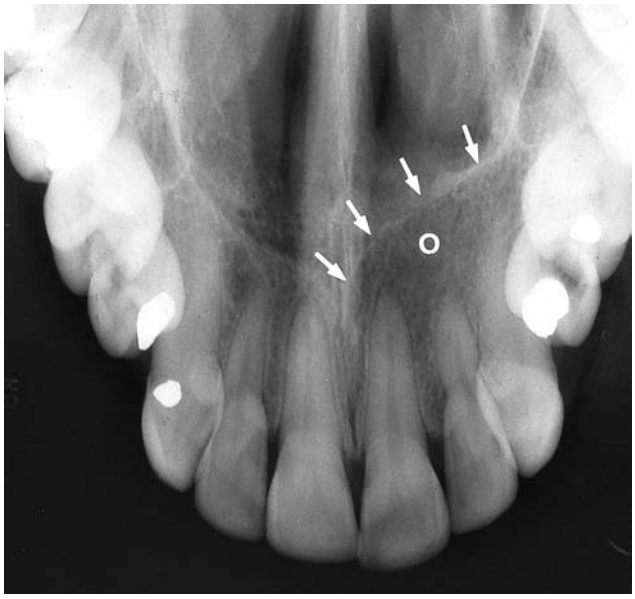


Fig. 10.4 Standard occlusal radiograph of a patient with a nasolabial cyst. There is a posterior convexity of the left half of the radiopaque line that forms the bony border of the nasal aperture. (Courtesy of Drs L.E.M. Chinellato and J.H. Damante.)

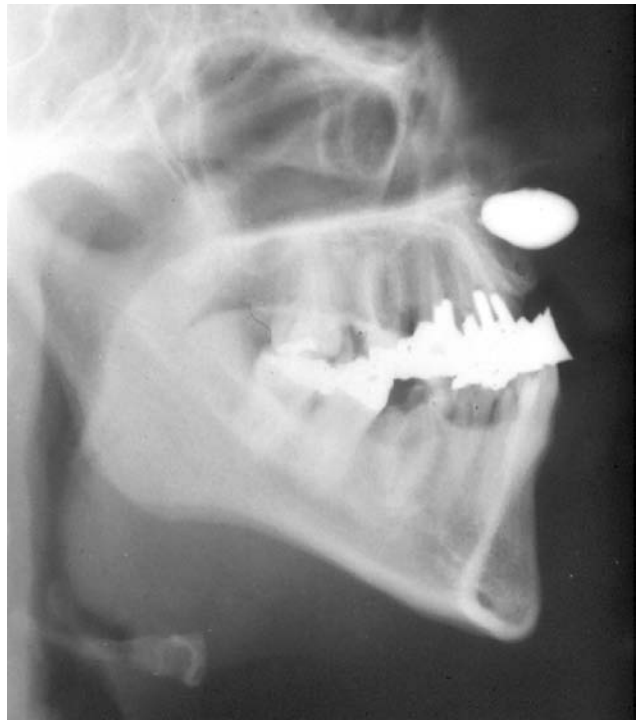


Fig. 10.5 Nasolabial cyst. The extraosseous position of the cyst is demonstrated by aspiration of its fluid contents and injection of a radiopaque fluid. (Courtesy of Drs L.E.M. Chinellato and J.H. Damante.)

duct. When the margins of the lateral nasal and maxillary bulges coalesce, the ectoderm along the boundary between them gives rise to a solid cellular rod which at first develops as a linear surface elevation, the nasolacrimal ridge, and then sinks into the mesenchyme and detaches from the overlying ectoderm. Its caudal end proliferates to connect with the caudal part of the lateral nasal wall while its cranial extremity later connects with the developing conjunctival sac. This solid rod then becomes canalised to form the nasolacrimal duct (Warwick and Williams, 1973; Sadler, 1995). The location of nasolabial cysts is such that they could conceivably develop from remnants of the embryonic nasolacrimal rod or duct, if not from the lower anterior portion of the mature duct. The mature nasolacrimal duct is lined by pseudostratified columnar epithelium and this is the type of epithelium usually found lining nasolabial cysts.

Histological features

A histological analysis of nine examples in the University of the Witwatersrand collection showed that all were lined predominantly by non-ciliated pseudostratified columnar epithelium (Fig. 10.6). Goblet cells, varying in number from very few to very many, were seen in seven of them. In two cases, there were small localised areas of squamous metaplasia. In seven cases, part of the epithelial lining consisted either of cuboidal epithelium or one to two layers of flat squamous cells. In some specimens the entire epithelial thickness was eroded leaving discontinuities.

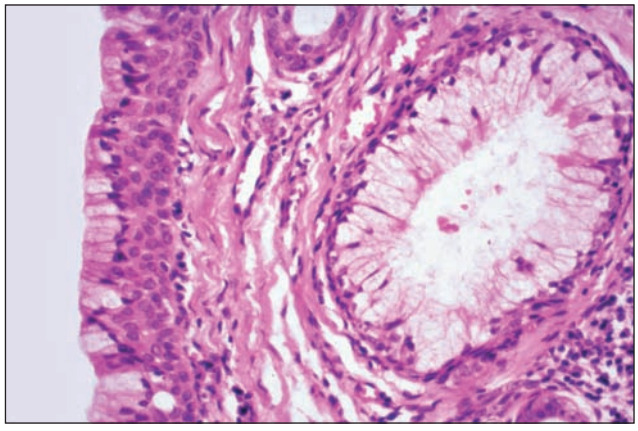


Fig. 10.6 Nasolabial cyst lined by a pseudostratified columnar epithelium containing many goblet cells. In the example illustrated here, mucous glands are present in the wall.

The fibrous cysts' walls were relatively acellular and either loosely or densely collagenous. Seven of the walls that comprised loose connective tissue were very haemorrhagic. One cyst wall was fairly intensely infiltrated with chronic inflammatory cells while the others were relatively uninflamed. Mucous glands lay close to the epithelial cyst lining in three instances.

In Roed-Petersen's review, 64 cases that had been evaluated histologically were summarised. Pseudostratified columnar epithelium was the only type of lining in 26 cases (41%). In nine, pseudostratified columnar epithelium was present in association with stratified squamous epithelium, and in 15 with cuboidal epithelium. Seven cases contained stratified squamous and cuboidal epithelium, four contained only cuboidal epithelium and three were lined by pseudostratified columnar, stratified squamous and cuboidal epithelium. In all, 53 of the cases (83%) were lined wholly or in part by pseudostratified columnar epithelium. Goblet cells were present in 33 cysts and ciliated cells in 22.

Su *et al.* (2006) questioned the view, based on light microscope observations, that ciliated cells occurred in the lining of some nasolabial cysts. Using material removed in the course of treatment by marsupialisation of 10 nasolabial cysts, scanning electron microscopic observations indicated that all the cysts were lined by non-ciliated columnar epithelium consisting mainly of goblet cells and basal cells. Instead of cilia, the epithelial cell surfaces were equipped with numerous short globular or irregular microvilli. Apical cytoplasm of adjacent cells did not adhere to each other. The authors suggested that the presence of microvilli instead of cilia probably resulted from lack of stimulation of air as occurred elsewhere in the respiratory tract.

Treatment

Although the nasolabial cysts are extra-osseous they lie subperiosteally, and careful surgical enucleation via a transoral sublabial approach is the treatment of choice. Su *et al.* (1999) reported on a transnasal endoscopic marsupialisation technique that they developed to treat 16 patients with nasolabial cysts. All but one of the patients were treated successfully. Postoperative endoscopic and radiological findings showed that the cyst was replaced by an air-containing sinus with a persistent opening at the anterior or anterolateral nasal floor. There was no evidence of mucus accumulation in the newly created sinus or cyst recurrence during a 16-month follow-up period.

11

Radicular Cyst and Residual Cyst

Inflammatory jaw cysts comprise a group of lesions that arise as a result of epithelial proliferation within an inflammatory focus due to a number of causes. *Radicular cysts* are the most common inflammatory cysts and arise from the epithelial residues in the periodontal ligament as a result of periapical periodontitis following death and necrosis of the pulp. Cysts arising in this way are found most commonly at the apices of the involved teeth, but may also be found on the lateral aspects of the roots in relation to lateral accessory root canals. Quite often a radicular cyst remains behind in the jaws after removal of the offending tooth and this is referred to as a *residual cyst*.

Rarely, inflammatory cysts may occur towards the cervical margin of the lateral aspect of a root as a consequence of an inflammatory process in a periodontal pocket. This lesion has been referred to as an inflammatory periodontal cyst or *inflammatory collateral cyst* (Main, 1970a,b). Cysts of inflammatory origin occurring on the lateral aspects of the roots of partially erupted mandibular third molars with an associated history of pericoronitis have been described by Craig (1976) and termed the *paradental cyst*. A similar lesion, usually occurring on the buccal surfaces of the mandibular molars in young children, has been described by Stoneman and Worth (1983) and named the *mandibular infected buccal cyst*.

The radicular and residual cyst are considered in this chapter. The remaining inflammatory jaw cysts, which may not all be of odontogenic origin, are considered together in Chapter 12.

Clinical features

Frequency

Radicular and residual cysts are by far the most common cystic lesions in the jaws, comprising 1825 of 3498 (52.2%) jaw cysts and 62% of odontogenic cysts in our South African series (see Table 1.1). This is a somewhat lower frequency than the figure of 68% in the series of Killey *et al*. (1977), but is similar to the frequency in our Sheffield series. In Sheffield, Jones *et al*. (2006) found 4297 radicular and residual cysts over a 30-year period, representing 60.3% of all odontogenic cysts.

Age

The age distribution of 948 patients in our series of South African patients is shown in Fig. 11.1. Very few cases are seen in the first decade, after which there is a fairly steep rise, with a peak frequency in the third decade. There are large numbers of cases in the fourth and fifth decades, after which there is a gradual decline. A very similar age distribution was reported by Donath (1985). The low frequency in the first decade has been shown in a number of studies and indicates that although dental caries is very common in children, radicular cysts are not often found associated with deciduous teeth.

Interestingly, an age distribution analysis of 1970 cases from Sheffield (Fig. 11.2) suggests that these cysts are found at a somewhat older age in the English than the South African group. The mean age of all radicular cysts in Sheffield was 37.3 years (Jones *et al*., 2006). Statistically, the difference is significant ($P < 0.02$) and may mean that the South African group is exposed to the relevant aetiological factor, mainly dental caries, at an earlier age than the English group.

Gender

Of 948 cases in the South African series, 555 (58.5%) were in men and 393 (41.5%) in women, a statistically significant difference ($P < 0.002$). In the Sheffield series, 1914 (51.5%) were in men and 1801 (48.5%) in women (Jones *et al*., 2006), but this gender difference was not significant. The lower frequency in women, which has also been reported by other workers, may be because they are less likely to neglect their teeth, particularly the maxillary anterior incisors, where most radicular cysts occur. Men, moreover, may be

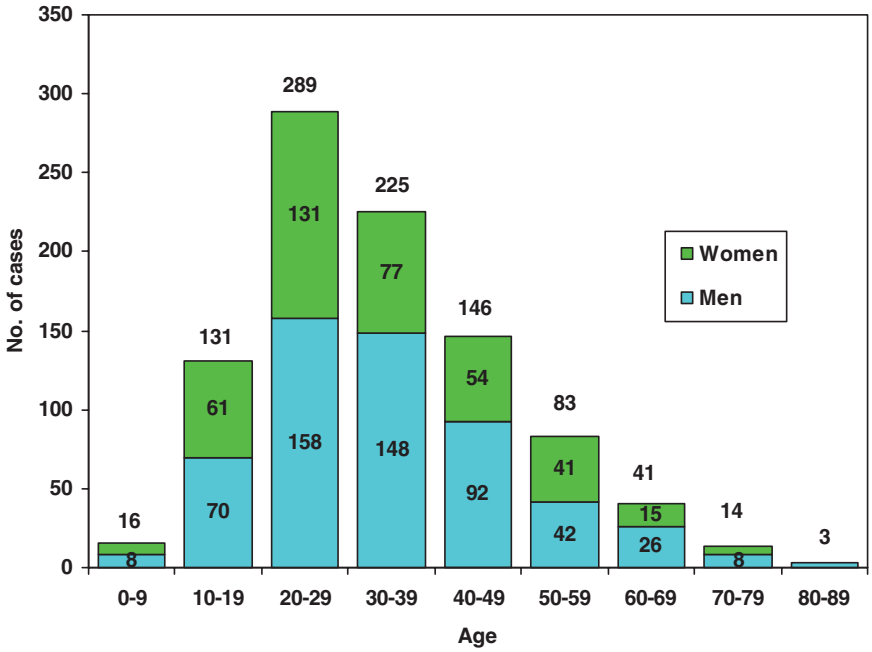


Fig. 11.1 Age distribution of 948 South African patients with radicular cysts.

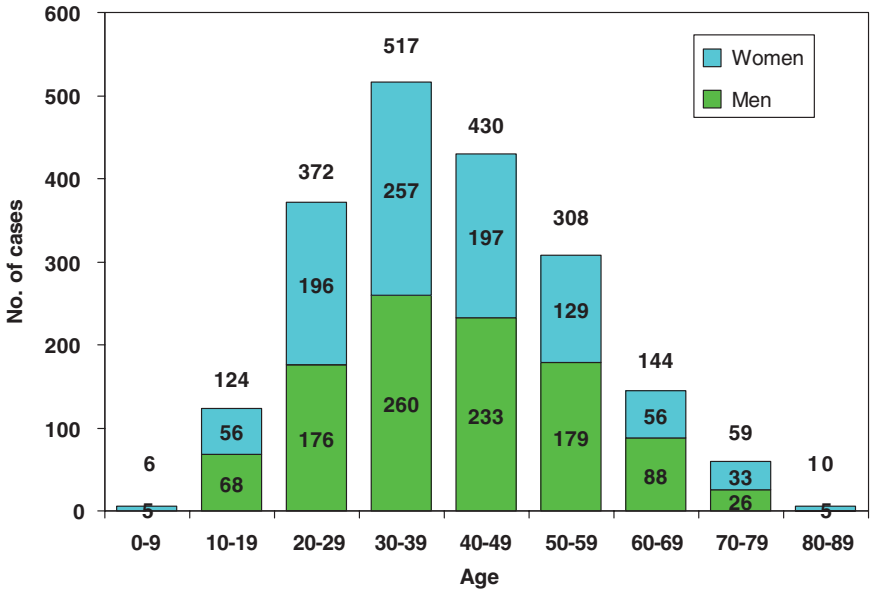


Fig. 11.2 Age distribution of 1970 patients with radicular cysts from Sheffield, England, 1990–2004 (n=1970).

more likely to sustain trauma to their maxillary anterior teeth.

Site

The anatomical distribution of 1111 cysts from South African (Johannesburg) and 1974 English (Sheffield) patients are shown and compared in Fig. 11.3. They occur in all tooth-bearing areas of the jaws, although about 60% are found in the maxilla and 40% in the mandible. There is a particularly high frequency in the maxillary anterior region; there are a number of possible reasons for this. In addition to the hazard posed by dental caries, maxillary incisors have in the past, perhaps more frequently than other teeth, had silicate restorations placed in them, with consequent high risk to their pulps. If this is the case, then the prevalence of cysts at this site may reduce in future generations. Second, there is the high prevalence of palatal invaginations in the maxillary lateral incisors and the frequency with which pulp death supervenes in these teeth. Third, maxillary anterior teeth are probably more prone than others to traumatic injuries which may lead to pulp death.

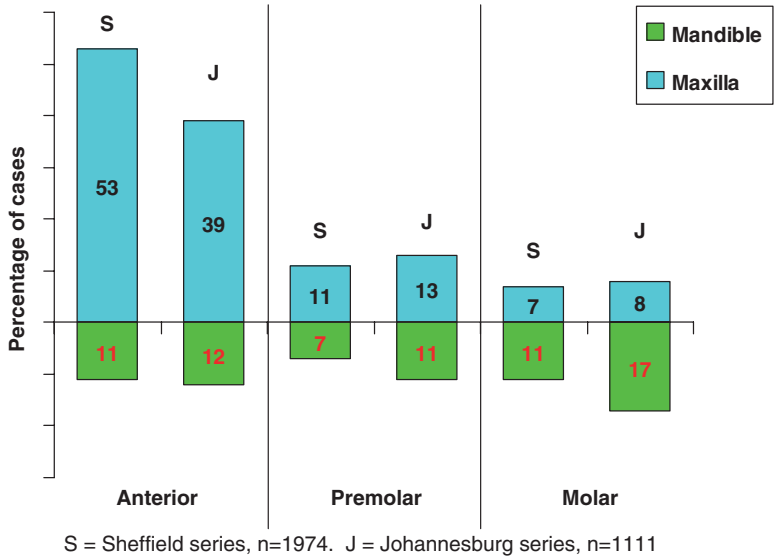


Fig. 11.3 Site distribution of radicular cysts. A comparison of 1111 cases from South Africa (Johannesburg) and 1974 cases from England (Sheffield).

Clinical presentation

Many radicular cysts are symptomless and are discovered when periapical radiographs are taken of teeth with non-vital pulps. Overall, however, radicular cysts are probably the most common cause of swelling of the jaws and slowly enlarging swellings are often complained of. At first the enlargement is bony hard but as the cyst increases in size, the covering bone becomes very thin despite subperiosteal bone deposition and the swelling then exhibits 'springiness' or 'egg shell crackling'. Only when the cyst has completely eroded the bone will the lesion be fluctuant. In the maxilla there may be buccal or palatal enlargement, whereas in the mandible it is usually labial or buccal and only rarely lingual.

Pain and infection are other clinical features of some radicular cysts. It is often said that radicular cysts are painless unless infected. However, there seems to be no clear correlation between infection and symptoms. Vier and Figueiredo (2002) examined 102 periapical lesions. Of 24 radicular cysts included in the analysis, 21 (88%) were described as containing pus-filled cavities. Although these authors did not correlate this finding to clinical symptoms, it seems unlikely that there is a relationship because experience tells us that most cysts are symptomless. Some patients complain of pain although no evidence of infection is found clinically and no evidence of acute inflammation is seen histologically after the cyst has been removed. Likewise, some patients have clinically infected and histologically inflamed cysts which are not painful (Shear, 1961a).

A *sine qua non* for the diagnosis of a radicular cyst is the related presence of a tooth with a non-vital pulp. Occasionally, a sinus may lead from the cyst cavity to the oral mucosa.

Quite often, more than one radicular cyst may be found in a patient (Shear, 1961a; Stoelinga, 1973) and this has led a number of authors to believe that there are cyst-prone individuals who show a particular susceptibility to develop radicular cysts (Oehlers, 1970). This view is supported by the fact that radicular cysts are relatively rare in relation to the vast numbers of grossly carious teeth with dead pulps. It is possible that an immune mechanism may inhibit cyst formation in most individuals and that cyst-prone subjects have a defective immunological surveillance and suppression mechanism (Toller, 1970a). It is also possible that some individuals have a genetic tendency to develop radicular cysts. Multiple radicular cysts may also be seen in patients with hereditary dental defects (e.g. multiple dens-in-dente or dentinogenesis imperfecta), but in these cases this is because of morphological defects resulting in early exposure and death of the pulp.

Radicular cysts arising from deciduous teeth appear to be very rare. In a survey of the documents of 1300 radicular cysts recorded in the University of the Witswatersrand department over a 25-year period, only seven were associated with deciduous teeth (0.5%). In an extensive review of the literature from 1898 (Lustmann and Shear, 1985), only 28 cases were found. The frequency is probably higher than these figures would suggest. Radicular radiolucencies related to deciduous teeth tend to be neglected and probably resolve after removal of the offending teeth. Nevertheless, the frequency is substantially lower than of those associated with permanent teeth and one may speculate on the reasons for this. Pulpal and periapical infections in deciduous teeth tend to drain more readily than those of permanent teeth and the antigenic stimuli that evoke the changes leading to the formation of radicular cysts may be different. Periapical granulomas associated with

deciduous teeth have not been subjected to the same extensive investigations that have been carried out on periapical granulomas of permanent teeth, which are discussed later in this chapter, in the section on pathogenesis.

Grundy *et al*. (1984) reported a series of cases of radicular cysts associated with deciduous teeth which had been treated endodontically with materials containing formocresol which, in combination with tissue proteins, is antigenic and has been shown to elicit a humoral and cell-mediated response. Some of the cysts in their series showed rapid buccal expansion and non-refractile eosinophilic material was observed in the epithelial linings.

In the study of Lustmann and Shear (1985), 23 personally observed cases were reported. The patients' ages ranged from 4 to 12 years with one exceptional case aged 19 years. The male : female ratio was 1.6 : 1. The mandible was affected more frequently than the maxilla and the deciduous molars were the teeth most often involved. In nine cases buccal expansion was noticed and in eight cases the permanent tooth buds were displaced. Caries was the most common aetiological factor.

Residual radicular cysts are those that are retained after removal of the offending non-vital tooth. There have been relatively few publications on the subject although it has been estimated that they represent approximately 10% of all odontogenic cysts (Main, 1970a; Killey *et al*., 1977). High and Hirschmann (1986, 1988) have reported studies on series of asymptomatic and symptomatic residual cysts. They were interested in the factors that decide whether a radicular cyst will resolve or persist after tooth removal and the natural history and behaviour of these cysts once established. With regard to the asymptomatic cysts, they showed that there was a decrease in size with increasing age ($r=0.5$; $P<0.005$). There was an unexpectedly large number in the mandibular premolar region and there was a direct relationship between the age of the cyst and the radiological and histological evidence of mineralisation ($P<0.001$). There was an overall reduction in epithelial thickness with cyst age and all cysts showed minimal chronic inflammatory changes. They concluded that the vast majority of residual cysts are slowly resolving lesions. Nevertheless, they do persist and the authors did not provide evidence of complete resolution.

In their second paper on their series of symptomatic cysts that produced pain or swelling or both, High and Hirschmann (1988) showed that the mean cyst size was larger than that of the asymptomatic sample, and that the negative correlation of size with cyst age was not as strong as with the asymptomatic sample ($r=0.39$; $P<0.05$). Cyst ages varied from 1 month to 20 years and there was again a perplexingly high frequency in the mandibular premolar region. Acute and chronic inflammatory cell infiltration showed variable intensity and there was an inverse relationship between the percentage of polymorphonuclear leucocytes in the inflammatory infiltrate and cortication of the cyst wall radiographically ($P<0.001$). There were no obvious causes for the inflammation in deeply positioned residual cysts. A chronic inflammatory process would certainly be present when the offending tooth is removed and the authors posed the question whether this could persist and gradually worsen as a result of lysosome or other irritant chemical release from dead or dying cells, and at some point trigger an acute inflammatory reaction.

Nair (1998, 2003) considered that the type of cyst was important with regards to persistence after treatment. Although he discussed non-healing cysts after endodontic treatment, his conclusions were pertinent to residual cysts. He confirmed the work of Simon (1980) who showed that there were two types of radicular cyst. These are discussed in more detail later in this chapter but, to summarise, there is the *true radicular cyst* which contains a closed cavity entirely lined by epithelium, and the *periapical pocket cyst* (originally called the 'bay cyst' by Simon) in which the epithelium is attached to the margins of the apical foramen in such a way that the cyst lumen is open to the affected root canal. Thus, it is expected that the pocket cyst would heal after treatment or tooth extraction, while the true cyst, being completely enclosed is 'self-sustaining' and may therefore persist in the absence of the cause. Nair *et al*. (1996) showed that only 15% of periapical lesions were radicular cysts and of these 61% were true cysts and 39% were pocket cysts. If only true cysts persisted after removal of the offending tooth, this may account for the relatively low frequency of residual cysts.

Of significance, however, is that residual cysts persist and may, in due course, produce symptoms.

Radiological features

Numbers of studies have shown that it is difficult to differentiate radiologically between radicular cysts and apical granulomas. Mortensen *et al*. (1970) examined histological material of 396 periapical lesions with a diameter of 5 mm or more, which had been classified preoperatively as cysts or granulomas on radiological evidence. A correct preliminary diagnosis had been made in 81% of 232 granulomas but in only 48% of 164 cysts. They also showed that the relative number of granulomas decreased with increasing size of the lesion whereas there was an increase in the relative number of cysts. Nevertheless, it is interesting to note that of all the lesions measuring 10–14 mm in radiographic diameter, there were almost as many granulomas as cysts, and that in their group of lesions measuring 15 mm or more, approximately one-third were granulomas. Moreover, a little over one-third of their lesions measuring 5–9 mm were cysts on histological examination. Similar findings were reported by Stockdale and Chandler (1988).

These data certainly indicate that one cannot rely on the size of the lesion to establish a diagnosis except where the radiographic lesion is 2 cm in diameter or larger (Natkin *et al.*, 1984). In addition, the large number of cysts that were incorrectly diagnosed as granulomas suggested to Mortensen *et al.* (1970) that because of infection many cysts had a diffuse radiographic margin and therefore lacked the circumscribed appearance usually ascribed to radicular cysts.

Shrout *et al.* (1993) used radiometric methods to analyse the grey levels on digitised images of periapical lesions. In a pilot study of only 10 mandibular lesions, they showed that analysis of grey levels could correctly identify four of six granulomas and all four cysts. They concluded that it may be feasible to differentiate between radicular cysts and periapical granulomas on the basis of radiographic density. With the advent of digital radiography and powerful software to routinely analyse images, it would be interesting to see if these findings could be confirmed.

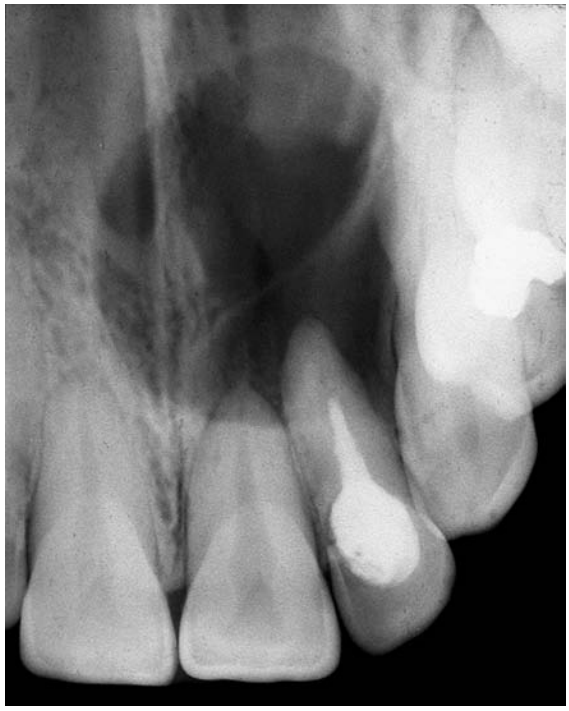


Fig. 11.4 Radiograph of a radicular cyst. The lesion is a well-defined radiolucency associated with the apex of a non-vital root filled tooth.

Biochemical procedures have been advocated to differentiate between periapical cysts and granulomas (Morse *et al.*, 1973, 1975, 1976). Aspirates of root canal fluids from patients with cysts showed an intense albumin pattern and definite patterns in the globulin zones, on polyacrylamide-gel electrophoresis. Fluids associated with periapical granulomas, however, showed only a faint to moderate pattern in the albumin zone. Although potentially useful, this technique does not seem to have been widely used in clinical practice.

The classic description of the radiological appearance of radicular cysts is that they are round or ovoid radiolucencies surrounded by a narrow radiopaque margin which extends from the lamina dura of the involved tooth (Fig. 11.4). In infected or rapidly enlarging cysts, the radiopaque margin may not be present. This can lead to diagnostic problems in the case of residual cysts. High and Hirschmann (1988) demonstrated a negative correlation between the loss of radiographic cortication and increasing intensity of acute inflammation ($r=0.83$; $P<0.001$). With a residual cyst, moreover, the differential diagnosis of keratocyst must be considered (Fig. 11.5). A radicular cyst on the lateral margin of a root in association with an accessory root canal must be differentiated from a lateral periodontal cyst. Root resorption is not often seen on routine radiographs, but it may occur.

There is a poor correlation between radiological evidence of resorption and actual tooth resorption on histology. Laux *et al.* (2000) compared the radiological and histological findings in 114 periapical lesions, 15% of which were radicular cysts (Nair *et al.*, 1996). Ninety-three (81%) of the lesions showed histological evidence of tooth resorption, but in only 21 cases (19%) was there

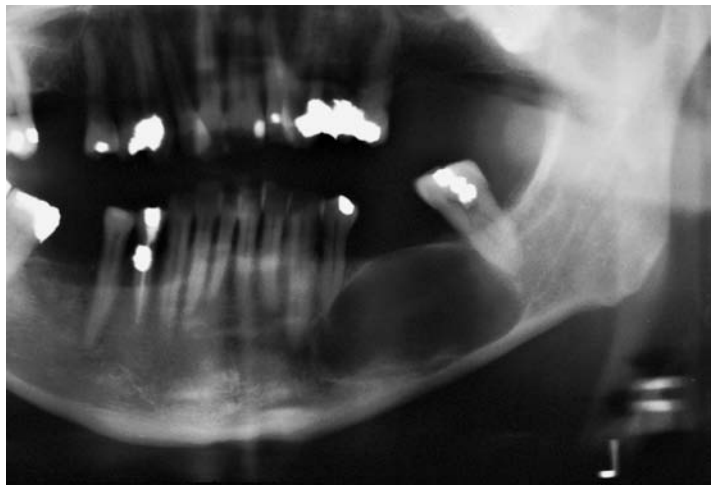


Fig. 11.5 Radiograph of a residual cyst. The lesion is at the site of a previously extracted tooth. The lesion must be differentiated from a keratocyst.

evidence of resorption on the radiographs. It should be noted, however, that only 30 of the 93 lesions with histological resorption showed dentine involvement. In the majority (63 cases) only cementum was involved and it was acknowledged that this would not normally be visible on a plain radiograph.

Vier and Figueiredo (2002, 2004) reported similar findings. In their first study (2002), they examined 102 periapical lesions, comprising 77 periapical granulomas and 25 radicular cysts, by histology and scanning electron microscopy. Ninety-one per cent of cases showed evidence of resorption in the region of the apical foramen In a second, similar study, Vier and Figueiredo (2004) examined a further 75 periapical lesions of which 15 (20%) were radicular cysts. In this study, 56 (75%) cases showed internal resorption at the apical foramen. In neither of these studies did they correlate their findings to radiological features. Also, none of these studies found any differences in the incidence of resorption between periapical granulomas and radicular cysts.

Pathogenesis

It is convenient to consider the pathogenesis of radicular cysts in three phases: the phase of initiation, the phase of cyst formation and the phase of enlargement. The mechanisms involved in all phases have been the subjects of extensive investigation and speculation and a great deal has been learnt over the past few years.

The phase of initiation

It is generally agreed that the epithelial linings of these cysts are derived from the epithelial cell rests of Malassez in the periodontal ligament which come to lie in periapical granulomas associated with teeth with necrotic, often infected, pulps. Thus, the epithelial cell rests are initiated to proliferate by inflammation as a result of necrotic debris and bacterial antigens derived from the dead pulp. A key factor, which may initiate the inflammation and immune response and may directly cause epithelial proliferation, is now thought to be bacterial endotoxins released from the necrotic pulp. Meghji *et al*. (1996) studied cyst fluids and cultured cyst explants from radicular cysts, keratocysts and follicular cysts. They showed high levels of endotoxins in radicular cysts compared with negligible levels in the other cyst types. In a separate experiment they demonstrated that endotoxins from *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis* and *Escherichia coli* could directly stimulate epithelial proliferation in a dose-dependent manner. They proposed that bacterial endotoxins derived from the necrotic pulp are the key initiating factor in the pathogenesis of radicular cysts.

Immunological studies have made an important contribution in understanding periapical granulomas and radicular cysts, and both humoral and cell-mediated reactions have been implicated in the pathogenesis. Studies have also shown an important role for inflammatory cytokines in the proliferation of epithelial cell rests. Immunoglobulin G (IgG) is the predominant class of immunoglobulin demonstrated by immunofluorescence techniques in the cells of periapical granulomas. Stern *et al*. (1981) showed that 74% of the antibody-producing lesional cells in periapical granulomas and cysts synthesised IgG, 20% IgA, 4% IgE and 2% IgM. There were no significant differences between the solid and cystic periapical lesions. Smith *et al*. (1987) found 85% IgG, 14% IgA and 2% IgM plasma cells, in their sample of radicular cysts. Complement C3 is also demonstrable in the connective tissues. The antigens involved were presumed to be derived from bacteria. When these antigens gain entrance to the pulp or periapical tissues at certain concentrations, antigen–antibody complexes may form and coactivate complement, leading to increased vascular permeability and a leucotactic response (Pulver *et al*., 1978). Complement activation may also occur directly under the influence of endotoxins. The presence of both IgE-containing cells and mast cells, some of which undergo degranulation, suggested that anaphylactic hypersensitivity reactions may also have a role in periapical granulomas (Pulver *et al*., 1978; Yanagisiwa, 1980; Torabinejad *et al*., 1981; Johannessen *et al*., 1983; Perrini and Fonzi, 1985; Kontiainen *et al*., 1986).

Infiltrates of T lymphocytes, indicating that cellular immune reactions are involved in their pathogenesis, were demonstrated by Stern *et al*. (1982) and by Skaug *et al*. (1984b) in human periapical granulomas. Skaug *et al*. (1984a) concluded that because of low complement component C3d receptor activity, B lymphocytes form only a minor component of the mononuclear cells in these lesions. However, the authors considered that further studies were necessary before conclusions could be made as to the significance of these findings. T helper cells (CD4) were found by Nilsen *et al*. (1984) to be more numerous than suppressor/cytotoxic T (CD8) cells and were considered to have an important role in the differentiation of B lymphocytes into immunoglobulin-producing plasma cells as well as in the activation of suppressor/cytotoxic cells. By contrast, Kontiainen *et al*. (1986) and Babál *et al*. (1987) showed that cells of the suppressor/cytotoxic phenotype (CD8) dominated. Gao *et al*. (1988a) also found that suppressor/cytotoxic cells generally outnumbered T helper cells in periapical granulomas, whereas the two cell types were of equal number, or the T helper cells predominated, in the cysts that they examined. The range of the cell ratios found by Gao *et al*. indicated to them the complex nature of the immune interactions in periapical lesions and that the ratio may

be affected by many factors, including the stage of the lesion. This may also explain the discrepancy in the results reported by different workers. In a similar study on odontogenic cysts, including radicular cysts, Matthews and Browne (1987) found that although the helper T subset always predominated over the suppressor/cytotoxic T subset, the ratios varied between sites within individual specimens and inverse ratios were detected at some sites in several specimens.

The proportion of B lymphocytes in the study of Kontiainen *et al.* (1986) was approximately 20%, and that of plasma cells was 2%, lower than the 13% plasma cells reported by Stern *et al.* (1982). B and T lymphocytes, predominantly the latter, were demonstrated in periapical granulomas by Torabinejad and Kettering (1985) and in granulomas and cysts by Gao *et al.* (1988a) who, like Nilsen *et al.* (1984), suggested that these lesions probably result from activation of both humoral and cell-mediated immunological reactions in response to egress of potential antigens from the root canal system into the periapical tissues.

A more recent study (Liapatas *et al.*, 2003) has confirmed most of these findings. They showed that T cells predominated and that helper cells predominated over cytotoxic/suppressor cells in most periapical granulomas and cysts. In cysts, however, they found increased numbers of plasma cells suggesting that humoral immune reactions may take on a more important role in cysts.

There is no doubt that the epithelial cell rests proliferate within the inflamed tissues of a periapical granuloma. Precisely how these epithelial cells are stimulated to proliferate is not clear but it would seem that products of a dead pulp may initiate the process and, at the same time, evoke an inflammatory reaction. There is evidence that proliferating odontogenic epithelium is associated with the presence of an acute inflammatory cell infiltration (Shear, 1963a). A feature of this infiltrate is that the polymorphonuclear leucocytes are found in the proliferating epithelium (Shear, 1964; Cohen, 1979; Johannessen *et al.*, 1983; Johannessen, 1986). It is now apparent that it is endotoxins and inflammatory cytokines that are the main stimulators of the epithelial proliferation (Browne and Smith, 1991; Meghji *et al.*, 1996, Nair, 2003) as well as acting as pro-inflammatory and chemotactic molecules.

Meghji *et al.* (1989) identified a bone resorbing factor in cyst explants that had significant interleukin-1 (IL-1) activity. Later, this same group (Bando *et al.*, 1993) used immunocytochemistry to localise cytokines and adhesion molecules in the walls of radicular cysts. All cysts showed positive staining for IL-1α, IL-1β and IL-6 in the epithelial lining and in vascular endothelial cells. Tumour necrosis factor (TNF) and IL-8 were occasionally seen in macrophages. The cell adhesion molecules ICAM-1 and ELAM-1 were also identified in all lesions and were localised to endothelial cells. ICAM-1 was also found in the epithelium and on inflammatory cells. These studies confirmed that the epithelial lining of radicular cysts may synthesise cytokines that are known to be important in bone resorption. A later study confirmed and extended these findings and provided evidence that cytokines may be important in directly stimulating epithelial proliferation (Meghji *et al.*, 1996). In this study, the authors studied 16 radicular cysts, eight keratocysts and seven follicular cysts. As well as endotoxins, they analysed cyst fluids and explants for cytokine activity. All cysts contained IL-1α and IL-6 but radicular cyst explants produced significantly more IL-6 than either keratocysts or follicular cysts. Keratocyst fluid contained significantly more IL-1α than the other cyst types. Only radicular cysts produced IL-1β, although all cysts contained mRNA for this cytokine. Further experiments showed that IL-1 and IL-6, and culture supernatants from cyst fibroblasts were able to stimulate epithelial proliferation in a bell-shaped, but dose-dependent manner.

Kusumi *et al.* (2004) have produced further evidence for the pivotal role of IL-6. They studied a number of cytokines in tissues from 19 radicular cysts and compared expression with that found in normal gingivae and periodontal ligament. Using reverse transcriptase polymerase chain reaction (RT-PCR) they found variable expression of cytokines in all tissues, but most cysts expressed IL-1β, IL-6, IL-8, TNF-α, γ-interferon (IFN-γ), and transforming growth factor β1 (TGF-β1) and most of these showed increased expression compared with normal tissues. In a further experiment they cultured fibroblasts from the same three sources and used immunoassay and RT-PCR to show that fibroblasts from radicular cysts secreted constitutively high levels of IL-6. All other cytokines were secreted at low levels and there were no differences between the cell types.

The results of these studies suggest that endotoxins have a major initiating role in the pathogenesis of radicular cysts. As well as a direct effect on epithelial proliferation, endotoxins initiate an inflammatory response resulting in production of cytokines with pro-inflammatory and bone-resorbing activities. The major cytokines identified, IL-1 and IL-6, also have a direct effect on epithelial proliferation. Other factors produced by fibroblasts and inflammatory cells undoubtedly are also involved, resulting in a complex cytokine network with multiple activities.

Gao *et al.* (1988a) contributed some ideas as to the reasons for the proliferation of the epithelium in periapical lesions, while acknowledging that these were not clear. In their study they observed that dense infiltrates of lymphocytes, human leucocyte antigen Dr (HLA-Dr) positive cells, and lysozyme- and α_1-antitrypsin-positive macrophages were always closely related to the proliferating epithelium in periapical granulomas and near the

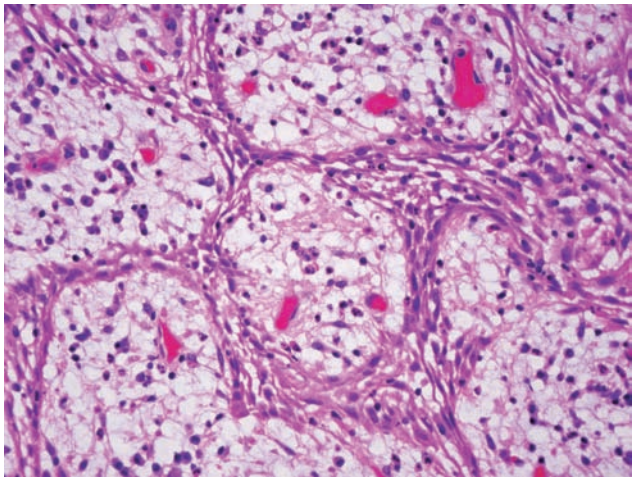


Fig. 11.6 Arcades and rings of proliferating epithelium in an apical granuloma (haematoxylin and eosin [H & E]).

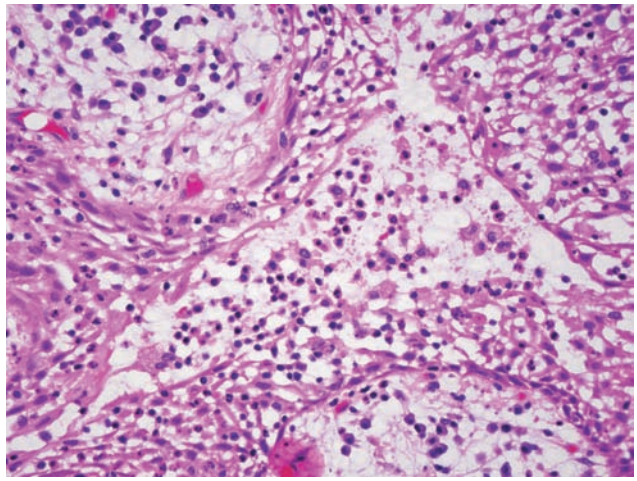


Fig. 11.7 Degeneration of cells in the centre of a mass of proliferating epithelium in an apical granuloma. There is an intense infiltration of lymphocytes and polymorphonuclear leucocytes. Accumulations of intercellular fluid coalesce to form a microcyst (H & E).

epithelial linings of the cysts. T helper lymphocytes were seen more frequently in the connective tissue around the epithelium and suppressor/cytotoxic lymphocytes within the epithelium. They speculated that activated T cells in periapical granulomas produced cytokines that may act on the rests of Malassez causing proliferation and altered differentiation leading to cyst formation. The more recent studies discussed above (Bando *et al.*, 1993; Meghji *et al.*, 1996; Kusumi *et al.*, 2004) supported this because activated lymphocytes are an important source of many of the relevant cytokines.

Numbers of workers (Contos *et al.*, 1987; Matthews and Browne 1987; Gao *et al.*, 1988a) have demonstrated Langerhans' cells in the epithelial linings of radicular cysts. In areas of intense inflammation, as evidenced by large numbers of lymphocytes, polymorphonuclear leucocytes and plasma cells, greater numbers of S-100-positive and HLA-Dr-positive cells (Langerhans' cells) were observed. The finding of lymphocytes adjacent to Langerhans' cells suggested increased antigen challenge and antigen-processing activity and that T lymphocytes may act as effector cells in the pathogenesis of the cyst, after receiving information from stimulated Langerhans' cells.

There is also some evidence that local changes in the supporting connective tissue may contribute to activating the cell rests (Grupe *et al.*, 1967). The increasing size of a periapical granuloma may result in a decrease in oxygen and increased carbon dioxide tension. Grupe *et al.* (1967) used periodontal ligament explant cultures to show that a high carbon dioxide tension resulted in a local reduction in pH and was accompanied by proliferation of the rest cells of Malassez. A similar mechanism associated with the chronic inflammation in a periapical granuloma may be an important factor.

Phase of cyst formation

The next phase in the pathogenesis of a radicular cyst is the process by which a cavity comes to be lined by the proliferating odontogenic epithelium. Two possibilities have been generally recognised, both of which are feasible and which may operate independently of one another. One concept proposes that the epithelium proliferates and covers the bare connective tissue surface of an abscess cavity or a cavity which may occur as a result of connective tissue breakdown by proteolytic enzyme activity (Summers, 1974). The other, and perhaps more widely supported theory, postulates that a cyst cavity forms within a proliferating epithelial mass in an apical granuloma by degeneration and death of cells in the centre.

There is histological evidence for the latter hypothesis. The proliferating epithelial masses show considerable intercellular oedema. These intercellular accumulations of fluid coalesce to form microcysts containing epithelial and inflammatory cells (Figs 11.6 and 11.7). The demonstration of high levels of acid phosphatase activity in the central cells of apical granulomas (Grupe *et al.*, 1967) and in the exfoliating epithelial cells of radicular cysts (Lutz *et al.*, 1965), and the fact that Summers (1972, 1974) found that weak proteolytic activity was present centrally within the proliferating epithelium, suggest that these cells are undergoing autolysis. Ultrastructurally, the epithelial cells in apical granulomas adhere to each other by fewer desmosomes than in normal squamous epithelium (Summers and Papadimitriou, 1975) and evidence of death of the central cells has been demonstrated in experimentally induced lesions (Ten Cate, 1972). Microcysts

may increase in size by coalescence with adjacent microcysts and, once established, the cyst increases in size by mechanisms which are discussed later. Established radicular cyst fluid showed no spontaneous proteolytic activity (Ylipaavalniemi and Tuompo, 1977), but activation of proteolysis with 3M sodium thiocyanate suggested that a pro-enzyme might be present.

In his histological study of experimentally induced radicular cysts in monkeys, Valderhaug (1972) did not see evidence of intra-epithelial degeneration with formation of microcysts. However, he did observe quite frequently that the degenerated central area of an apical granuloma became surrounded by proliferating epithelial cells.

In some periapical lesions, sheets of epithelial cells with distinct clefts are seen (Shear, 1963a) and in certain instances the cyst may be initiated in this way (Fig. 11.8). Torabinejad (1983) has postulated that it is not the lack of blood supply that accounts for the death of the central epithelial cells in an apical lesion, but that the development of the cavities in proliferating epithelium and the final destruction of these cells are mediated by immunological reactions. He suggested different ways in which activated epithelial cell rests can acquire antigenic properties, but did not explain why the central and not the peripheral proliferating cells are targeted in this manner. Nevertheless, the participation of immunological processes in the breakdown of proliferating epithelium must be given serious consideration. Despite the extensive studies describing the role of immunological mechanisms in the development of the periapical granuloma and epithelial proliferation that have been described earlier in this chapter, relatively sparse attention has been given to the role of immune processes in the proliferation and central disintegration of the epithelium.

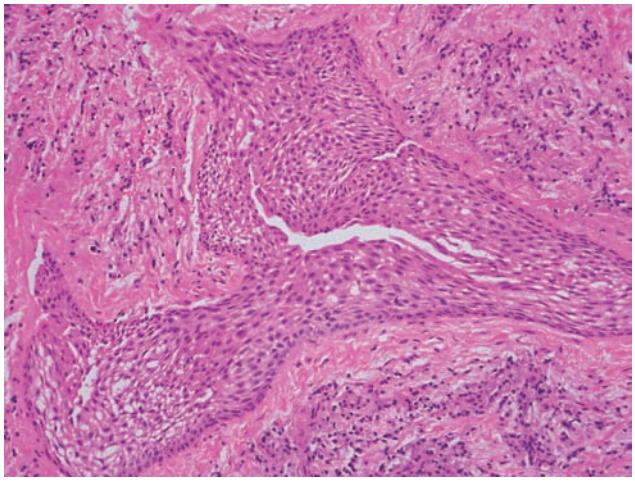


Fig. 11.8 Sheet of epithelial cells in a periapical lesion. A distinct cleft has formed and this may initiate a radicular cyst (H & E).

Collagenases may also be important. Matrix metalloproteinase-13 (MMP-13) is secreted by epithelial cells and fibroblasts as well as plasma cells. Leonardi *et al.* (2005) stained 17 periapical granulomas for MMP-13 and found expression in all lesions in fibroblasts and plasma cells. In 10 lesions that contained proliferating epithelium, MMP-13 was also strongly expressed on the epithelial cells. They concluded that MMPs may be involved in degradation of the matrix and that MMP-13 may have a role in the pathogenesis of cysts by facilitating epithelial cell proliferation and invasion of the granulation tissue.

Growth and enlargement of the radicular cyst

The third phase in the pathogenesis of the radicular cyst, its enlargement, has been the focus of considerable experimental work. Toller's studies provided evidence for the hypothesis that osmosis makes a contribution to the increase in the size of cysts. Toller (1970b) showed that the mean osmolality of the fluid from 21 apical and residual cysts was 290±14.93 mOsm and was greater than the mean serum osmolality of 279±4.68 mOsm (P <0.01). Lytic products of the epithelial and inflammatory cells in the cyst cavity provided the greater numbers of smaller molecules which raised the osmotic pressure of the cyst fluid. Toller believed that the upper limit of permeability in most cysts was close to the molecular size of albumin (molecular weight 69 kDa) and that particles of larger size would find difficulty in diffusing across a cyst lining. Toller's (1966b) *in vivo* dialysis experiments using a radioactive crystalloid and a radioactive colloid, showed that the diffusion rate of the crystalloid was fairly rapid in every case but that the colloid tended to be retained, whether subsequent histological examination revealed that the cyst wall was entirely lined by epithelium or not. This tended to confirm that cyst walls have the properties of a semi-permeable membrane.

Electrophoretic studies (Toller, 1970a) demonstrated that radicular cyst fluids contained fewer, if any, of the larger protein molecules than the patients' own sera. α-Globulins were greatly diminished. γ-Globulin varied greatly in quantity but in cysts that were not inflamed was present in small concentration. The small molecular sized albumin and β_1-globulin were present in quantities comparable with serum but β_2-globulin was usually absent. This suggested that these cyst fluids were simple dialysates from plasma through the cyst membranes which discriminate against the larger molecules. Skaug (1977) disagreed with this view. His studies on fluids from non-keratinising cysts showed electrophoretic patterns that strongly indicated that serum-derived immunoglobulins were also present. However, Skaug did not distinguish the radicular from the other non-keratinising cysts. Koskimies *et al.* (1975) and Ylipaavalniemi *et al.* (1976a and b) have, nonetheless, shown that the protein patterns of radicular

cyst fluids resemble those of serum. They were similar to those of dentigerous cysts, but keratocysts and residual cysts had considerably fewer protein zones than plasma.

Electrophoretic studies of the fluids of radicular and other non-keratinising cysts have shown that more than half display levels of γ-globulin much higher than the patient's own serum (Toller and Holborow, 1969; Toller, 1970a). In 19 cyst fluids in which levels of IgG, IgA and IgM were measured independently, all three were significantly raised in most of the non-keratinising cysts. Immunofluorescent staining showed that lymphoid cell aggregates in the walls of radicular cysts often included numerous plasma cells, many of them producing IgG, IgA or IgM, but IgA-staining cells were predominant. Pulver *et al*. (1978) have confirmed that there were larger numbers of IgA-containing cells in radicular cyst walls compared with periapical granulomas. While finding the potential role of IgA difficult to explain in this site, they pointed out that IgA-synthesising plasma cells were the predominant immunoglobulin-containing cells in the lamina propria of the intestinal tract and bronchial and nasal mucosa, where they presumably represented an immune response to multiple antigenic stimuli, chiefly microorganisms. These authors also found only traces of complement C3 in the cyst walls and suggested that this might have been consumed during the formation of antigen–antibody complexes.

The immunoglobulin-producing cells appear to be actively mobile and even capable of penetrating several layers of intact epithelial cells, thereby entering the cyst cavities. Sakuma (1973), Skaug (1974) and Ylipaavalniemi *et al*. (1976a) supported the view that the γ-globulins were of local origin and contributed to the protein levels of cyst fluids. Toller believed that this evidence suggested that there was an antigenic stimulus in the cyst wall and in the absence of demonstrable infection either the occult epithelium or its breakdown products were antigenic. This, he suggested, may be the mechanism whereby cysts undergo spontaneous regression. Those people who have a particular tendency to develop cysts may have an ineffective immunological surveillance and suppression mechanism. The question of regression of radicular cysts is discussed further in the section on their treatment at the end of this chapter.

Toller (1966b) also proposed the hypothesis that the contents of cyst cavities were subject to an osmotic imbalance with the surrounding tissues because of the absence of lymphatic drainage. He demonstrated this absence of lymphatic drainage by evacuating cyst cavities and refilling them with an aqueous solution of patent blue dye. At operation 3–24 hours later, he was unable to detect any dye outside the cyst cavity. Neither the patients nor their urine were discoloured.

Main (1970b), however, felt that the retention of colloid in Toller's experiment may have resulted from a reduced internal hydrostatic pressure following aspiration of the fluid contents. He estimated the protein concentrations of cyst fluids by means of specific gravity and concluded that the radicular cyst fluid was essentially an inflammatory exudate. Skaug (1973, 1976a, 1977) confirmed that fluid from non-keratinising jaw cysts contained high concentrations of protein but supported the view that accumulation of cyst fluid resulted essentially from inadequate lymphatic drainage of the cyst cavity. He suggested that plasma protein exudate and hyaluronic acid, as well as the products of cell breakdown, contributed to the high osmotic pressure of the cyst fluid. Ylipaavalniemi (1977) proposed that when the inflammation ceased, a balance was probably established between the protein concentrations in cyst fluid and in serum.

Skaug (1974, 1977) has also commented on the question of permeability of cyst walls. He pointed out that the cyst capsule was not directly comparable to the biological membranes such as capillary walls or cell membranes because of the many layers of cells of diverse function: the vascular endothelium, basement membranes, ground substance and cyst wall epithelium. The view that the cyst wall functioned as a simple semi-permeable membrane was therefore probably an over-simplification. It may nevertheless still be preferable to use the term permeability in connection with the passage of substances into or away from the cyst cavity.

Skaug found that the concentration of non-immunoglobulin plasma proteins in cyst fluids was proportionate to their concentration in plasma and, as Toller did, that these were in inverse proportion to their molecular weights. The demonstration in cyst fluid of appreciable amounts of high molecular weight proteins suggested that the vascular permeability of cyst capsules was increased compared to the permeability of normal capillaries but there was nevertheless still a considerable restriction to free diffusion of plasma protein across the cyst capsule. Suzuki (1975) also demonstrated that there was an active transport mechanism for $NaSP^+$ and KSP^+ ions across the cyst wall and that there was a selective mechanism for the transfer of protein.

Toller (1948) showed that the internal hydrostatic pressures in 51 radicular cysts ranged from 56.6 to 95.0 cm water with a mean of 70.0 cm. This figure was higher than that of capillary blood pressure and as the cyst expanded there was resorption of the surrounding bone. Skaug (1976a) conducted similar experiments using a pressure transducer and either cannulation of the cyst cavity or cementing a two-way valve into a tooth which communicated through its root canal with a cyst. With a sample of 14 radicular cysts, he found that the initial intracystic pressures ranged from 25 to 66 with a mean and SD of

47±14.5 mmHg. In three cases in which pressure measurements were repeated 7–14 days after aspiration of cyst fluid, intracystic pressures in the same range as those originally recorded were found. This indicated that more fluid filters into the cyst cavity than was removed by the venous and lymphatic channels. The direction and the rate of fluid flow were determined by the balance of the differences in hydrostatic and osmotic pressures between cyst fluid and plasma (Skaug, 1976a).

This pioneering work on the role of hydrostatic pressure in the growth of odontogenic cysts was mostly undertaken during the 1970s, but it has not been superseded or refuted by more contemporary experiments. Only recently has this issue been re-evaluated, but the outcome is that hydrostatic pressure is still considered to be of primary importance in the growth of all cyst types. Kubota *et al.* (2004) measured the intracystic fluid pressure of odontogenic keratocysts, dentigerous cysts and radicular cysts. They confirmed the early results of Toller and Skaug, that the pressure was greater than the local blood pressure and that there were no differences between the three cyst types. They also measured cyst volume and showed that volume correlated to the area of the cysts measured on panoramic radiographs. They correlated the pressure to the areas of the cysts and found pressures of $337.6 \pm 126.0\,mmHg\,cm^{-2}$, $258.2 \pm 160.9\,mmHg\,cm^{-2}$ and $254 \pm 157.3\,mmHg\,cm^{-2}$ for keratocysts, dentigerous cysts and radicular cysts, respectively. Furthermore, these authors showed that the intracystic pressure in all cyst types was inversely correlated to the cyst size. They therefore concluded that increased pressure played a pivotal part in early cyst growth.

Ward *et al.* (2004) used mathematical modelling to simulate odontogenic cyst growth. They assumed a spherical cyst lined by a semi-permeable membrane and with a central osmotic pressure as a result of accumulation of degraded cellular material. The model supported the conclusions of the early experimental work, that osmotic pressure played an important part in cyst growth. Interestingly, the model also confirmed the findings of Kubota *et al.* (2004), and showed that as the cyst became larger, osmotic pressure played a lesser part and cell proliferation became more important.

It seems that epithelial proliferation continues as long as there is an inflammatory stimulus, and Harris and Toller (1975) suggested that this contributed to enlargement of the cyst. When the stimulus to epithelial proliferation ceased, a situation that often occurred in a residual cyst, the epithelium was able to differentiate to a certain extent (Fig. 11.10), although keratinisation was very rare. Although cell proliferation probably continued, this was at a relatively low level in radicular cysts. Thus, further increase in the capacity of the cyst cavity at this stage probably leads to thinning of the epithelial lining.

Reference has been made in earlier chapters of this book to a series of papers on glycosaminoglycans which were present in the walls and fluids of odontogenic cysts (Smith *et al.*, 1984, 1988a,b, 1989). These substances were derived from several sources in the cyst wall and diffused into the cyst fluid where they probably contributed to the expansile growth of the cyst.

There do not appear to be data on the rate of radicular cyst growth, although it has been estimated at approximately 5 mm in diameter annually (Livingston, 1927). They tend to expand progressively and if untreated may grow to a large size. The larger the cyst, the slower its relative increase in size.

Growth of the cyst must also be accompanied by degradation of adjacent connective tissues and bone resorption. Harris and Goldhaber (1973) demonstrated that small fragments of vital cyst tissue produced resorption of mouse calvarium in tissue culture, whereas control tissue devitalised by rapid freezing and thawing failed to resorb bone. They postulated that intra-osseous cyst expansion is facilitated by local enzyme or hormone-induced bone resorption and suggested that the active principle is a prostaglandin. In subsequent publications (Harris *et al.*, 1973; Harris, 1978) it was shown that cyst walls did release prostaglandin-like material in tissue culture. The synthesis of prostaglandins, their bone resorbing capacity and their possible role in the enlargement of jaw cysts is now well established in further experimental work (Matejka *et al.*, 1985a,b; Meghji *et al.*, 1989) and is described in Chapter 4.

In a detailed investigation of lipids in cyst walls and fluids, Suzuki (1984) suggested that jaw cyst enlargement was related to lipo-peroxide and prostaglandin-like substances produced by lipid peroxidation of the cyst wall and fluid. In a study on the walls of radicular cysts, Matejka *et al.* (1986) used immunohistochemistry and radio-thin layer chromatography to show that prostaglandin E_2 (PGE_2) was produced predominantly by plasma cells and histiocytic elements as well as endothelial cells and fibroblasts. Epithelial cells and granulocytes gave minimal positive staining, and lymphocytes gave a variable weak reaction to anti-PGE_2. On the other hand, 6-oxo-PGF_{1A} (the stable biologically inactive metabolite of PGI_2 – prostacyclin) was primarily found in endothelial cells and fibroblasts. The negative reaction of the cyst epithelium to both antibodies indicated that the granulation tissue and the inflammatory cells were the main source of prostaglandin synthesis in the walls of radicular cysts and may therefore be responsible for the resultant osteolytic activity. The authors cautioned, however, that it was not yet certain whether the *in vitro* phenomena observed are also of biological relevance *in vivo*. The further studies of Harris's group described earlier in this chapter (Bando *et al.*, 1993; Meghji *et al.*, 1996) have confirmed these findings and have also shown

that IL-1 and IL-6 are the predominant cytokines with bone resorbing activities. In immunocytochemical studies (Bando *et al.*, 1993), it was shown that these cytokines appeared to be synthesised primarily by the epithelial cells of the cyst lining. Kusumi *et al.* (2004) also showed that IL-6 was the predominant cytokine in radicular cysts and found evidence for synthesis by fibroblasts in the cyst wall.

More recent studies have provided evidence for osteoclast recruitment and differentiation in the walls of odontogenic cysts including radicular cysts (Tay *et al.*, 2004). Bone resorption is a complex process involving highly coordinated interactions between osteoblasts and osteoclasts that are modulated by the RANKL/RANK/OPG system. Receptor activator of nuclear κB ligand (RANKL) is secreted primarily by activated T cells and binds a cell surface receptor (RANK) to promote osteoclast differentiation and activation. Tay *et al.* (2004) showed immunostaining for RANKL within the fibrous wall of radicular cysts. That RANKL was involved in osteoclast recruitment was confirmed by the demonstration of tartrate-resistant acid phosphatase (TRAP) and calcitonin-receptor positive osteoclasts adjacent to the RANKL positive cells.

Collagenases also contribute to breakdown of the connective tissues and collagenolytic activity has been demonstrated in homogenates of radicular cyst walls and it has been suggested that this might influence their expansion (Uitto and Ylipaavalniemi, 1977). A number of recent studies have shown expression of MMPs in radicular cysts, including the gelatinases (MMP-2 and MMP-9) (Teronen *et al.*, 1995a), interstitial collagenase (MMP-1) (Teronen *et al.*, 1995b) and collagenases MMP-8 and MMP-13 (Wahlgren *et al.*, 2001), suggesting a role for these enzymes in cyst growth and development. Furthermore, MMP activity may be associated with the inflammatory response because IL-1 up-regulates active MMP-9 in odontogenic cysts (Kubota *et al.*, 2000) and increased numbers of mast cells (Rodini *et al.*, 2004) are not only associated with potentiation of the immune response and secretion of prostaglandins, but mast cell tryptase may also activate MMPs in odontogenic cysts (Teronen et *al.*, 1996). Inflammation in radicular cysts is also associated with increased expression of plasminogen activator (Tsai *et al.*, 2004) which indirectly forms plasmin which may also activate MMPs.

Studies in the experimental production of radicular cysts have been published by Valderhaug (1972, 1974) and Binnie and Rowe (1974). The latter authors studied 192 roots of immature pulpless teeth in eight young beagle dogs. The pulps had been filled with various materials. Epithelial cell rests were observed in 49 roots and proliferating epithelium in 14. Nine periapical cysts were found in four dogs. There was considerable variation between different dogs and this may reinforce the concept of individual susceptibility to the development of radicular cysts. In one dog, only one root showed epithelium, but in another there was epithelium associated with 19 of the 24 roots examined and four of these had formed cysts. All epithelial proliferations and cysts were associated with mild or severe periapical inflammation but their frequency was not related to the filling material used. An interesting feature of this study was the finding that epithelial remnants were present in only 37% of specimens. If a similar situation obtains in humans, this alone may explain the existence of cyst-prone and non-cyst-prone individuals.

Valderhaug (1974) induced periapical inflammation in monkey primary teeth by removing the pulp tissue and leaving the root canals open to the oral cavity. About one-third of the experimental teeth developed periapical abscesses, granulomas and cysts without communication with the oral cavity. Proliferating epithelium was not observed in association with abscess formation. However, many of the granulomas contained islands and strands of proliferating epithelial cells. Small periapical cysts developed in some animals after long observation periods and these were lined by stratified squamous epithelium. ^{3}H thymidine was incorporated into the epithelial linings of the cysts and into the epithelium of the granulomas in inflamed areas. Uptake by epithelium could not be demonstrated at a certain distance from the inflammation nor on the control side.

Pathological features

Frequently, a radicular cyst is surgically removed during an apicectomy operation where the apex of the tooth and associated soft tissue are removed and a filling material is placed in the root canal, thus enabling preservation and restoration of the affected tooth. Therefore the pathologist often receives the lesion as a fragmented or irregular curettage specimen. An intact specimen may be a spherical or ovoid intact cystic mass, but often they are irregular and collapsed. Lesions are usually 1.0–1.5 cm in diameter and rarely exceed 3 cm. The walls vary from extremely thin to a thickness of about 5 mm. The inner surface may be smooth or corrugated. Yellow mural nodules of cholesterol may project into the cavity. The fluid contents are usually brown from the breakdown of blood and when cholesterol crystals are present they impart a shimmering gold or straw colour.

Almost all radicular cysts are lined wholly or in part by stratified squamous epithelium. These linings may be discontinuous in part and range in thickness from 1 to 50 cell layers. The majority are 6–20 cell layers thick. The

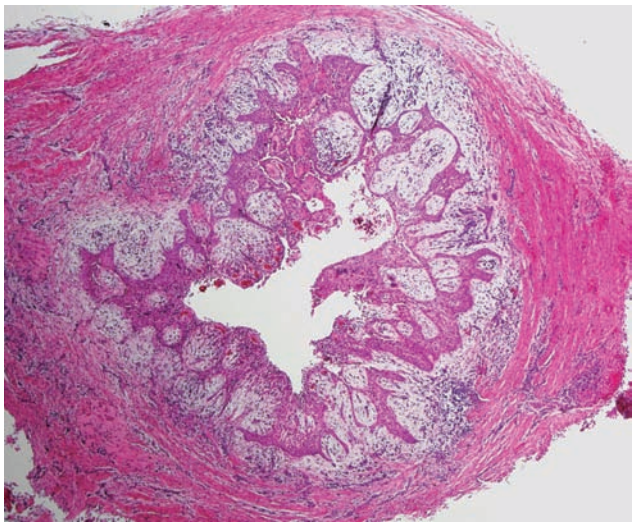


Fig. 11.9 This small cyst is lined by proliferating epithelium (H & E).

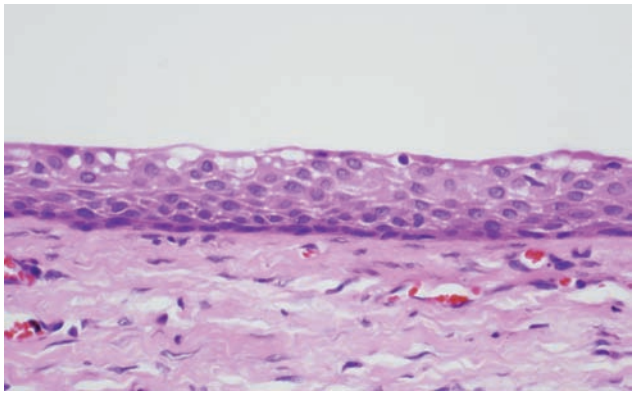


Fig. 11.10 Quiescent epithelium lining a mature, long-standing radicular cyst (H & E).

nature of the lining may depend on the age or stage of development of the cyst, or on the intensity of the inflammation. In early cysts, the epithelial lining may be proliferative and show arcading with an intense associated inflammatory process (Fig. 11.9) but as the cyst enlarges the lining becomes quiescent and fairly regular with a certain degree of differentiation (Fig. 11.10) to resemble a simple stratified squamous epithelium. Keratin formation is only seen in about 2% of radicular cysts and when present it affects only part of the cyst wall. Orthokeratinisation is most common, with evidence of a granular cell layer, but parakeratinisation may also be seen (Browne and Smith, 1991). When it does occur, it is different morphologically from that seen in keratocysts (see Fig. 3.1).

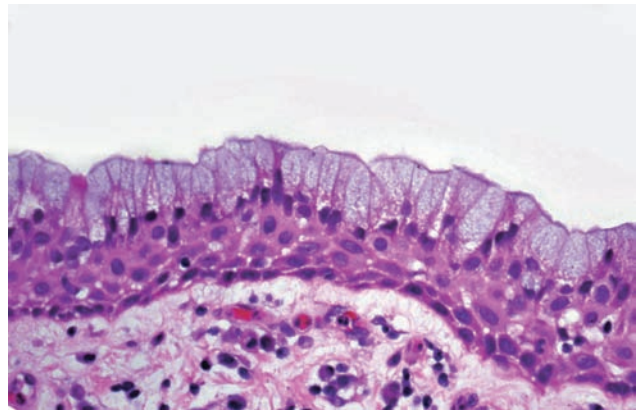


Fig. 11.11 Mucous cells in the surface layer of the stratified squamous epithelial lining of a radicular cyst (H & E).

The inflammatory cell infiltrate in the proliferating epithelial linings consists predominantly of polymorphonuclear leucocytes whereas the adjacent fibrous capsule is infiltrated mainly by chronic inflammatory cells (Shear, 1963a, 1964; Cohen, 1979; Johannessen *et al*., 1983; Johannessen, 1986). These proliferating epithelial linings show a considerable degree of spongiosis. When observed in the scanning electron microscope it is seen that the spongiotic spaces represent channels running between the epithelial cells and extending from the basal layer to the cyst lumen (Cohen, 1979). The polymorphonuclear leucocytes migrate along these channels and into the cyst cavity through interepithelial spaces on the luminal surface. Interepithelial spaces and channels in the cyst linings have also been demonstrated by means of transmission electron microscopy (Frithiof and Hägglund, 1966).

As the cyst enlarges, the wall may become less inflamed and fibrous. This is most noticeable distant from the apex of the tooth. Adjacent to the apex, where the cyst is constantly exposed to the infected root canal, inflammation may persist and polymorphonuclear leucocytes are invariably present even in long-standing lesions.

Metaplastic changes, in the form of mucous cells or ciliated cells, are frequently found in the epithelial linings of radicular cysts (Shear, 1960b; Browne, 1972; Browne and Smith, 1991; Slabbert *et al*., 1995). Mucous cells occurred in as many as 40% of Browne's series of radicular cysts. They may be present in the surface layer of the stratified squamous epithelial lining, either as a continuous row (Fig. 11.11) or as scattered cells, and they may be found associated with ciliated epithelium (Fig. 11.12). They are found in cysts occurring in all parts of the mandible and maxilla. Browne made the interesting observation that there was an increasing frequency of mucous cells with

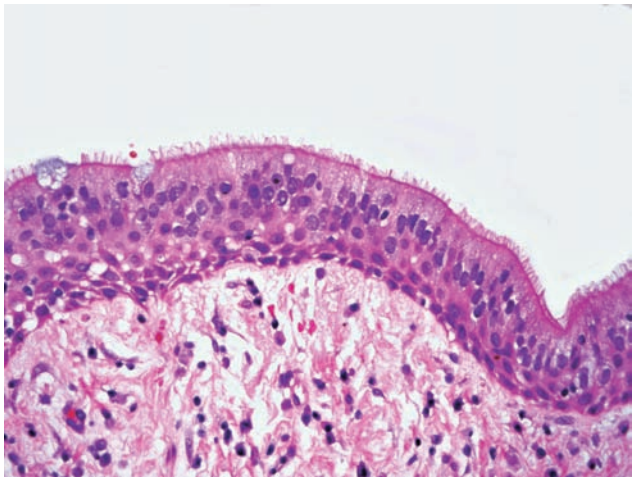


Fig. 11.12 Ciliated epithelium in a radicular cyst (H & E).

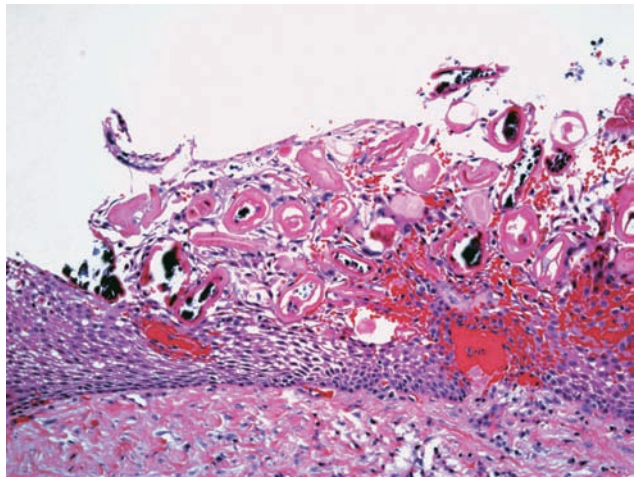


Fig. 11.13 Hyaline bodies in the epithelial lining of a radicular cyst (H & E).

age, at the rate of 7% per decade. Takeda *et al.* (2005) found mucous cells in 18% of radicular cysts, and in most cases they were arranged along the surface of the epithelium, but occasional intra-epithelial gland-like structures were also noted, most often in areas where the epithelium was hyperplastic. Mucous cells were more common in maxillary lesions (21%) than mandibular lesions (14%).

Slabbert *et al.* (1995) studied 154 mandibular radicular and residual cysts and found unequivocal mucous metaplasia in 15 (10%). In many cases they found that the mucous cells were associated with vacuolated cells, many of which were empty, but some contained fine granules or networks of periodic acid–Schiff (PAS) positive material. The authors observed that the vacuolated cells resembled those described by Fell (1957) in the process of metaplasia from stratified squamous to ciliated epithelium in explants of chick embryo skin grown under the influence of excess vitamin A. By analogy to Fell's findings, Slabbert *et al.* (1995) suggested that the vacuolated cells represented an intermediate stage in the process of mucous metaplasia. Their findings support the view that mucous cell differentiation is a process of metaplasia.

Ciliated epithelium is occasionally found in radicular cysts and it has been suggested that this most often occurs in maxillary lesions as a result of involvement of antral lining (Nair *et al.*, 2002). However, ciliated epithelium has been found in cysts in the anterior and posterior regions of the mandible. In the study of Takeda *et al.* (2005), ciliated cells were found in 11% of radicular cysts and in 12% and 9% of maxillary and mandibular lesions, respectively. The presence of secretory and ciliated epithelium in mandibular radicular cysts further confirms that these processes may arise as a result of metaplasia.

Fujiwara and Watanabe (1988) reported an ultrastructural study of mucus cells and ciliated epithelium in a mandibular radicular cyst. These cells were indistinguishable from those found in the maxillary sinus or nasal cavity. In addition, however, they commented on the presence of abnormal cilia belonging to the primary cilia group which have been documented in a variety of non-neoplastic and neoplastic tissues. The mechanism by which they are produced is obscure and the authors were unable to explain their significance in this radicular cyst.

In approximately 10% of radicular cysts, hyaline bodies, first described by Dewey in 1918 and often referred to as Rushton's hyaline bodies, are found in the epithelial linings (Fig. 11.13). Only very rarely are they present in the fibrous capsule. The bodies measure up to about 0.1 mm and are linear, straight or curved or of hairpin shape and sometimes they are concentrically laminated. They are brittle and frequently fracture. Circular or polycyclic bodies are also seen with a clear outer layer surrounding a central granular body.

Rushton (1955) believed that the hyaline bodies resembled, in appearance and the liability to fracture, the keratinised secondary enamel cuticle of Gottlieb. Special stains and histochemical studies (Shear, 1961b) indicated that they contained cystine and the author suggested that they were of odontogenic epithelial origin and probably a form of keratin. Wertheimer *et al.* (1962) and Wertheimer (1966) also found histochemical similarities to keratin but pointed out that the correspondence was not complete. They supported the view that the bodies were a secretory product of odontogenic epithelial cells formed in the same way as the secondary enamel cuticle, an opinion also held by Takeda (1985).

On the other hand, Bouyssou and Guilhem (1965) and Sedano and Gorlin (1968) believed that hyaline bodies

were of haematogenous origin, and were derived from thrombi in venules of the connective tissue that had become varicose and strangled by epithelial cuffs which encircled them, and that they reacted histochemically as haemoglobin. They suggested that the thrombi shrank centrifugally and underwent splitting, or they may calcify. Dent and Wertheimer (1967) stated that although hyaline bodies reacted to several haemoglobin and iron stains, the histochemical reactions for haemoglobin were not specific. Shear (unpublished observation) has found that hyaline bodies give a faint reaction with Pickworth's benzidine method for haemoglobin while a control of human erythrocytes stained intensely. Browne and Matthews (1985) stained cysts containing hyaline bodies for keratin, Factor VIII-related antigen, haemoglobin and fibrinogen, using immunoperoxidase methods. The hyaline bodies were negative for all these antigens but fibrinogen was detected in the cores of some circular and polycyclic forms. They concluded that their observations did not support the view that they were keratinous in nature, nor that they arose from erythrocytes or capillary endothelium, but they did tentatively propose that the presence of fibrinogen in the cores of some hyaline bodies could support the notion of a haematogenous origin of the granular bodies.

Although we agree that the circular or polycyclic forms are sometimes of a morphology that suggests that they are lying in a transversely sectioned blood vessel, there are some puzzling features about their distribution if they are of vascular and haemotogenous origin. For one thing, they are often seen in epithelium overlying connective tissue devoid of any blood vessels. For another, they are very rarely found in the fibrous capsules, and we have never seen them in this situation. Third, if their pathogenesis is as described, it is most surprising that they occur so exceptionally rarely in other situations. There are very few reports of hyaline bodies in cysts other than radicular cysts. Lam and Chan (2000) reported hyaline bodies in 7% of a series of 69 odontogenic keratocysts in Chinese patients, and Ide *et al.* (1996) reported an unusual glandular odontogenic cyst with hyaline bodies. Takeda *et al.* (1985) have described their presence in a plexiform ameloblastoma. These reports are unusual, but when they do arise they appear to be restricted to odontogenic lesions, and we have not seen them in nasopalatine duct cysts which are not of odontogenic origin.

Ultrastructural studies of the bodies (Allison, 1974; Jensen and Erickson, 1974; Morgan and Johnson, 1974) have been carried out on material recovered from paraffin blocks and from reserve tissue stored in formalin. The investigation of Morgan and Johnson failed to demonstrate any close relationships between the bodies and either red cells or blood vessels. They were also unable to demonstrate any cellular structures, or evidence of either cell stratification, desmosomes, or, except in one case, filamentous laminae. In this exceptional instance, they felt that there might be some similarity to the contents of poorly keratinising epithelial cells. On the whole, however, they believed that their ultrastructural findings ruled out a keratinous origin. They were not able to exclude the possibility that the hyaline bodies represented a type of dental cuticle. Their conclusion was that the bodies are a secretory product of odontogenic epithelium deposited on the surface of particulate matter such as cell debris or cholesterol crystals in a manner analogous to the formation of dental cuticle on the unerupted portions of enamel surfaces.

Later enzyme histochemical studies (Morgan and Heyden, 1975) lent support to this theory. El-Labban (1979) performed her ultrastructural study of hyaline bodies on formalin-fixed and on one fresh osmium tetroxide-fixed specimen. Her findings provided no support for the hypothesis that the bodies were keratinous nor that they form from epithelial secretory products. Her study indicated that the granular bodies were composed of amorphous material in which fragments of red blood cells could be seen. She concluded that the hyaline bodies were derived from degenerating red blood cells in which segregation of various components has occurred. She was not able to explain their almost exclusive occurrence in epithelium.

Further studies by Allison (1977a,b), including microprobe and microradiographic analyses, also led him to the conclusion that hyaline bodies arose as an epithelial secretion. Additional support for the view that hyaline bodies were a product of the epithelium is provided by the immunohistochemical, scanning electron microscopic studies and X-ray microanalysis carried out by Rühl *et al.* (1989) and Philippou *et al.* (1990). By X-ray analysis, foreign material could be demonstrated in the cyst epithelium which could be macrophages, erythrocytes or degenerating epithelium. The authors suggested that this irritated the epithelial cells to produce a fine-grained matrix which enclosed the coarse-grained foreign material and then underwent different degrees of 'homogenisation'. This they called the hyaline body type II. The type I hyaline body, they suggested, has no central granular component. Hyaline bodies types I and II always consisted of a fine-grained substance which underwent 'homogenisation' and consistently contained calcium and phosphate. Scanning electron microscopy showed that the hyaline bodies were more or less spherical structures consisting of concentrically laminated layers which on section resembled a cut onion. The surface of each layer had a fine-grained texture.

Although the origin of hyaline bodies remains obscure, it is generally now thought that they represent a secretory product of odontogenic epithelium. Further studies of enamel proteins in these structures may provide further clues as to their origin.

The presence of hyaline bodies may be suspected if, in examining the gross specimen, the pathologist sees small, smooth, white, dome-shaped swellings of the epithelial surface protruding into the cyst cavity.

Deposits of cholesterol crystals are found in many radicular cysts, but by no means in all (Shear, 1963b; Browne, 1971b; Trott and Esty, 1972). In Shear's series they were present in 28.5% of cases, and in Trott and Esty's 30%, whereas Browne reported a frequency of 43.5% in his larger sample. However, it is likely that if entire cyst linings were examined instead of random sections, the frequency would be higher. Browne has demonstrated a statistically significant correlation (P <0.01) between the presence of cholesterol and haemosiderin. He postulated that the main source of cholesterol was from disintegrating red blood cells in a form that readily crystallises in the tissues. Cholesterol from this source and also from serum accumulates in the tissues because of the relative inaccessibility of normal lymphatic drainage. Arwill and Heyden (1973) confirmed the origin from red blood cells. They showed that the crystals may form in congested capillaries in the inflamed areas as they appear to be enveloped by endothelial cells.

Trott *et al.* (1973) also found a close correlation between the occurrence of cholesterol and haemosiderin-containing macrophages as well as free haemosiderin in the tissues. Their regression analysis showed that only 35% of the cholesterol may be formed from this association. They suggested that slow but considerable accumulation of cholesterol could occur through degeneration and disintegration of lymphocytes, plasma cells and macrophages taking part in the inflammatory process, with consequent release of cholesterol from their walls.

The possibility that circulating plasma lipids were a further source of cholesterol in cysts, as they were in atherosclerosis, must also be considered. A mechanism may operate similar to that which it is thought might occur in atheroma (Shear, 1963b). β-Lipoproteins in the plasma pass through the fragile thin-walled blood vessels in the inflamed portions of cyst wall in the same manner as the extravasating erythrocytes. There, the β-lipoproteins split into cholesterol and its esters which are retained, and other lipid components such as phospholipids which are absorbed by the lymphatics. This view was supported by Skaug (1976b) who assayed cyst fluids for lipoproteins and cholesterol.

Once the cholesterol crystals have been deposited in the fibrous capsules of the cysts, they behave as foreign bodies and excite a foreign body, giant cell reaction (Fig. 11.14). In histological sections, the cholesterol crystals are dissolved out and clefts are seen surrounded by dense aggregations of multinucleate giant cells. The cholesterol masses are extruded from the fibrous wall by the foreign body reaction. Invariably, the path of least resistance is into the cyst cavity as the external surface of the cyst may consist of dense fibrous tissue, bone and mucosa. When the reaction reaches the epithelial lining, this ulcerates. The granulation tissue containing the cholesterol protrudes into the cyst cavity and appears macroscopically and microscopically as a 'mural nodule' (Fig. 11.15). Once the entire mass has passed into the cavity, the epithelial breach heals and the cholesterol crystals lie free in the cyst fluid (Shear, 1963b).

Buchner and David (1978) have demonstrated the presence of pigmented cells in the epithelial linings of a substantial proportion of radicular cysts. They identified these as macrophages containing the lipid pigment, ceroid

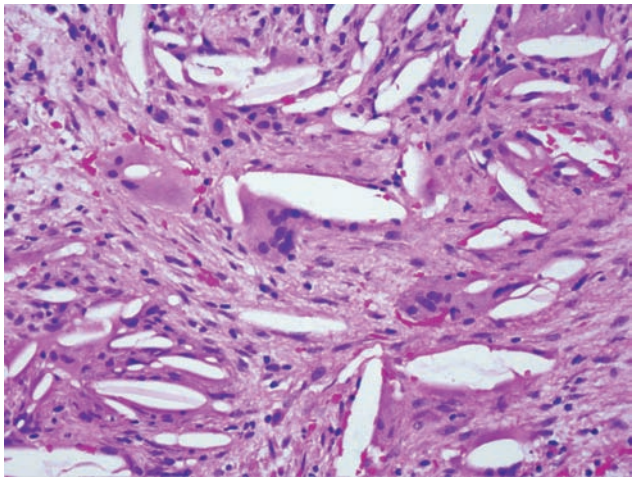


Fig. 11.14 Multinucleate foreign body giant cells on the surface of cholesterol clefts in the wall of a radicular cyst (H & E).

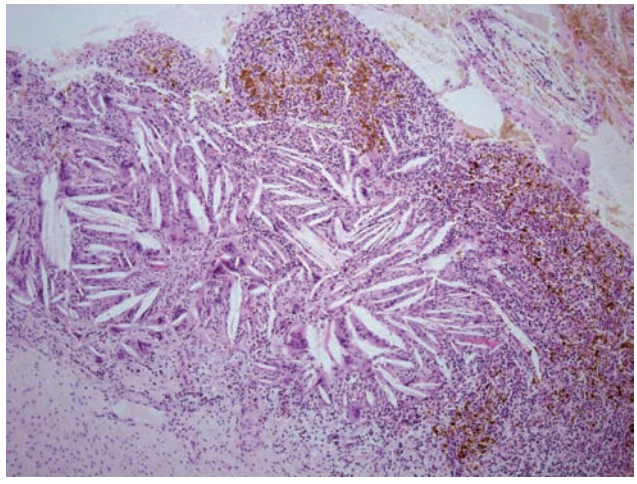


Fig. 11.15 Mural nodule of cholesterol-containing granulation tissue fungating into the cavity of a radicular cyst (H & E).

or lipofuschin. This, they thought, was derived in the same way as cholesterol, as part of the inflammatory process in the cyst wall.

A series of immunohistochemical investigations using monoclonal antibodies to study and compare the cytokeratin content and other antigens in the epithelial linings of odontogenic cysts, including radicular cysts, have recently been reported and are described in some detail in Chapters 3 and 4 (Hormia *et al*., 1987; Matthews *et al*., 1988) and have been reviewed by Shear (2002c).

Gao *et al*. (1988b) and Lu *et al*. (2002) have also investigated cytokeratin expression in radicular cysts. The study of Gao *et al*. showed strong keratin 19 expression in rest cells of Malassez and in the epithelium of periapical granulomas and radicular cysts. In the rests of Malassez, keratin 19 appeared to be paired with keratin 5. Unlike the situation in normal oral epithelium where staining for keratin 19 is found in the basal region, in proliferating epithelium in the periapical granulomas, staining tended to be suprabasal, while in cyst linings staining was often restricted to the most superficial layers of the epithelium. As an early change, epithelia in periapical granulomas also uniformly and strongly expressed keratin 14 and subsequently keratins 13 and 4. Further epithelial changes to form a cyst lining was associated with a more clearly differentiated phenotype of non-keratinised stratified squamous epithelium. Although expression was not always strong, staining for keratins 8 and 18 (typical of the simple epithelial phenotype) was consistently observed in proliferating epithelium in granulomas and in cyst linings. Gao *et al*. (1988b) suggested therefore that proliferating odontogenic epithelium appears to have a phenotype different from normal epithelia but one that is perhaps similar to that of epidermis during embryogenesis. Lu *et al*. (2002) confirmed some of these findings and showed that most cysts expressed simple keratins 8 and 18, as well as keratin 13. In a more detailed analysis they compared protein and mRNA expression in cysts to normal nasal and oral epithelium, and suggested that some maxillary cysts expressed a phenotype identical to respiratory epithelium. A keratin 18-positive, keratin 13-negative phenotype was only found in nasal epithelium, and in three maxillary cysts. They concluded that occasional maxillary radicular cysts may not be odontogenic in origin, but that their epithelium may derive from nasal or antral respiratory mucosa.

Yamada *et al*. (1989) carried out an immunohistochemical investigation of the distribution of involucrin in radicular cysts. Involucrin is a 92-kDa protein isolated from cultured human epidermal keratinocytes and synthesised in human squamous epithelial cells. It has been shown to be a useful histochemical marker for squamous cell differentiation. They showed that in proliferating epithelium lining radicular cysts there was an irregular distribution of involucrin, whereas in the relatively well-differentiated epithelium in a quiescent cyst involucrin deposition was evenly distributed throughout the epithelium except for the basal layer.

With regard to the relationship between the tooth and the cyst lining, there is some evidence for two distinct types of radicular cyst. Brief mention has already been made work by Simon (1980) who found that in some lesions a cavity may be present which is open to the root canal and is lined by epithelium that is attached to the root apex. For these lesions Simon (1980) coined the term 'bay cyst'. Nair *et al*. (1996) undertook meticulous serial sectioning of a large series of periapical lesions and found that of 256 lesions only 39 (15%) were radicular cysts. They also confirmed Simon's observations and were able to identify two types of cyst. The first had cavities completely enclosed by epithelium and were termed *apical true cysts*, whereas in the second type the cyst lumen was open to the root canal and these were termed *apical pocket cysts*. Of the 39 cysts, 24 (62%) were true cysts and 15 (38%) were pocket cysts. In further detailed considerations of these lesions, Nair (1998, 2003) showed that in pocket cysts the epithelium was attached at the root apex so that the lumen formed an extension of the root canal, and the intact epithelium acted as a barrier to seal off the contents of the infected root canal from the rest of the body. The cyst grows through accumulation of debris and necrotic tissue in the thus-formed 'pocket'. Nair (1998, 2003) attached considerable clinical significance to the distinction of the two cyst types and suggested that pocket cysts were likely to heal after tooth extraction or endodontic treatment, whereas a true cyst may be self-sustaining and can persist after treatment. From his data, apical true cysts only account for about 10% of all periapical lesions; this may explain the frequency of about 10% of persistent periapical lesions after conventional root canal treatment, and the low prevalence of residual cysts.

Ricucci and Bergonholtz (2004) consider that the pocket cyst may be problematic for the endodontist, because the cyst fluid may be under pressure and may continuously wet the root canal making instrumentation and filling difficult.

The fibrous capsule of radicular cysts is composed mainly of condensed collagen peripherally and a loose connective tissue adjacent to the epithelial lining. A histochemical and immunohistochemical study using the Sirius red F3BA method and the avidin–biotin–peroxidase complex to detect Factor XIIIa in the fibrous cyst wall of radicular cysts was carried out by Toida *et al*. (1990). Factor XIIIa-containing interstitial cells increase in number in various human tissues associated with fibrosis. They demonstrated that the fibrous capsule of the

radicular cyst was composed of three layers: an inner granulomatous layer, an outer fibrous connective tissue layer and an intermediate layer. Factor XIII was observed in certain connective tissue cells in all three layers. They were scanty in the inner layer where collagenous elements were also sparse but increased considerably in the moderately fibrous intermediate layer where they were dendritic or stellate-shaped. In the outer densely fibrous connective tissue layer, their numbers decreased slightly and they were slender and spindle-shaped. These results suggested that Facotr XIIIa-containing cells proliferated and differentiated prior to marked fibrosis and the authors proposed that these cells played an important part in the process of fibrosis in the radicular cyst wall.

Varying intensities of acute and chronic inflammatory cell infiltrate are present, particularly subepithelially. Acute inflammatory cells are seen particularly when the epithelium is proliferating. Usually, however, a chronic inflammatory cell infiltrate features in the fibrous capsule. Immunocytochemical studies on the walls of odontogenic cysts, including radicular cysts (Matthews and Browne, 1987), indicated that the cell populations were similar and consisted of HLA-Dr-positive macrophage type cells and a mixture of T and B lymphocytes. An account, in greater detail, of the immunocytochemical work in this area is to be found in the earlier part of this chapter (see p. 128). Russell bodies are seen in about 50% of cases.

Mast cells have been demonstrated in the epithelium and the connective tissue wall, particularly in the subepithelial zone (Mathiesen, 1973; Smith *et al*., 1989). Reference has been made elsewhere to their possible role in the pathogenesis of odontogenic cysts.

Remnants of odontogenic epithelium and occasional satellite microcysts may be found in the fibrous capsule and there have been reports of examples where epithelial proliferation is so extensive that it resembles squamous odontogenic tumour (Wright, 1979b; Simon and Jensen, 1985; Unal *et al*., 1987). The origin of this epithelium is almost certainly the cell rests of Malassez. When found in the wall of a dentigerous cyst, as has also been described (Wright, 1979b), or in the wall of a keratocyst (Hodgkinson *et al*., 1978), the origin is likely to be the remnants of the dental lamina (cell rests of Serres). All writers on the subject are agreed that the treatment is that of the cyst of origin and that no subsequent therapy is required if this observation is made during histological examination of the cyst wall.

George *et al*. (1984) described intraneural epithelial islands in the peripheral zone of the connective tissue capsule of a radicular cyst in the anterior maxilla.

Some cyst walls are markedly vascular. Haemorrhage is invariably present and haemosiderin deposits are seen in many specimens (Shear, 1963c).

Calcifications of various kinds are frequently present, and are a particular feature of residual radicular cysts that have been present for a long time (High and Hirschmann, 1986). Amorphous calcifications and trabeculae of woven bone occur most commonly and occasionally lamellar bone is found.

Frithiof and Hägglund (1966) examined 12 radicular cysts ultrastructurally. They found wide structural variations between specimens probably ascribable to differences in the degree of inflammation. In their ultrastructural study, Hansen and Kobayasi (1970a) found that the epithelium did not show the regular stratification usually seen in squamous epithelium. They described the presence of 'dark' and 'bright' cells. The dark cells they regarded as undergoing autolysis as they have a dense osmiophilic cytoplasm with indistinguishable organelles and they contain fat droplets, vacuoles and annular structures. Their nucleoplasm is dense and there are clumped chromatin masses. These cells also have poorly developed intercellular connections. The bright cells, on the other hand, have more distinct organelles, numerous mitochondria, ribosomes, granular endoplasmic reticulum and lyosomes, and are probably actively functioning cells.

Scanning electron microscopic observations on the inner surface of radicular cysts (Hurlen and Olsen, 1985) showed that sometimes the surface epithelium was fairly smooth with shallow foldings and ridges, and sometimes irregular and ruffled. Interepithelial spaces were seen in nearly all specimens. These were irregular in size and outline, and leucocytes could be seen penetrating them and lying on the surface of the epithelium, as were red blood cells in varying amounts. Four different types of crystal were seen, including cholesterol.

Studies suggest that bacteria are not found in radicular cysts and do not normally penetrate into the lumina. In their study of fluids and explants from 16 radicular cysts, Meghji *et al*. (1996) found endotoxins, but were unable to grow any bacteria using aerobic and anaerobic culture methods. In their histological analysis of a series of cases, Ricucci and Bergenholtz (2004) found bacteria in the pulp canals and in the immediate region of the apical foramena, but not in the cyst walls or lumina.

However, other studies have shown that infected cysts may not be sterile. In a microbiological study of the fluids of infected jaw cysts, predominantly radicular and residual, Iatrou *et al*. (1988) found that Gram-positive anaerobic cocci were the most frequent bacterial group, followed by Gram-negative anaerobic rods and Gram-positive aerobic cocci. Antibiotic sensitivity tests on the isolated organisms showed that the anaerobic cocci were most sensitive to chloramphenicol and minocycline, while all anaerobic rods tested were sensitive to metronidazole.

Residual cysts

The histopathological features of the residual cyst are similar to those described above for conventional radicular cysts. However, because the cause of the cyst has been removed, residual cysts may progressively become less inflamed so that eventually the cyst wall is composed of uninflamed collagenous fibrous tissue. The epithelial lining may be thin and regular and indistinguishable from a developmental cyst such as a dentigerous cyst or lateral periodontal cyst. In these cases it is important to establish the relationship of the lesion to the teeth.

Carcinomatous change

A few well-documented cases have been reported which indicate that squamous carcinoma may occasionally arise from the epithelial lining of radicular and other odontogenic cysts. Single cases arising in a residual radicular cyst have been reported by Kay and Kramer (1962), Schwimmer *et al.* (1991), van der Wal *et al.* (1993) and Swinson *et al.* (2005). The case of Ward and Cohen (1963) appears from their published photomicrograph to have originated in a keratocyst. Examples occurring in a radicular and in a dentigerous cyst were illustrated by Pindborg and Hjørting-Hansen (1974). Eversole *et al.* (1975) reviewed series of cases of central epidermoid carcinoma and central muco-epidermoid carcinoma of the jaws. They found that 75% of the former were associated with a cyst lining and 48% of the latter were associated with either a cyst or an impacted tooth. A detailed review of the literature on the subject was published by Gardner (1969). He examined the evidence presented with each of 63 cases reported during the period 1889–1967 and concluded that 25 of these fulfilled the criteria for origin of squamous carcinoma from odontogenic cyst lining epithelium. Van der Waal *et al.* (1985) reported five cases of squamous carcinoma arising in odontogenic cysts: three residual, one keratocyst and one dentigerous cyst. Pearcey (1985) documented two cases treated with radiotherapy and suggested that such treatment might be an acceptable alternative to wide surgical resection.

Before the diagnosis of carcinoma arising from a cyst lining can be established, a number of alternative possibilities must be excluded (Kay and Kramer, 1962; Swinson *et al.*, 2005). It is possible that cyst and neoplasm may have developed independently adjacent to one another and ultimately fused in some parts. Careful questioning of the patient and clinical examination are necessary to exclude the possibility that the neoplasm arose primarily from the oral mucosa, or that it is a metastatic deposit in the jaw. A further possibility to be considered is that the lesion was initially an epithelial neoplasm which underwent secondary cystic change.

Histological evidence of transition from a cyst lining through epithelial dysplasia to infiltrating squamous carcinoma provides acceptable proof (see Figs 3.18–3.20).

Despite the undoubted examples that occur from time to time, the frequency of neoplastic change is exceptionally rare in relation to the large numbers of cysts that are seen. Browne and Gough (1972) have suggested that keratin metaplasia in long-standing radicular and dentigerous cysts may precede malignant change and examples of epithelial dysplasia are occasionally seen in jaw cysts without any evidence of carcinomatous transformation. There is no evidence, however, that cyst epithelium is at particular risk and there is therefore no justification for regarding cysts as precancerous lesions.

Treatment

It is not intended to give an account here of the surgical treatment of the radicular and residual cysts. However, we would like to give a pathologist's view on the question of the non-surgical treatment of these lesions.

Oehlers (1970) believed that many periapical lesions left *in situ*, including cysts, are eliminated by the body once the causative agents are removed. This view was supported by Bhaskar (1972), who suggested that the vast majority of radicular cysts underwent resolution following conservative endodontic therapy. His hypothesis was based on endodontists' claims that 85–90% of apical lesions disappeared or become markedly reduced in size following conservative endodontic procedures. As available statistics indicated that 40–50% of all apical lesions are radicular cysts and as it is difficult to distinguish between apical granulomas and radicular cysts on radiographs alone, Bhaskar concluded that the majority of radicular cysts can undergo resolution following root canal therapy and do not require surgical intervention. He suggested that during the endodontic procedure, instrumentation should be performed slightly beyond the apical foramen. This produced a transitory acute inflammation which may destroy the epithelial linings of the radicular cysts and convert them into granulomas, thus leading to their resolution.

We have some difficulty in accepting Bhaskar's argument. First, it is difficult to obtain an accurate assessment of the relative proportions of periapical granulomas and cysts, and other workers have reported a lower frequency of cysts than did Bhaskar (Morse *et al.*, 1973; Nair *et al.*, 1996). Many periapical granulomas are not submitted for histological examination and their frequency in pathology department archival material is no reflection of their incidence. Pathologists differ in the criteria that they use for the diagnosis of a cyst. Some require the presence of an epithelial lining, whereas it has been clearly demonstrated that epithelial discontinuities occur to a greater or lesser

extent in a substantial proportion of radicular cysts (Toller, 1966a). The contention that destruction of cyst lining epithelium will lead to resolution of the cyst is therefore untenable. Production of a transitory acute inflammation may, on the contrary, merely stimulate epithelial proliferation. What may happen to a cyst when endodontic instrumentation is performed beyond the periapical foramen is that it becomes temporarily decompressed through the reduction of intracystic pressure. Bone deposition outside the cyst would show radiologically as an apparent reduction in size of the lesion.

Nair (1998, 2003) takes a more pragmatic pathologist's view of this issue. He considered that the type of cyst was important and that the true cyst is self-sustaining and may persist after treatment. In contrast, the lumen of a pocket cyst is continuous with the root canal and thus dependent on the pulpal infection for its growth and persistence. Pocket cysts therefore resolve and heal after conventional endodontic treatment. In support of his earlier study, Nair *et al.* (1996) showed that only 15% of periapical lesions were radicular cysts, and of these, 61% were true cysts and 39% were pocket cysts. If only true cysts persisted after treatment this would account for the low frequency (10–15%) of recurrent or persistent periapical lesions.

Useful analyses of published work on the non-surgical treatment of periapical lesions have been presented by Natkin *et al.* (1984) and more recently by Nair (2003, 2004) and in systematic reviews by Sathorn *et al.* (2005) and Torabinejad *et al.* (2005).

12
Inflammatory Paradental Cysts

The 1992 WHO classification (Kramer *et al.*, 1992) included two categories of inflammatory odontogenic cyst, the radicular cyst as discussed in the previous chapter, and the *paradental* (inflammatory collateral, mandibular infected buccal) cyst. This latter entity was defined as an inflammatory cyst arising on the lateral aspect of a vital tooth as a result of an inflammatory process in the periodontal pocket.

Such a lesion was first reported in the English literature by Main (1970a,b, 1985) who used the term inflammatory periodontal cyst or *inflammatory collateral cyst* to distinguish it from a radicular cyst associated with a lateral accessory root canal of a non-vital tooth, and from a developmental lateral periodontal cyst. The first reported cases of this lesion have been ascribed to Hofrath (1930) who described a 'marginal wisdom tooth cyst' which Philipsen *et al.* (2004) believe met all the criteria for a paradental cyst as currently defined.

The first detailed account of the paradental cyst was by Craig (1976) who described a cyst of inflammatory origin which occured on the lateral aspect of the roots of partially erupted mandibular third molars where there was an associated history of pericoronitis (Figs 12.1 and 12.2). He suggested that the term 'paradental cyst' was appropriate for this lesion.

Craig's series consisted of 49 cases, which represented about 5% of 1051 odontogenic cysts seen in his department over a 21-year period. Two-thirds of the cases occurred in patients in their third decade and there was a definite male preponderance (84%). In all cases the involved tooth was associated with a history of pericoronitis. The teeth were vital. Radiologically, a well-demarcated radiolucency occurred distal to the partially erupted tooth, but there was often buccal superimposition. The radiolucency sometimes extended apically but an intact periodontal ligament space provided the evidence that the lesion did not originate at the root apex (Fig. 12.1).

Twenty-six cysts in Craig's series were located on the buccal aspect of the roots, 19 were distal and four were mesial. Craig was of the opinion that there was some buccal involvement even in those cysts designated as of mesial or distal location. Macroscopically, the cysts on the buccal aspect of the roots covered the bifurcation and varied in size, some covering the entire buccal root surface (Fig. 12.2). Of considerable interest is the fact that in 20 of 28 cases where the associated tooth was available for study, removal of the cyst from the buccal root surface revealed a developmental enamel projection extending from the amelocemental junction towards the root bifurcation.

In the series of Main (1970a,b), seven of the eight lesions arose in association with a mandibular third molar and Craig was of the opinion that the paradental cyst and the lesion described by Main as an inflammatory collateral cyst were the same clinicopathological entity. Although the exact pathogensis of these lesions is still debated (see p. 147), it is generally now regarded that the lesions described by Main and detailed by Craig are one and the same.

It seems clear that the paradental cyst is of inflammatory origin and that it arises from odontogenic epithelium. Craig (1976) suggested that either the cell rests of Malassez or the reduced enamel epithelium might provide the cells of origin. He favoured the latter source, arguing that in his study the rests of Malassez always appeared inactive and that if the Malassez rests were responsible the lesions should be equally distributed around the root surface. His serial sections indicated that the development of the paradental cyst may follow hyperplasia and cystic change in reduced enamel epithelium. He suggested that the presence of an extension of reduced enamel epithelium over the enamel projections might be the source, and could explain the frequent buccal location of the cyst.

Craig's paper on the paradental cyst was, for a number of years, the only detailed account of the entity. Later, however, three substantial papers on the subject appeared which corroborated Craig's observations (Ackermann *et al.*, 1987; Fowler and Brannon, 1989; Vedtofte and Praetorius, 1989). In 1983, Stoneman and Worth described a lesion that is similar to the paradental cyst but which arose primarily on the mandibular first and second molars. They named this entity the *mandibular infected buccal cyst* to emphasise its origin in inflamed periodontal tissues of partially or fully erupted molars. Subsequently,

others have reported similar lesions (Trask *et al*., 1985; Camarda *et al*., 1989; Wolf and Hietanen, 1990).

Stoneman and Worth did not refer to the reports of Main or Craig and although they emphasised their lesion as being on first and second molars, three of their cases involved the third molar region. It seems therefore that the mandibular infected buccal cyst and paradental cyst share similar pathogenic mechanisms and histological features and should be regarded as variants of the same lesion. This is suggested by more recent papers which have reappraised these lesions and consider them to be the same entity (Packota *et al*., 1990; Thurnwald *et al*., 1994; Magnusson and Borrman, 1995; Thompson *et al*., 1997).

In a review of 342 cases from the world literature, Philipsen *et al*. (2004) concur with this view and prefer the term *inflammatory paradental cyst* to encompass all the collateral cysts of inflammatory origin. They point out, however, that the variations in clinical presentation and appearance justify considering the groups of paradental cysts separately. The most common lesions, representing 61.4% of paradental cysts, arose in adults and were associated with a mandibular third molar. The second group, comprising 35.9% of lesions, were related to the first and second molars and arose in younger individuals with a characteristic clinical presentation. These can be regarded as a distinct group and we suggest the term *juvenile paradental cyst* for these lesions.

Rare lesions may be found associated with other partially erupted teeth including a single case on a maxillary molar (Vedtofte and Praetorius, 1989) and a number of cases in the globulomaxillary region (Main 1970a; Vedtofte and Holmstrup, 1989). Recently, four cases were reported associated with erupting mandibular premolar teeth (Morimoto *et al*., 2004). The key features of each type of paradental cyst are summarised in Table 12.1.

Clinical features

Frequency

In the sample of 3498 jaw cysts in our South African series (see Table 1.1), there were 109 paradental cysts representing 3.0% of all cysts and 3.7% of odontogenic cysts. The series of 50 cases of paradental cyst reported by Ackermann *et al*. (1987) represented 3% of a sample of 1852 odontogenic cysts observed over a 20-year period, and de Sousa *et al*. (2001) reported 54 lesions representing 4.3% of all odontogenic cysts.

In Craig's original series (Craig, 1976), paradental cysts comprised 4.7% of 1051 odontogenic cysts, and in a

Table 12.1 Key features of the clinical variants of the inflammatory paradental cyst. Data derived from Philipsen *et al*. (2004), Vedtofte and Holmstrup (1989)[1] and Morimoto *et al*. (2004).[2]

	Paradental cyst	**Juvenile paradental cyst**		**Maxillary paradental cyst[1]**	**Premolar paradental cyst[2]**
Site	Mandibular third molar	Mandibular first/second molar		Globulomaxillary region	Mandibular premolar
Frequency	61%	36%		2.7%	<1%
Age: mean (range)		First molar	Second molar		
Male	29.8 (20–40)	8.1 (6–11)	19.8 (10–40)	18.8 (M & F together)	10.0 (only 1 case)
Female	24.7 (18–47)	9.0 (5–47)	13.6 (12–16)		9.5 (9–10)
Male : female	1 : 0.4	1 : 0.9		8 : 1	1 : 3
Location	Distal or disto-buccal	Buccal		Medial to canine	Buccal
Proportion bilateral	4%	25%		NR	NR
Clinical features	History of pericoronitis associated with partially erupted tooth. Cyst is continuous with the pericoronal pocket	Usually signs of infection, swelling, painful and may be suppuration. Tooth tipped buccally, deep pockets in continuity with cyst lumen		Incidental findings, may be swelling. Teeth fully erupted. Pockets communicate with cyst lumen	Swelling and pain. Lingual displacement of the tooth
Radiology	Well-demarcated distal or disto-buccal radiolucency, superimposed over roots. Distal follicular space preserved	Well-demarcated radiolucency over buccal aspect of roots, buccal expansion with corticated outline		Well-demarcated radiolucency between incisor and canine. 'Inverted pear shape' with divergent roots	Well-demarcated buccal radiolucency and expansion with corticated outline

NR, not reported.

recent study from the same department (Jones *et al.*, 2006) a diagnosis of paradental cyst was made on 402 occasions over a 30-year period (1975–2004) representing 5.6% of 7121 odontogenic cysts.

Philipsen *et al.* (2004) reported relative frequencies ranging between 0.9 and 4.7% of odontogenic cysts. It is probable, however, that paradental cysts are underreported because many cases received within pathology departments may have insufficient clinical information to establish the diagnosis and many may have been diagnosed as inflamed dentigerous cysts, pericoronitis or inflamed follicles. In departments where the diagnosis is made on a regular basis, the paradental cyst appears to be a common lesion. In the series of Colgan *et al.* (2002), paradental cysts comprised 15 of 60 (25%) cystic lesions associated with lower third molars. This was the second most common diagnosis after dentigerous cyst (30%). It is interesting that these figures contrast starkly with some data from the USA. In a study of 2646 pericoronal lesions associated with partially erupted teeth, Curran *et al.* (2002) did not identify a single case of paradental cyst. Sixty-seven per cent (1776 lesions) were diagnosed as follicular tissue and of the remaining pathologically significant lesions, 77.5% were diagnosed as dentigerous cysts. This suggests that in this centre, paradental cysts were not recognised as an entity and highlight the need for clearer criteria for diagnosis and further studies of prevalence and frequency.

Age

For all types of paradental cyst, there is a wide age range (Table 12.1), but as most lesions arise on an erupting tooth or may be initiated during tooth eruption, the mean ages of presentation correlate well with the chronological stage of eruption with lesions most often presenting a few years after the eruption of the associated tooth. The mean age of presentation of the juvenile paradental cyst depends on the tooth affected and differs for males and females, with males affected slightly later (Philipsen *et al.*, 2004). Lesions on the first molar affect individuals between 6 and 47 years with a mean age at presentation of 9.0 years for males and 8.1 years for females. Lesions on the second molar present between 10 and 40 years with mean ages of 19.8 years and 13.6 years for males and females, respectively. Cases arising on premolars also reflect the early eruption of these teeth; the four cases reported by Morimoto *et al.* (2004) presented at ages 9 or 10 years.

Paradental cysts on third molars present in an older age group. Virtually all the cases in the study by Ackermann *et al.* (1987) occurred between the ages of 10 and 39 with two-thirds of their sample in the third decade; the same as in Craig's material and in the recent Sheffield series (Jones *et al.*, 2006). Five of the six cases in the study of Fowler and Brannon (1989) affected patients in the third decade. In their review of the world literature, Philipsen *et al.* (2004) reported similar age distributions with mean ages in the third decade (Table 12.1).

Gender

In Craig's original study (1976) and in the large series of Ackerman *et al.* (1987), there was a considerable preponderance of males with paradental cysts associated with third molars. Philipsen *et al.* (2004) recorded more than twice as many lesions in males than in females (male : female ratio of 1 : 0.4) and the large series from Sheffield showed a male : female ratio of 1 : 0.7.

Site and clinical presentation

Over 60% of all paradental cysts involve the mandibular third molars and there is usually a history of recurrent or persistent pericoronitis. Lesions are most often located in a buccal or disto-buccal location and cover the root surface (Figs 12.1 and 12.2), usually involving the bifurcation. Colgan *et al.* (2002) showed that the precise site of the lesion may depend on the angle of impaction of the associated tooth. Cysts were located on the mesial aspect of mesioangular impacted teeth, buccal to vertical impactions and distal or disto-buccal to disto-angularly impacted teeth. Swelling and pain are not prominent features. The cyst lumen may be continuous with the periodontal or 'pericoronal' pocket. The tooth is always vital, which allows a lateral radicular cyst to be excluded. Craig (1976) showed that lesions were often associated with a buccal enamel spur projecting down towards the bifurcation and this was confirmed by Fowler and Brannon (1989) and Ackermann *et al.* (1987). Bilateral examples have been reported in about 4% of cases (Philipsen *et al.*, 2004).

Juvenile paradental cysts account for about 36% of lesions (Philipsen *et al.*, 2004). They typically affect the permanent mandibular first and second molar teeth although premolars may also be affected. Although the juvenile and third molar lesions represent different manifestations of the same disease process, both brought on by inflammation arising around the crowns of erupting teeth, the process in younger children, probably because of anatomical differences in the mandible, may be more extensive and present more severe clinical symptoms and signs (Fig. 12.3). It is for these reasons that the lesion warrants its own designation, and has been given the distinctive designation 'juvenile paradental cyst' in this book.

Stoneman and Worth (1983), who first reported this lesion as 'mandibular infected buccal cyst', stated that the cyst may produce few or no clinical symptoms and minimal signs, but that there may be discomfort, pain, tenderness, painful occlusion and, rarely, suppuration

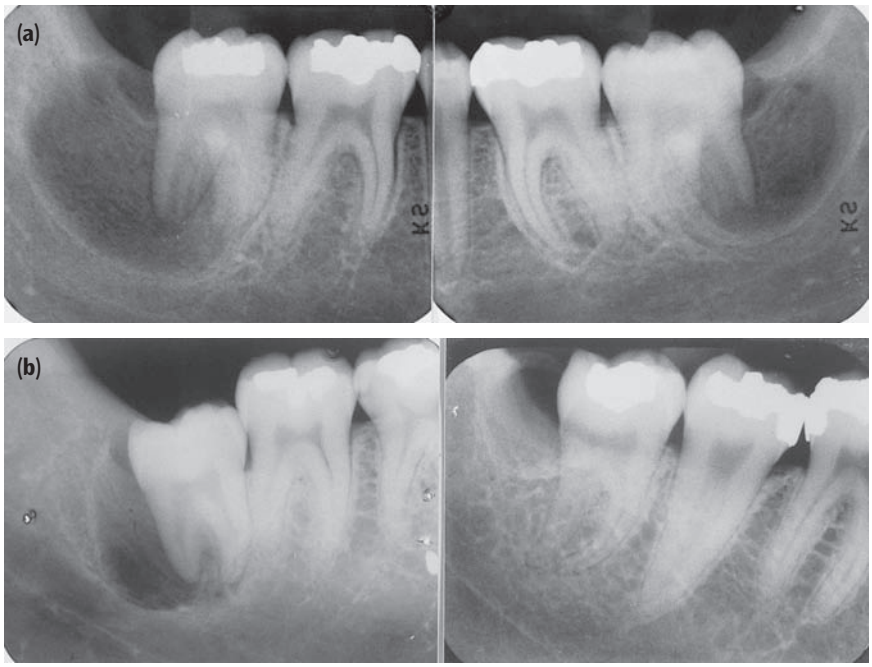


Fig. 12.1 (a,b) Two cases of bilateral paradental cysts associated with erupting mandibular third molar teeth. The cysts are distal and buccal to the involved teeth. Note that the periodontal ligament space is not widened and that the distal part of the cyst is separate from the distinct distal follicular space. (By courtesy of Drs P. Vedtofte and F. Praetorius, and C.V. Mosby Co. Previously published (1989) The inflammatory paradental cyst. *Oral Surgery* **68**, 182–188, Figs. 1 and 3.)

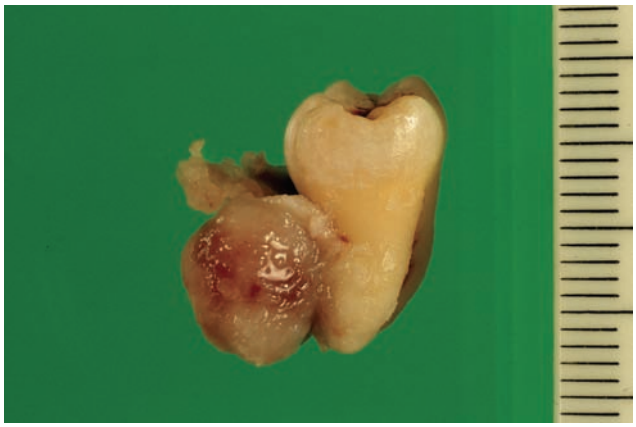


Fig. 12.2 Gross specimen of a paradental cyst involving the distal and buccal surfaces of an impacted mandibular third molar tooth with pericoronitis. (By courtesy of Dr G.T. Craig.)

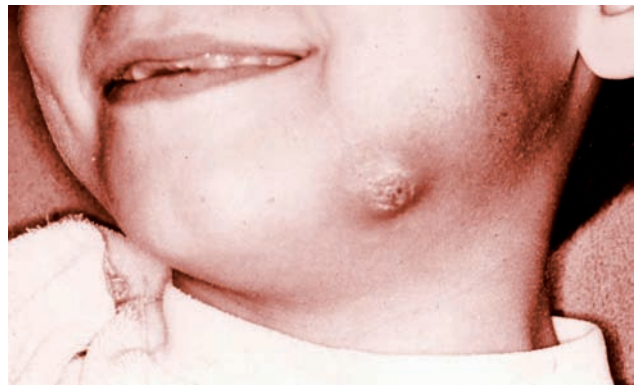


Fig. 12.3 Young boy with mandibular infected buccal cyst involving newly erupted mandibular first permanent molar. Infection has extended through the bone and led to a facial abscess. (By courtesy of Dr D.W. Stoneman [colour has been added to a black and white image]).

(Fig. 12.3). Swelling is the clinical feature most likely to induce the patient to seek advice. The diagnostic features are the young age of the patients, the mandibular molar site, the buccal periostitis, the usually vital pulp and the radiographic preservation of the continuity of the apical lamina dura. The cyst is always situated on the buccal surface of a mandibular molar, most frequently the first permanent molar, after partial or complete eruption. The associated tooth is usually tilted so that the apices are adjacent to the lingual cortex, a feature that is demonstrable in occlusal radiographs (Fig. 12.4). The size of the cyst varies and may extend beyond the limits of the involved tooth and impinge upon and displace the crypt of the adjacent unerupted tooth. The extension of the cyst in a buccal direction is variable, but frequently the outer bony cortex is lost. Facial swelling may follow and this may be inflamed. Rarely, an abscess forms and may point (Fig 12.3).

Paradental cysts in the globulomaxillary region probably arise in association with the erupting canine and present as an inverted pear-shaped radiolucency between the incisor and canine teeth which are vital and show divergent roots. Most lesions have been chance findings and seem to present as symptomless swellings. There is sometimes a communication between the periodontal pocket of the teeth and the cyst lumen.

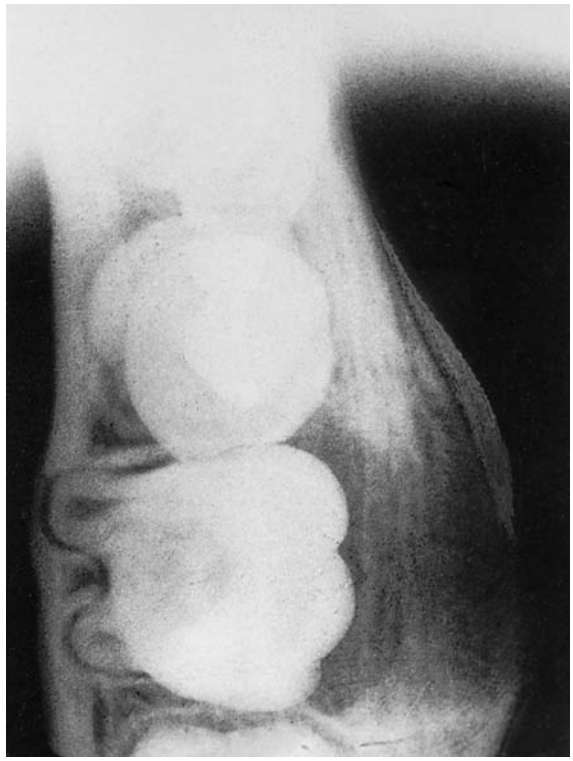


Fig. 12.4 Occlusal view of mandibular infected buccal cyst. There is a displacement and tilting of the right mandibular first molar tooth so that its apices lies close to the lingual margin. There is resorption of bone on the buccal aspect of the tooth and buccal expansion. Subperiosteal new bone has been deposited buccally, giving a laminated appearance. (By courtesy of Dr D.W. Stoneman and the Eastman Kodak Co. Previously published (1983) *Dent Radiography and Photography* **56**, 1–14, Fig. 12.)

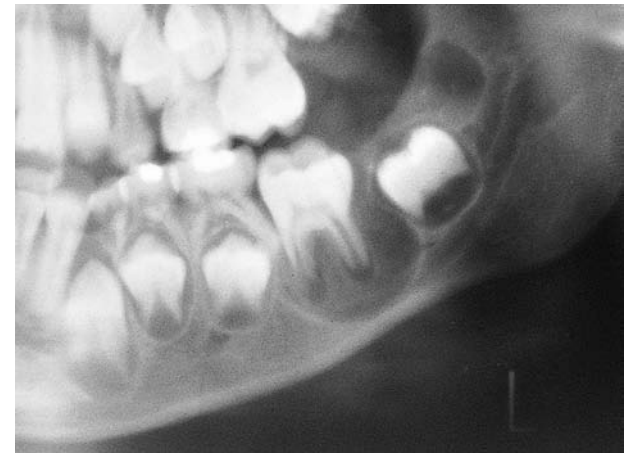


Fig. 12.5 Mandibular infected buccal cyst involving erupting mandibular first permanent molar. (By courtesy of Dr D.W. Stoneman.)

Radiological features

All authors reported a variable radiological picture but there are some features, originally described by Craig (1976), that appear consistently and which are useful in contributing to the diagnosis. The lesions are often superimposed on the buccal root face as well-demarcated radiolucencies, often with a corticated margin. In all types of paradental cyst the periodontal ligament space is not widened and the lamina dura is intact around the roots. In paradental cysts associated with third molars there is usually a distal as well as a buccal radiolucency. The distal element is well defined and is distinct from the distal follicular space. This is well illustrated in Fig. 12.1, which shows radiographs from the paper by Vedtofte and Praetorius (1989). Colgan *et al.* (2002) identified this feature in nine of their 15 cases and considered it to be an important and helpful diagnostic feature.

Radiological examination of the juvenile paradental cyst should include periapical, occlusal and panoramic views. The cyst presents as a well-demarcated radiolucency overlying the buccal aspects of the tooth roots. Buccal expansion may be apparent and with involvement of the periosteum new bone may be laid down, either as a single linear band or laminated if there are two or more layers (Fig. 12.4). Sometimes the new bone may be homogeneous. Usually there is involvement of the bone in the furcation and the entire interradicular bone may be lost. The inferior margin of the cyst is concave and rarely the cyst may extend to the inferior border of the mandible but not leading to any external deformity (Fig. 12.5).

Pathogenesis

There is no unanimity with regard to pathogenesis. Ackermann *et al.* (1987) agreed with Craig (1976) and favoured an origin from reduced enamel epithelium but suggested that cyst formation occurs as a result of unilateral expansion of the dental follicle secondary to inflammatory destruction of periodontium and alveolar bone. This, they suggested, was different from the histogenesis of a dentigerous cyst where expansion of the follicle is the primary event with consequent bone destruction. In two of their cases they were able to demonstrate continuity of cyst

lining with reduced enamel epithelium. Craig (1976) suggested that the downward extension of the reduced enamel epithelium at the site of an enamel spur may provide a site of stagnation during episodes of pericoronitis. While accepting that the paradental cyst was an entity, Fowler and Brannon (1989) suggested that it may be a variant of the dentigerous cyst or derived from an occluded periodontal pocket. Vedtofte and Praetorius (1989) were satisfied that the cyst was of inflammatory origin, initiated by a pericoronitis at the time of tooth eruption, and considered rests of Malassez and reduced enamel epithelium the most likely source of the cyst epithelium. It would seem that there is evidence to support origin from either rests of Malassez or reduced enamel epithelium.

On the other hand, many reports (Craig, 1976; Ackermann *et al.*, 1987; de Sousa *et al.*, 2001) have demonstrated continuity of cyst lining with reduced enamel epithelium, or with the periodontal or pericoronal pocket around the associated tooth (Fig. 12.6) (Philipsen *et al.*, 2004; Colgan *et al.*, 2002). Some workers require an opening to the surface as a diagnostic criterion (de Sousa *et al.*, 2001). These latter workers obtained sections of the cyst in continuity with their associated teeth and showed that the cyst linings were attached at the cement–enamel junction and were continuous with the oral epithelium. These studies suggest that the paradental cyst is equivalent to a dilated follicle lined by hyperplastic and proliferative follicular (reduced enamel) epithelium. Thus, a descriptive designation of 'inflammatory pocket cyst' may be appropriate and Slater (2003) has suggested that the third molar lesions should be called 'eruption pocket cysts'. It is possible that swelling associated with inflammation leads to occlusion of the opening of the pocket, thus allowing accumulation of debris and cyst growth by osmotic pressure in a similar process to that described for radicular cysts.

Colgan *et al.* (2002) suggested that food impaction may have an important part to play. In 13 of their 15 cases the associated tooth was opposed by a maxillary molar and they proposed that the angulation of the affected tooth could promote food impaction into the gingival tissues around the crown of the erupting tooth. As further evidence for this they showed that four cases contained giant cells consistent with a foreign body reaction.

Histological features

There is agreement that histologically the paradental cyst is indistinguishable from the radicular cyst. The cysts are lined by a hyperplastic, non-keratinised, stratified squamous epithelium which may be spongiotic and of varying thickness. An intense inflammatory cell infiltrate was present associated with the hyperplastic epithelium and in the adjacent fibrous capsule (Fig. 12.7). The

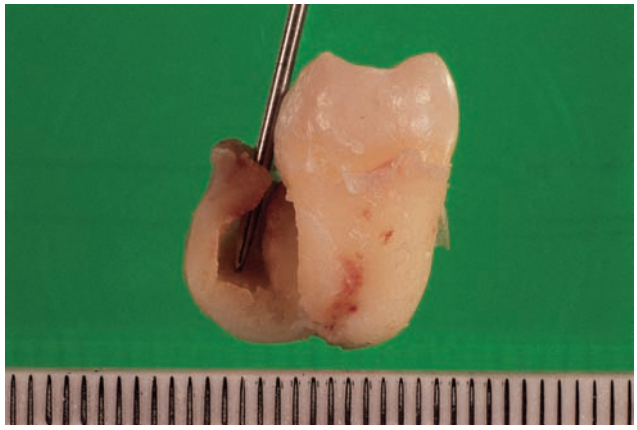


Fig. 12.6 Paradental cyst on the buccal aspect of a partially erupted third molar. The cyst is open towards the coronal aspect and is in continuity with the reduced enamel epithelium and the pericoronal pocket. (By courtesy of Dr G.T. Craig.)

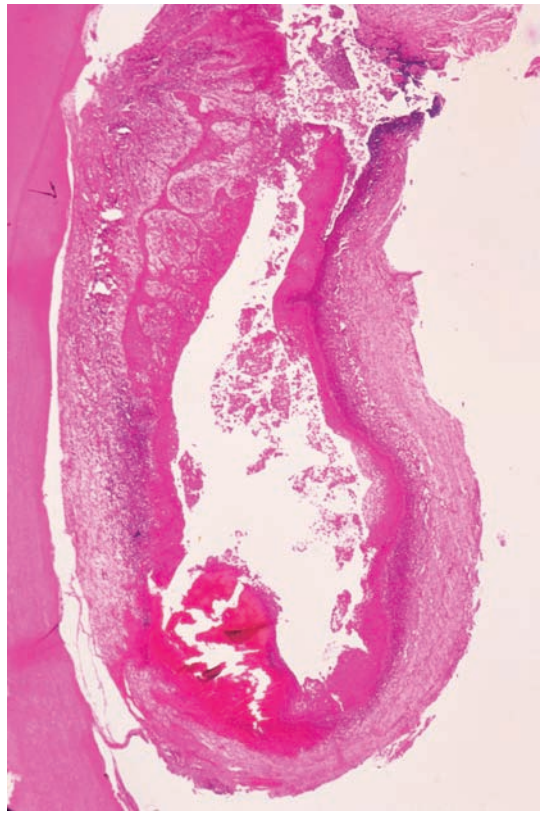


Fig. 12.7 Paradental cyst adjacent to the root of an impacted mandibular third molar. The cyst is lined by non-keratinised stratified squamous epithelium of variable thickness and showing areas of proliferation (H & E). (By courtesy of Dr G.T. Craig.)

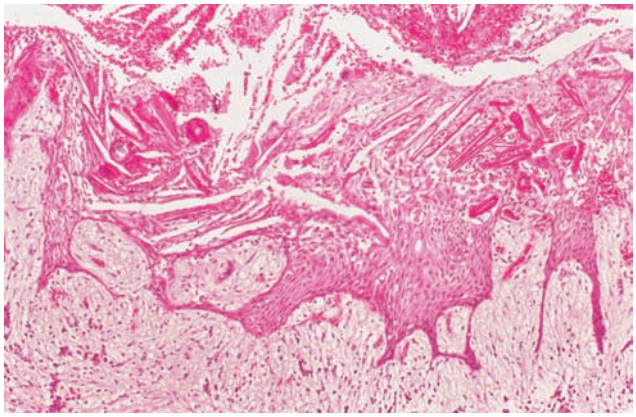


Fig. 12.8 Part of the lining of a paradental cyst showing proliferative epithelium and cholesterol clefts (H & E). (By courtesy of Dr G.T. Craig.)

fibrous capsule is the seat of an intense chronic or mixed inflammatory cell infiltrate. As in radicular cysts, haemosiderin deposits or accumulations of cholesterol crystals may be seen (Fig. 12.8). Colgan *et al.* (2002) described a subset of cysts (three of their 15 cases) which showed less inflammation and in which the epithelium was thinned with budding and an oedematous superficial layer. They did not speculate on the cause of this or on the origin of these cysts but they commented on the importance of differentiating these lesions from cystic ameloblastoma which may have a similar epithelial lining.

Other inflammatory collateral cysts

There is general consensus that the paradental cyst is an inflammatory odontogenic cyst derived from cystic proliferation of epithelium derived from the dental follicle (reduced enamel) epithelium or the early epithelial attachment. However, the original descriptions of collateral cysts considered rest cells of Malassez to be a likely source of the epithelium (Main 1970a,b, 1985). While the evidence suggests that the vast majority of cases are derived from reduced enamel epithelium, there is little doubt that some inflammatory lateral lesions arise from rests of Malassez, presumably stimulated by inflammation at the apical portion of a periodontal pocket or by pericoronitis. This has been discussed above. It is also possible that some lateral inflammatory cysts take their origin from cystic dilation of a periodontal pocket and become lined by crevice or pocket epithelium.

What is surprising, therefore, is that inflammatory collateral cysts are relatively so rare. In view of the high frequency of chronic periodontitis, the occurrence of inflammatory collateral cysts is very much lower than one might expect. If occlusion of the opening of the pocket is a requirement for cyst development and growth, then the explanation for this may be that drainage occurs more readily from the lateral periodontium than from the apical periodontium in the case of radicular cysts. The antigenic stimuli and the environment may therefore not be conducive to cyst formation.

Treatment

The lesions are benign and there is no evidence to suggest that recurrence is a problem. Paradental cysts associated with third molars are usually removed along with the offending tooth, but it is generally agreed that for juvenile lesions enucleation of the cyst without removal of the associated tooth is the treatment of choice.

13
Aneurysmal Bone Cyst

The aneurysmal bone cyst is an uncommon lesion which has been found in most bones of the skeleton, although the majority occur in the long bones and in the spine (Kransdorf and Sweet, 1995). The true nature of the lesion remains uncertain, although most regard it as probably reactive. Although the lesion is characteristically cystic and blood filled, the term 'aneurysmal bone cyst' was suggested by Jaffe and Lichtenstein (1942) to describe the characteristic 'blown-out' contour of the bone seen in radiographs of the lesion.

Clinical features

Frequency

The first report of aneurysmal bone cysts involving the craniofacial skeleton appears to be that of Bernier and Bhaskar (1958). In the following year, Bhaskar *et al.* (1959) described five cases. Gruskin and Dahlin (1968) reviewed the literature, and reported 13 cases including two of their own. Daugherty and Eversole (1971) reviewed 17 cases including their own and detailed analyses of the literature have been carried out subsequently by Steidler *et al.* (1979), El-Deeb *et al.* (1980), Struthers (1980), Struthers and Shear (1984a,b), Gingell *et al.* (1984), Toljanic *et al.* (1987) and Motamedi (1998).

Aneurysmal bone cysts of the jaws are rare. In our 1984 studies we found that while approximately 650 cases involving the entire skeleton had been reported, only 42 well-documented examples involving the jaws had been recorded in the literature. Since then only a total of about 60–70 cases have been published. Fifteen cases have been recorded in our South African series, representing 0.4% of 3498 jaw cysts (see Table 1.1). The data for age, gender and site recorded below are those used in the publication by Struthers and Shear (1984a), derived from the 42 reported cases and 14 of our own specimens which have not been reported previously.

Age

In our series from the University of the Witwatersrand, 42 of 45 (93%) cases were in the first three decades of life with a peak in the second decade (Struthers and Shear 1984a). Twenty-nine patients were younger than 20 years (64%). In the Sheffield series, only 11 aneurysmal bone cysts were recorded over a 30-year period, representing 0.15% of 7224 jaw cysts (Jones and Franklin, 2006a,b). The lesion was relatively more common in children accounting for four (0.7%) of 590 jaw cysts in under 16 year olds. The age and gender distribution of the combined series of 56 cases is shown in Fig. 13.1.

Gender

Reports of the relative frequency in males and females vary. At all sites, aneurysmal bone cyst appears to be slightly more common in females (Kransdorf and Sweet, 1995). Of the 56 cases in Fig. 13.1, 33 were females (59%) and 23 males, but in a series of 17 cases reported by Motamedi (1998) there was no differences in frequency between males and females.

Site

All the series quoted above have shown that the mandible is the most common site. Of the 45 cases reported by Struthers and Shear (1984a), 28 were in the mandible (62%) and 17 in the maxilla. One cyst was found close to the orbital floor and another in the zygomatic arch. The anterior region of the mandible was rarely involved. Most of the cases were located in the molar regions of the mandible and maxilla and a number of the mandibular cases extended posteriorly to involve the angle and ascending ramus. Only very occasional cases have involved the mandibular condyle (Motamedi, 2002), including one associated with a benign osteoblastoma (Svensson and Isacsson, 1993).

Clinical presentation

Aneurysmal bone cysts of the jaws produce firm swellings which have been described as painful in fewer than half of the reported cases. The swelling and malocclusion frequently become progressively worse and the rate of

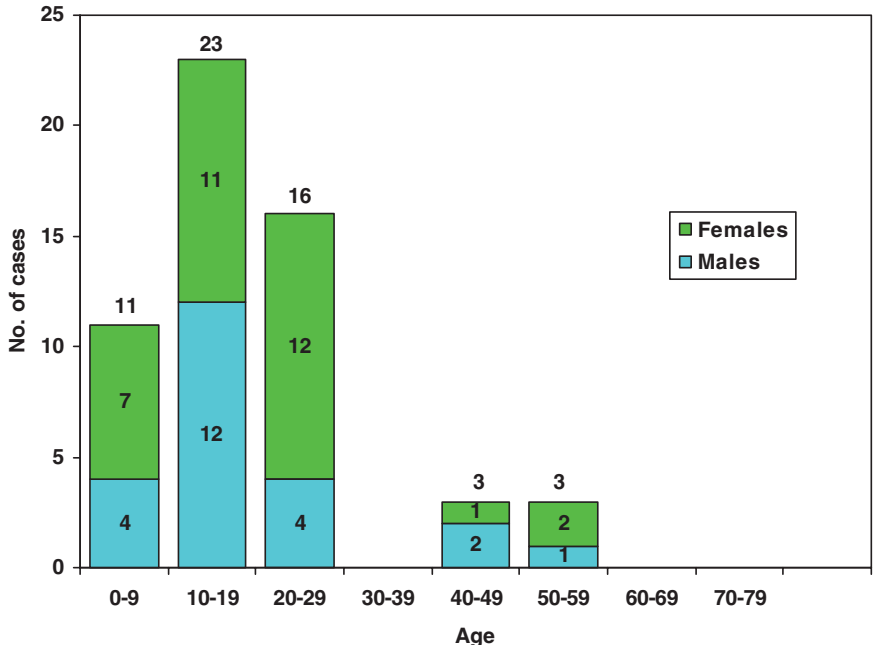


Fig. 13.1 Age distribution of 56 patients with aneurysmal bone cyst of the jaws. Data represent combined cases from South Africa and Sheffield, England.

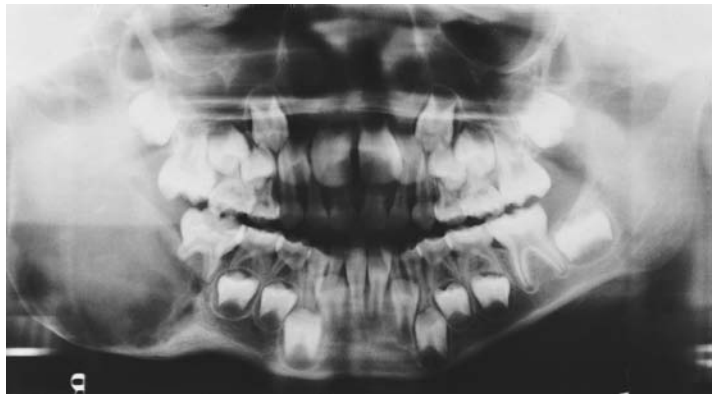


Fig. 13.2 Radiograph of an aneurysmal bone cyst involving the angle and ascending ramus of the mandible. There is a ballooning expansion of the cortex. (By courtesy of Professor E. Raubenheimer.)

enlargement is often described as relatively rapid. Occasionally, there is a history of recent displacement of teeth, which remain vital. When the lesion perforates the cortex and is covered by periosteum or only a thin shell of bone, it may exhibit springiness or egg-shell crackling, but is not pulsatile. Bruits are not heard. According to the patients' histories, trauma does not seem to have a significant aetiological role. There may be some difficulty in opening the mouth if there is impingement of the lesion on the capsule of the temporomandibular joint.

Radiological features

The aneurysmal bone cyst has a characteristic 'ballooning' growth pattern which results in a radiolucent area with elevation of the periosteum to produce an ovoid or fusiform expansion of the bone with the typical 'blown-out' cortical expansion (Fig 13.2). Subperiosteal new bone may not be visible on plain radiographs but computerised tomography (CT) scanning may reveal a thin uninterrupted cortex (Kransdorf and Sweet, 1995). Lesions are usually unilocular (Fig. 13.2) but longer-standing lesions may show a 'soap-bubble' appearance and may become progressively calcified (Kransdorf and Sweet, 1995). CT scans and magnetic resonance imaging (MRI) may more accurately outline the lesion and may also demonstrate fluid levels in the cystic areas (Revel *et al.*, 1992). Teeth may be displaced and root resorption has been described (Hardee *et al.*, 1992). Radiological differentiation from other expansile jaw lesions may be difficult.

Pathogenesis

The pathogenesis of the aneurysmal bone cyst is controversial and numbers of theories have been proposed. The original cases reported by Jaffe and Lichtenstein (1942) were in the long bones and showed eccentric bone expansion indicating a juxtacortical or subperiosteal lesion.

Subsequently, it has become apparent that the aneurysmal bone cyst may have a juxtacortical or intramedullary location. This has led to the concept of aneurysmal bone cyst being the end result of a common pathophysiological process with a variety of causes (Kransdorf and Sweet, 1995). Juxtacortical lesions that are found in a subperiosteal location are thought to be primarily of traumatic origin, whereas intramedullary lesions reflect secondary change within pre-existing lesions. Juxtacortical lesions have not been reported in the head and neck and although trauma has been postulated, there is little evidence to support this as a cause of jaw lesions. Kransdorf and Sweet (1995) suggested that the cysts may result from a vascular disturbance in the form of sudden venous occlusion or the development of an arteriovenous shunt. This would usually occur in more vascular, newly formed parts of the immature skeleton and in a pre-existing lesion.

The concept that the aneurysmal bone cyst is a secondary phenomenon arising in a pre-existing bone lesion has gained considerable support, and there is undoubtedly good evidence to sustain it. As early as 1940, Ewing described what appeared to be an aneurysmal bone cyst and suggested that it was a benign giant cell tumour modified by communication with large blood vessels. Jaffe (1950) proposed that the cyst may result from modification of some other lesion of bone, most of which may be destroyed by haemorrhage. Clough and Price (1968) described two cases, one of which contained areas with the appearance of fibrous dysplasia and the other with features of chondromyxoid fibroma. They suggested that the cyst may be either a primary occurrence or a secondary phenomenon in both benign and malignant lesions of bone.

Biesecker *et al.* (1970) showed evidence of an associated lesion of bone in 21 of 66 cases (32%) of aneurysmal bone cyst. These were non-ossifying fibroma, chondroblastoma, giant cell tumour of bone, osteoblastoma, giant cell granuloma, fibrous dysplasia, myxofibroma and solitary bone cyst. They postulated that the primary lesion initiated an arteriovenous malformation in the bone and that its haemodynamic forces established the aneurysmal bone cyst. In a similar study, Levy *et al.* (1975) reported 57 aneurysmal bone cysts associated with other lesions of bone. The most frequently associated lesions were solitary bone cysts, giant cell tumours and osteosarcomas, but the change was also observed secondarily to non-ossifying fibroma, osteoblastoma, haemangioendothelioma and haemangioma. Some of their cases were secondary to fractures or other bone trauma. They acknowledged, however, that the aneurysmal bone cyst could develop as a primary lesion.

In their review of 53 cases of aneurysmal bone cyst of the jaws, El-Deeb *et al.* (1980) reported that 11 (21%) were associated with pre-existing lesions. These were ossifying fibroma (two cases), cementifying fibroma (one case), fibrous dysplasia (four cases) and giant cell granuloma (four cases). Robinson (1985) carried out a similar review, probably sampling much of the same material, and confirmed that of 58 cases of aneurysmal bone cyst of the jaws 13 were associated with other bone disease. His own case showed an associated cementifying fibroma.

In our South African study, Struthers (1980) and Struthers and Shear (1984b) concluded that an associated lesion could be identified in 33 reported cases. Two were ossifying fibromas, two cementifying fibromas, four fibrous dysplasias, 24 central giant cell granulomas and one was an osteosarcoma. Of our own five cases available at the time of the study, three were associated with tissue identical to that seen in the central giant cell granuloma of the jaws and two with ossifying fibroma. Two cases circulated by the WHO International Reference Centre for the Histological Definition and Classification of Odontogenic Tumours, Jaw Cysts and Allied Lesions were associated with ossifying fibroma and two with central giant cell granuloma.

Working on the hypothesis that the aneurysmal bone cyst was a secondary phenomenon which developed by breakdown of part of a pre-existing lesion of bone, histological material from 303 pathological lesions of bone of various kinds was studied to look for evidence of early changes which might indicate a potential for development into aneurysmal bone cyst (Struthers, 1980; Struthers and Shear, 1984b). As reference material, the authors studied 19 established aneurysmal bone cysts from various parts of the skeleton, including the jaws, because in such lesions smaller blood-filled spaces and numerous microcysts were usually found at the periphery of the large blood-filled spaces. Changes of this kind were seen particularly in central giant cell granulomas. In a sample of 54 cases of central giant cell granuloma, they observed such microcyst formation in 15 (28%). In three of these the changes were strikingly similar to those seen in the aneurysmal bone cyst. The same changes were also recognised, although with a much lower frequency, in the fibrous dysplasias (8%), ossifying fibromas (4%) and cementifying fibromas (3%) studied. One case of Paget's disease of bone showed the presence of large blood-filled spaces, as did several of the malignant lesions.

Struthers and Shear (1984b) suggested that the initiating change in the primary lesion appeared to be the microcyst. They pointed out that the formation of microcysts in fibrous dysplasia had been described by Geschickter and Copeland (1949), Jaffe (1953) and Fisher (1976). The central giant cell granuloma has a propensity to form microcysts because of its loose, oedematous, fibrillar connective tissue stroma in which lie many thin-walled blood vessels and extravasated erythrocytes. Microcyst formation is facilitated by localised areas of necrosis in the

stroma brought about by stagnation and ischaemia. The resulting microcysts are lined by stromal connective tissue and in giant cell lesions multinucleate giant cells may form part of their margins. They enlarge by further stromal breakdown and coalesce with each other. Loss of stromal support leads to dilatation and rupture of the thin-walled vessels and haemorrhage into the stroma and the microcysts. An association of dilated blood vessels and microcysts is frequently observed (Fig. 13.3). Once a vascular connection is established between a larger vessel and a microcyst, haemodynamic pressure participates in its enlargement and little supportive resistance is offered if the surrounding stroma is loose and oedematous. The spaces now assume the dimensions of macrocysts which are surrounded by a layer of compressed stroma and these multiple expanding blood-filled cysts produce a pressure resorption of bone. Endosteal resorption of the cortical plates occurs ultimately and once these are breached a 'blow out' of the lesion, covered with periosteum, occurs. A layer of periosteal new bone may be deposited to form a thin shell covering the aneurysmal bone cyst (Fig. 13.2).

Struthers and Shear (1984a) were of the opinion that a malignant lesion was less likely to produce the classic clinicopathological features of an aneurysmal bone cyst because of its tendency to break out of bone. Nevertheless, of 42 fibrosarcomas that they studied histologically, six showed large blood-filled spaces, as did eight of 75 cases of osteosarcoma. They believed that the latter represented the telangiectatic form of osteosarcoma which several authors have described as resembling the aneurysmal bone cyst. The rare development of aneurysmal bone cyst in malignant lesions probably explains the so-called malignant form of the cyst occasionally reported in the literature (Levy *et al*., 1975).

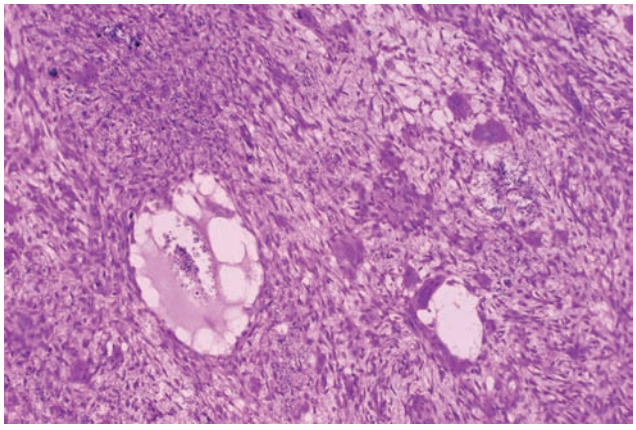


Fig. 13.3 Dilated blood vessels and microcysts in part of an aneurysmal bone cyst. The intervening solid tissue suggests that the lesion has developed in a giant cell granuloma (H & E).

To conclude this discussion of the possible pathogenesis of the aneurysmal bone cyst, it should be stated that there are a number of authorities who dispute the theory that the cyst is a secondary phenomenon. Tillman *et al*. (1968) studied all tissue removed from 95 aneurysmal bone cysts and concluded that there was no evidence of precursor lesions in these cases. Similarly, Ruiter *et al*. (1977) did not identify other bone lesions in their series of 105 cases. However, both groups of authors did admit that areas may have been present that resembled other lesions. Schajowicz (1981) has stated that areas similar to those of the aneurysmal bone cyst may be found in many bone lesions but that they usually occupy only a minor portion of the process and that they are probably the result of haemorrhage. Kransdorf and Sweet (1995) considered that the diagnostic morphology of the pre-existing lesion may often be obliterated or reduced to small residual portions, which would be consistent with the observations of Tillman and of Ruiter *et al*. They also pointed out that the most commonly associated lesions were giant cell tumours or giant cell granulomas which have in any case similar histological features. They discussed the possibility that small cystic areas in giant cell tumours in children may progress to lesions with features of aneurysmal bone cyst alone with no identifiable precursor lesion.

Pathology

At operation, an intact periosteum and a very thin shell of bone usually covers the cyst. When this is removed, dark venous blood wells up. Bleeding may be profuse and difficult to control until the cyst has been removed. The cyst contains variable amounts of soft tissue consisting of friable vascular tissue which subdivides the cavity into a number of blood-filled locules (Fig. 13.4). Part of the lesion may contain areas of more solid tissue. These may represent either areas of repair or remnants of a pre-existing lesion. No direct communication with any vessels can be demonstrated at operation.

Histological features

The lesions consist of many capillaries and blood-filled spaces of varying size lined by flat spindle cells and separated by delicate loose-textured fibrous tissue (Fig. 13.3). Most lesions contain small multinucleate cells and scattered trabeculae of osteoid and woven bone. In some of the solid areas, sheets of vascular tissue, containing large numbers of multinucleate giant cells, fibroblasts, haemorrhage and haemosiderin, look very much like giant cell granuloma of the jaws (Fig. 13.5). Other solid areas may have the appearance of fibrous dysplasia, ossifying fibroma (Fig. 13.6) and possibly other jaw tumours,

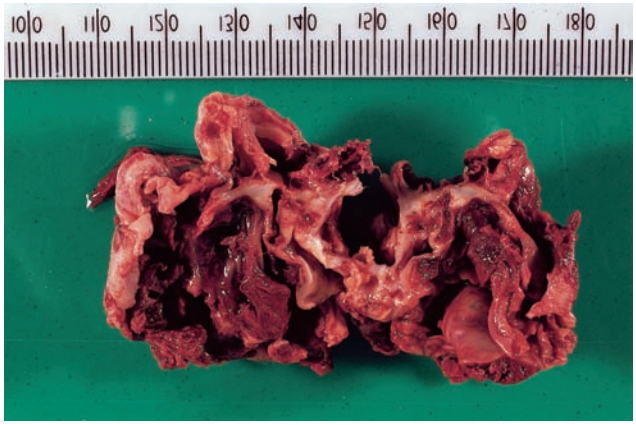


Fig. 13.4 Section through a gross specimen of an aneurysmal bone cyst of the mandible. Solid areas are interspersed with multiple cysts or locules.

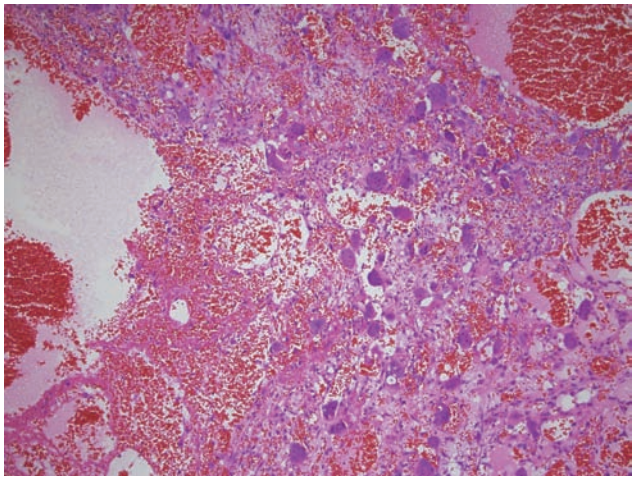


Fig. 13.5 Aneurysmal bone cyst in which the solid areas have histological features identical to those of the central giant cell granuloma of the jaws (H & E).

and this gives credence to the view that the aneurysmal bone cyst may represent secondary change in a pre-existing lesion. The blood-filled spaces have no elastic tissue or smooth muscle around them. There are no cellular features suggestive of malignant neoplasia (Clough and Price, 1968) unless, of course, the cyst has developed in a malignant tumour. Occasional lesions may be solid (Perroti *et al*., 2004) and show the characteristic vascular fibrous tissue with osteoid and woven bone, but without the blood-filled cyst-like spaces. The diagnosis is made primarily on the basis of the clinical and radiological features because histologically such solid lesions may be indistinguishable from giant cell granuloma.

Liu *et al*. (2003) undertook a comparison of the histopathology of giant cell lesions of the jaws. They

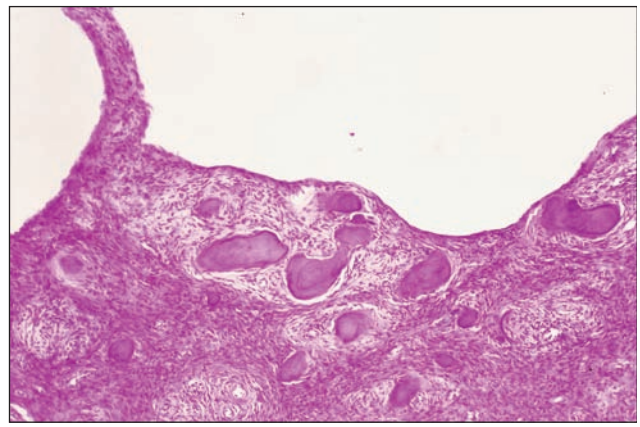


Fig. 13.6 Aneurysmal bone cyst of the mandible. The solid areas show the features of cemento-ossifying fibroma and a portion of one of the many cystic spaces is present at the top of the photomicrograph (H & E).

studied 40 cases of giant cell granuloma (34 central, six peripheral), seven cases of cherubism and six aneurysmal bone cysts. Histologically, all the lesions showed similar features and contained multinucleate giant cells with a similar morphology and distribution, although 'cavernous or sinusoidal blood filled spaces' were only found in aneurysmal bone cysts. They also undertook immunohistochemical and *in situ* hybridisation studies and showed that in all cases the giant cells were positive for markers, including tartrate-resistant acid phosphatase, CD68 and osteoprotegerin, which are indicative of an osteoclast phenotype. This study supports the concept that the aneurysmal bone cyst is primarily a giant cell lesion and is related to giant cell granuloma of the jaws.

Treatment

The treatment of the aneurysmal bone cyst must be determined by the nature of any associated lesion. According to El-Deeb *et al*. (1980), the most frequent form of treatment in reported cases of aneurysmal bone cysts of the jaws has been curettage. Their review indicated a recurrence rate of 26% for jaw cases. In the review carried out by Gingell *et al*. (1984) there was a 19% recurrence rate of jaw lesions including three cases with multiple recurrences. Recurrences also occur with lesions involving other bones with rates ranging from 21% to 44% (Gingell *et al*., 1984). Clough and Price (1968) reported continued growth even after careful curettage and bone grafting and recommended complete excision provided this would not interfere with function. One of the cases in our own series, which was associated with an ossifying fibroma, recurred twice following curettage. Thorough curettage of lesions

associated with central giant cell granuloma are probably less likely to recur. As most aneurysmal bone cysts of the jaws appear to involve central giant cell granulomas, this would account for the successful conservative treatment recorded by a number of workers. There is no place for radiotherapy in the treatment of jaw lesions unless it is one of the very rare examples that may have developed secondarily to a malignant tumour.

In view of the tendency for certain cases to recur, there should be a careful appraisal of each case after histological evaluation and patients should have periodic postoperative examinations.

14
Solitary Bone Cyst

Solitary bone cysts are fluid-filled or empty intra-osseous lesions found most commonly in the proximal metaphyseal region of the long bones in children and adolescents. Identical lesions, probably of similar aetiology, are found in the mandible and very seldom in the maxilla. Uncertainty about the nature of these lesions is reflected by the number of synonyms found in the literature. Commonly used terms include *simple bone cyst*, *traumatic bone cyst*, *haemorrhagic bone cyst* and *unicameral bone cyst*.

Clinical features

Frequency

The solitary bone cyst is not a common lesion. In our South African series we have had only 35 specimens during the 46-year period under review (1% of jaw cysts) (see Table 1.1), although other cases have been treated in the clinical departments of the dental school of the University of the Witwatersrand without any contents having been found for histological examination. There were 19 cases in the series of 3353 jaw cysts reported by Hoffmeister and Härle (1985), a frequency of 0.6%. In a review of Sheffield specimens there were only 36 cases reported over a 30-year period, representing 0.5% of 6869 cysts of the jaws (Jones and Franklin, 2006a,b). In view of the rarity of the lesion, the review published by Howe in 1965 was useful. His material consisted of six of his own cases and 54 from the literature published over the period 1929–63. The well-documented series of 66 cases of Hansen *et al.* (1974), the 23 cases of Killey *et al.* (1977), the 30 examples in 26 patients of Beasley (1976), the review of 161 cases including 67 new cases reported by Kaugars and Cale (1987), as well as the reviews of Mayer *et al.* (1967), Huebner and Turlington (1971), Braun (1975) and Copete *et al.* (1998), all provided valuable data on the condition.

In determining which cases to include, Howe used the following criteria. The cyst should be single, have no epithelial lining and show no evidence of acute or prolonged infection. It should contain principally fluid and not soft tissue and the walls should be of bone which is hard although possibly thin in parts.

Age

The solitary bone cyst occurs in young individuals. The age distribution of the 60 patients included in Howe's analysis is shown in Fig. 14.1. The patients ranged in age from 2.5 to 35 years and 46 of the 60 (78%) were in their second decade. Killey *et al.* also recorded a peak frequency in the second decade, but one patient was over 50 and another over 60. In the series of Hansen *et al.*, the age range was 7–75 years and more than half were in the second decade. In Beasley's study, 17 of 26 patients were in their second decade and 24 were younger than 40 years. The ages of the patients in the personal series of Kaugars and Cale ranged from 9 to 68 years with a mean of 24.3 years. Of the 36 cases in the Sheffield series, 19 (53%) were encountered in children under 16 years of age (Jones and Franklin, 2006a). The mean age in adults was 34 years.

Gender

Thirty-six cases in Howe's analysis were recorded in males and 23 in females, a male : female ratio of 1.6 : 1. However, Killey *et al.* (1977) reported a frequency of 13 females and 10 males and there was an equal gender distribution in the series of Mayer *et al.*, Hansen *et al.* and in the Sheffield cases. In the review of Kaugars and Cale (1987), there was an equal gender distribution in both their literature survey of 161 cases and in their own sample.

Site

The overwhelming majority of solitary bone cysts of the jaws occur in the mandible. Howe stated that only one atypical case had been reported in the maxilla. This was confirmed by Mayer *et al.* In the review of Kaugars and Cale, 95% of cases reported in the literature occurred in

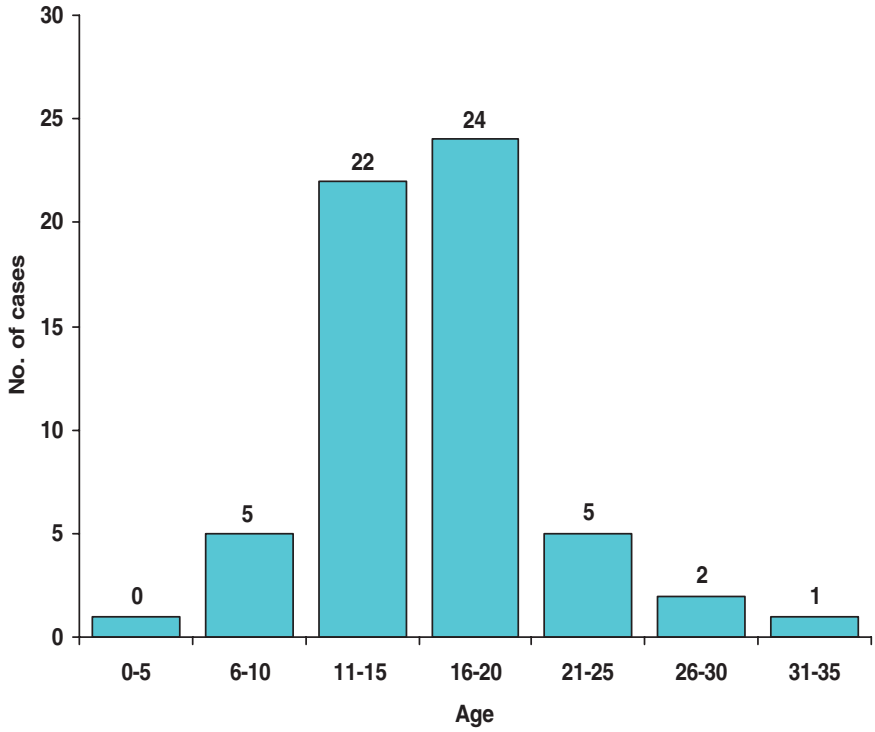


Fig. 14.1 Age distribution of 60 patients with simple bone cysts of the jaws. (After Howe, 1965.)

the mandible, as did all but one of their own 66 cases. In the report of Hansen *et al*. (1974), however, about one-third occurred in the maxilla, but Copete *et al*. (1998) reported only one of 44 (2%) cases in the maxilla and this was in the posterior region.

Almost all the maxillary cases have involved the anterior regions and the majority of the mandibular cases have been reported in the body and symphyseal areas. Beasley (1976) described a number that occurred in the ramus as well as the body of the mandible. One of his cases involved the ascending ramus only, as did two examples described by Hosseini (1979), and one by Hall (1976). Cases reported by Persson (1985), Rubin and Murphy (1989), Telfer *et al*. (1990) and Kuttenberger *et al*. (1992) were found in the mandibular condyle. In the review of Kaugars and Cale, about one-fifth of cases occurred bilaterally and 10 patients in their literature review had multiple lesions.

Clinical presentation

In Howe's survey, the majority of cases (60%) were diagnosed fortuitously and almost all of these were chance radiographic findings. Swelling was the presenting symptom in 27%, pain in 10%, while 2% complained of labial paraesthesia and in 2% there was both pain and swelling. Over half of the patients gave a history of significant trauma to the area; the time-lag between injury and diagnosis varied from 1 month to 20 years. Howe felt that trauma may have a role in at least some cases.

On clinical examination, 35% had a mandibular swelling, most frequently buccal and labial, and only occasionally lingual. The related teeth were all vital in 67% of cases. Of the 61 patients in the series reported by Hansen *et al*., 44 (72%) were completely symptomless and only eight reported definite symptoms. In Beasley's series, 77% were symptomless and in only seven of his patients (27%) was there a positive history of trauma. In the literature review of Kaugars and Cale, 60% of patients had symptoms, whereas in their own sample only 26% did. There was a positive history of trauma in only six of their cases and they regarded the role of trauma in the development of the lesion as of minor importance.

Multiple lesions have been present in 11% of reported cases (Kaugars and Cale, 1987).

Radiological features

Careful interpretation of good radiographs is most valuable in the diagnosis. The cyst appears as a radiolucent area with an irregular but definite edge and slight cortication (Fig. 14.2). An occlusal view shows the radiolucency extending along cancellous bone. In a review of the radiological features of 44 cases, Copete *et al*. (1998) described a characteristic cone-shaped radiographic

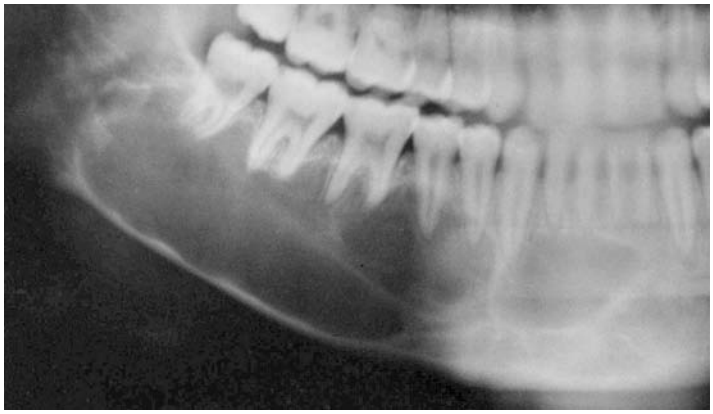


Fig. 14.2 Radiograph of a solitary bone cyst involving an extensive area in the right body of the mandible. This example has a well-defined margin with cortication. Interradicular scalloping is a prominent feature. (By courtesy of Professor C.J. Nortjé.)

morphology. In 28 (64%) cases, at least one lateral margin of the lesion formed an angular interface with normal bone with two planes converging at a 45° angle to produce a sharp cone effect. Most often (66%) the cone pointed anteriorly towards the midline.

There is usually little effect on the buccal and lingual plates (Poyton and Morgan, 1965). Of the reviewed cases, 63% showed some degree of marginal condensation but not as sharp or opaque as with radicular cysts. The radiological appearances of lesions in different parts of the mandible are similar. In 72% of cases, usually in the posterior mandible, the cyst enveloped the roots of erupted teeth. Scalloping is a prominent feature of solitary bone cysts and was seen in 30 (68%) of the 44 cases reported by Copete *et al.* (1998). Scalloping occurs both between teeth and away from teeth. The lamina dura may or may not be lost and occasional root resorption may occur. Bony septa may be present (Braun, 1975) and the lesions are sometimes interpreted as multilocular (Beasley, 1976; Gait, 1976; Markus, 1978–79; Gowgiel, 1979; Mitchell and Ward-Booth, 1984), which can lead to an erroneous diagnosis.

Pathogenesis

The pathogenesis of the solitary bone cyst is not known but there are numbers of theories which have been examined. Olech *et al.* (1951) suggested the following possible pathogenesis, based upon a traumatic aetiology, and Howe proposed an essentially similar natural history. Olech *et al.* introduced their hypothesis with the premise that following trauma to a bone, which causes intramedullary haemorrhage, a failure of early organisation of the haematoma in some of the marrow spaces and subsequent liquefaction of the clot can lead to the formation of a traumatic cyst. The crucial point, therefore, is the explanation of this failure. The assumptions that these authors postulated appeared to explain, they believed, all the peculiar features of the pathogenesis, location and age incidence of these cysts. These cysts seem to develop only after injury to those areas of bone where spongy bone containing haemopoietic marrow is enclosed in a heavy compact cortical layer. This would explain the most frequent sites in the metaphyses of long bones and in the mandible. It would also explain the fact that most solitary bone cysts develop in young individuals.

There are arguments against this proposal, particularly the fact that it is difficult to establish a history of trauma in so many instances. It is also likely that trauma will initiate a radiographic examination resulting in a chance finding of solitary bone cysts in some patients. Nevertheless, it seems that at least in some cases trauma may be the initiating factor. Trauma, or some other stimulus, leads to rupture of thin-walled sinusoids and intramedullary haemorrhage occurs.

According to Olech *et al.*, the primary haematoma will not be organised if it is not in contact with reactive and fibrous connective tissue and this will not be present if the intramedullary haemorrhage has led to necrosis of the bone marrow itself and related endosteum. The trabeculae of medullary bone are then slowly resorbed by osteoclastic activity on their opposite surfaces and by the time the viable connective tissue gains contact with the haematoma, the latter has liquefied. The breakdown of haematomas and their failure to organise, particularly if they are large is, however, a well-known problem in surgery and it is perfectly conceivable that this can occur following intramedullary haemorrhage even in the presence of reactive and fibrous connective tissue. In his detailed histological study of 30 solitary bone cysts, Beasley (1976) observed areas of haemorrhage associated with necrosis and myxoid degenerative changes in a substantial number of cases.

Although the majority of solitary bone cysts are found at operation to contain only air or some other gas, the fact that some contain blood or serosanguineous fluid tends to support the concept of a haematoma breaking down. The breakdown products of haemolysis produce a local rise in osmotic pressure. Toller (1964) has confirmed experimentally that the osmotic tension of a solitary bone cyst fluid was greater than that of the patient's blood. This in turn

leads to a transudation into the cyst fluid. In the presence of intact cortical bone there is an increase in intra-osseous pressure which leads to resorption of bone by osteoclastic activity and sometimes swelling by concurrent periosteal bone deposition. Occasional tooth displacement occurs. As transudation into the cyst occurs, the fluid is diluted so that intracystic pressure drops, but further bleeds may be responsible for progression of the lesion. Once no more bleeding occurs, there will be gradual absorption of the serous fluid in the cavity, which becomes empty. The fact that the cysts are rarely found in patients over 30 years suggests that they are self-limiting and that many undergo spontaneous regression. When the space is filled with blood as a result of surgical intervention, the defect heals and it has been suggested that a spontaneous haemorrhage into an empty cyst cavity may do the same.

However, the main problem in accepting the pathogenesis described above is that essentially it proposes that, on the one hand, intrabony haemorrhage is responsible for initiating and then maintaining the process, whereas on the other hand haemorrhage into the cyst cavity in the course of treatment leads to ready repair, and spontaneous haemorrhage is postulated as the reason for resolution without treatment. Olech *et al*. explained this by the fact that the new blood clot which fills the cyst cavity is in contact with healthy connective tissue of the flap from which the organisation of the clot commences. When a pathological fracture occurs through a solitary bone cyst, they suggested that the reason for the cyst healing is not only the formation of a fresh blood clot, but also its contact with the vital connective tissue of the periosteum. Although no further evidence as to the pathogenesis of the solitary bone cyst has been published in the years since the paper by Olech *et al*., there are nevertheless aspects of their hypothesis that require further elucidation and we should like to see some experimental evidence that similar cysts can be produced by trauma.

Pathology

When the cyst cavities are opened at operation, they are frequently found to be empty. In other cases, blood, serosanguineous or serous fluid may be present. In 58% of Howe's sample, no visible lining was seen and in the other cases either a thin membrane, granulation tissue or blood clot were described. Ultrastructural study has confirmed the absence of any epithelium in the lining (Schwenzer *et al*., 1985).

Histological features

The solitary bone cyst consists of a loose vascular fibrous tissue membrane of variable thickness with no epithelial lining, although fragments of fibrin with enmeshed red cells may be seen. Haemorrhage and haemosiderin pigment are usually present and scattered small multinucleate cells are often found (Fig. 14.3). Some cyst walls, possibly cases of longer standing, are more densely fibrous. The adjacent bone, when included in the specimen, shows osteoclastic resorption on its inner surface. Beasley (1976) described areas of haemorrhage associated with necrotic tissue or tissue showing myxoid degeneration. These occurred in cavities adjacent to areas of bone resorption. Thrombi were not observed in any of the specimens that he examined.

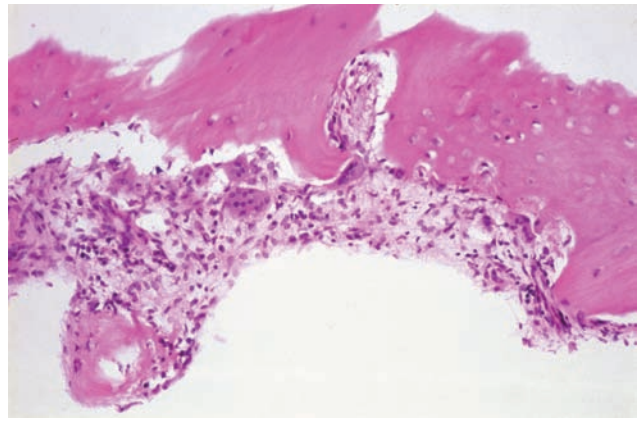


Fig. 14.3 A solitary bone cyst of the jaw. The lining is composed of loose vascular fibrous tissue with osteoclastic activity on the surface of the adjacent bone (H & E).

Numbers of reports have described an association between solitary bone cysts and fibro-osseous lesions including fibrous dysplasia (Hara *et al*., 1990) and cemento-osseous dysplasias (Melrose *et al*., 1971; Kaugars and Cale, 1987; Higuchi *et al*., 1988; Horner and Forman, 1988; Wakasa *et al*., 2002). The relationship is uncertain, but in some cases the cysts were multiple and the finding of empty cystic cavities appeared to be secondary to cystic degenerative changes in a pre-existing lesion (Hara *et al*., 1990, Higuchi *et al*., 1988).

Treatment

Solitary bone cysts are usually treated as part of the diagnostic process. To determine the nature of the lesion, the cyst lumen is opened to reveal an empty cavity as described above. The cyst wall is then curetted but caution is needed so as not to damage the tooth roots or inferior alveolar nerve. In the vast majority of cases this intervention results in uneventful healing and resolution of the problem. As discussed above, it is presumed that granulation tissue and eventually new bone proliferate and replace the haemorrhage caused as a result of the

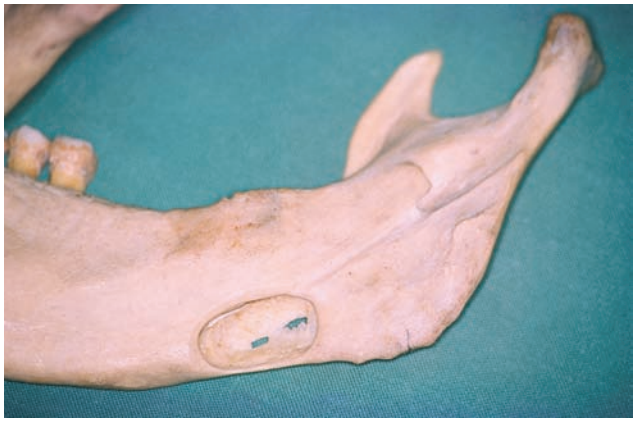


Fig. 14.4 Developmental lingual salivary gland depression of the mandible. (By courtesy of Professor P.V. Tobias.)

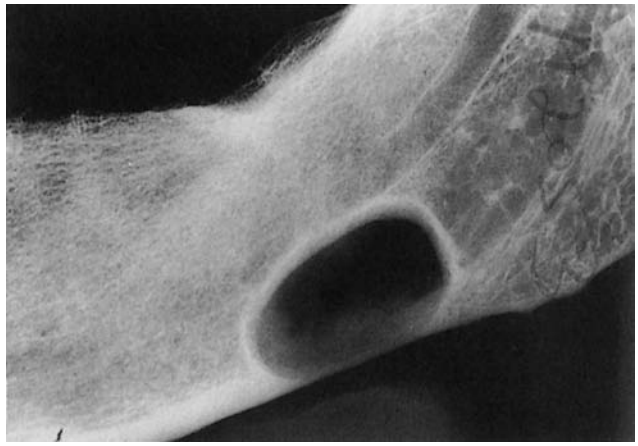


Fig. 14.5 Radiograph of dry mandible illustrated in Fig. 14.4. (By courtesy of Dr H. Mirels.)

surgery. Recurrence is unusual but has been reported (Horner *et al.*, 1988; Baqain *et al.*, 2005), including a case in the condyle which recurred in a bone graft (Kuttenberger *et al.*, 1992).

LINGUAL MANDIBULAR BONE DEFECT

(Stafne cavity, static bone cavity, latent bone cyst)

The lingual mandibular bone defect (Fig. 14.4) is not a cyst. However, it does produce a cystic appearance on radiographs, and as it is occasionally confused with the solitary bone cyst a brief note on the entity is included here. Of importance in the differential diagnosis is that the solitary bone cyst almost invariably lies above the inferior alveolar canal while the lingual mandibular bone defect lies below the canal.

A description of 35 cases was first reported by Stafne (1942) and since then the features have become well documented. The cavities are usually discovered fortuitously during radiographic examination. They appear as round or ovoid radiolucencies varying from 1 to 3 cm diameter below the inferior alveolar canal approximately in line with the position of the third molar tooth (Fig. 14.5). Fordyce (1956) pointed out that apart from the outer distinct cortication, a second inner ring could frequently also be identified which encircles an area of more marked radiolucency.

Oikarinen and Julku (1974) found 10 examples in a survey of 10 000 orthopantomograms, a frequency of 0.1%. All patients were males and with the exception of one 19 year old, all were over the age of 40. In a similar survey, Correll *et al.* (1980) discovered 13 cases in 2693 panoramic radiographs (0.48%) taken in a Veterans' Medical Center where 96% of patients were men. As the defect apparently occurs predominantly in males, this could account for a higher frequency than that shown by Oikarinen and Julku.

Most cases are located just anterior to the angle of the mandible. A few cases have been reported in the anterior mandible (Correll *et al.*, 1980; Katz *et al.*, 2001) and a similar lesion has been described in the ascending ramus associated with the parotid gland (Barker 1988). Buchner *et al.* (1991) evaluated 20 cases from the literature and added another four of their own. Histological examination of the contents of the defect in their four cases showed sublingual salivary gland tissue in three and adipose tissue in one. Eighteen of the other 20 reported cases showed salivary gland tissue consistent with sublingual gland origin. They supported the view that resorption of the bone was a reaction to pressure from a lobe of the sublingual gland and that the lesions were evident radiographically only when they were advanced.

Surgical exploration of these cavities has indicated that they represent developmental defects on the lingual aspect of the mandible which are occupied by a lobe of normal salivary gland, suggesting that the salivary gland has an aetiological role in the development of the defect. Magnetic resonance imaging (MRI) of a typical case clearly demonstrated that the cavity was filled by a lobular extension of normal submandibular gland (Branstetter *et al.*, 1999). These authors suggested that MRI was the imaging modality of choice in cases of doubt and had the advantage of avoiding the discomfort of sialography.

The defects are not necessarily congenital. Tolman and Stafne (1967) have shown that radiological evidence of their development may first appear after the patients have reached middle age. This is supported by well-documented evidence that the bone defect has been observed only very rarely in individuals below the age of 40 years. There has been the suggestion that the defect may increase very slowly with age, yet some examples in which follow-up radiographs have been performed after a number of years have not demonstrated any change (Stafne, 1942;

Oikarinen and Julku, 1974; Correll *et al*., 1980). With regard to pathogenesis, the evidence tends to suggest that in some individuals, particularly middle-aged or elderly males, a lobe of the submandibular salivary gland may produce a localised pressure atrophy of the lingual surface of the mandible. Lello and Makek (1985), who reported an extensive review of the literature, suggested that the bone defect was the result of an ischaemic process in an area adjacent to the passage of the facial artery. Tensile muscle forces together with haemodynamic forces, they proposed, pulled the artery from the lingual cortex, thus compromising its nutrition. This theory does not, however, take account of the relative rarity of lingual bone defects.

15
Cysts Associated with the Maxillary Antrum

In the previous edition of this book there were two cysts that were considered under this heading: the benign mucosal cyst of the maxillary antrum and the postoperative maxillary cyst or surgical ciliated cyst of the maxilla. Benign mucosal cysts included a range of lesions often referred to synonymously as mucocoele, retention cyst or pseudocyst. It is now apparent that these lesions can be separated into distinctive entities with different clinicopathological features and behaviours. The distinctive features and criteria for diagnosis have recently been reviewed (Meer and Altini, 2006) and a simple classification is given in Table 15.1.

MUCOCOELE OF THE MAXILLARY ANTRUM

A true antral mucocoele completely fills the sinus and is caused by blockage of the ostium, which may be secondary to inflammatory changes associated with chronic rhinosinusitis. The lesion is a true cyst filled with mucus and lined by the mucoperiosteum of the involved sinus. It causes ballooning expansion with destruction and perforation of the surrounding bone and displacement of adjacent structures. This may result in nasal blockage, proptosis and a range of other clinical symptoms which may be mistaken for more aggressive disease. The lesion has characteristic clinicopathological features which serve to differentiate it from other cystic lesions of the antrum. This, along with its locally destructive behaviour and the importance of early diagnosis and management, warrants its separate consideration in this chapter.

Clinical features

Frequency

From the early literature it is difficult to determine the relative frequency of this lesion because on plain radiographs it was difficult to distinguish it from simple sinusits, and because early studies did not differentiate between this lesion and other types of antral cyst.

Overall, mucocoeles are common cystic lesions affecting the paranasal sinuses, but the frontal and ethmoid sinuses are most often affected with only about 10% arising in the maxillary sinus (Natvig and Larsen, 1978). Despite this, there are few recent series of cases and true antral mucocoeles appear to be rarely encountered. Marks *et al.* (1997), in what they thought was the largest series at the time, collected only nine maxillary sinus mucocoeles over a 10-year period. Four of these, however, were associated with trauma or previous surgery, leaving only five true mucocoeles. Busaba and Salman (1999) applied more strict criteria and reported 13 cases collected over a period of 4 years. In a study of cystic masses of the maxilla, Han *et al.* (1995) reported the computerised tomography (CT) and magnetic resonance imaging (MRI) findings on 28 cases, but only one appeared to be a true mucocoele. Most of the remainder were postoperative cysts (17 cases) or cysts of odontogenic or uncertain origin. In a study of symptomless young men, Savolainen *et al.* (1997) examined radiographs of 404 subjects and recorded 'cysts or polyps' in 7.2%. However, only 3.3% had a completely opacificed sinus, suggesting that this would be the highest possible prevalence of true mucocoeles.

Other radiological or epidemiological studies have not distinguished between true mucocoeles causing complete antral opacification and other antral cysts. Because true mucocoeles appear to be relatively rare, these studies are probably reporting pseudocysts and retention cysts and are discussed later in this chapter.

Age

In Busaba and Salman's series of 13 cases, the age range was 13–71 years with a mean age of 49.9 years. This is similar to the five cases reported by Marks *et al.* (1997), which had a range of 24–80 years and a mean age of 45.8 years.

Gender

There appears to be no gender predilection for this lesion; of the total of 18 cases referred to above, nine were in men and nine in women.

Table 15.1 Cysts of the maxillary antrum. (After Meer and Altini, 2006.)

	Key features
Mucocoele	Occupies the entire sinus. Cystic structure filled with mucus and lined by antral epithelium. Associated with blockage of the ostium and may be secondary to chronic sinusitis. Expansile and may destroy and perforate adjacent bone
Retention cyst	Epithelial lined cyst caused by mucus retention as a result of blockage of a duct. Often small and clinically silent and found associated with thickened mucosa in sinusitis or in polyps. Dome-shaped radiopacity of antral wall, may be indistinguishable from a pseudocyst or polyp
Pseudocyst	Inflammatory in origin caused by accumulation of exudates that raise the mucosa from the bone of the antral floor. Most often secondary to odontogenic infection. Dome-shaped radiopacity on the floor of the sinus
Postoperative maxillary cyst	Secondary to an operative procedure. Most often a Caldwell–Luc incision into the antrum, or an osteotomy. Probably arises from entrapped antral lining. True cyst filled with mucus and lined by antral epithelium

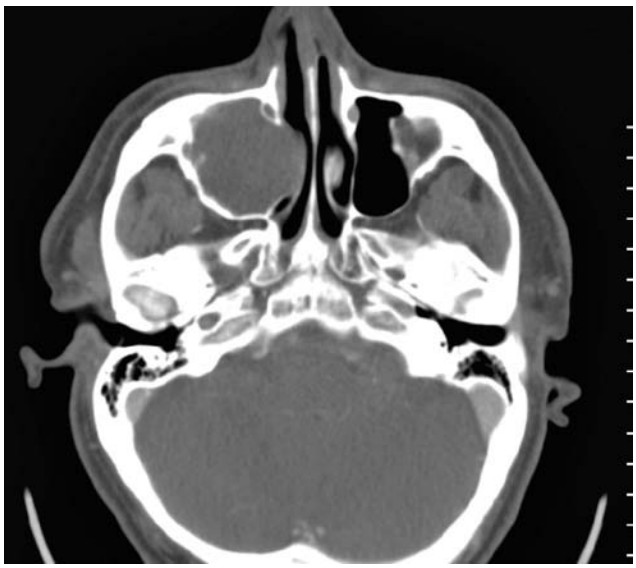


Fig. 15.1 CT of a mucocoele of the left maxillary antrum. There is complete opacification of the antrum with medial bulging into the nose. (By courtesy of Mr T. Westin.)

Clinical presentation

The characteristic clinical presentation is of a gradually enlarging swelling of the cheek and lateral nasal region with obliteration of the nasolabial fold or of the buccal sulcus intra-orally (Meer and Altini, 2006). The lesion is expansile and in over 75% of cases there is bulging of the medial wall of the antrum causing partial obliteration of the nasal cavity (Marks *et al.*, 1997; Busaba and Salman, 1999). Other features include pain or tenderness of the cheek or teeth, nasal drainage, headache and occasionally the orbit is involved causing proptosis.

Radiological features

In the early stages there may be no defining radiological features on plain radiographs. Cloudy radiopacity may be noticeable but in the early lesion the bony walls of the antrum appear normal. As the lesion develops there may be a well-defined radiolucency with expansion and perforation of the bone margins. The lesion is often quite spherical in outline except inferiorly where it embraces the roots of the teeth. There is always medial expansion (Busaba and Salman, 1999) and the lesion may also raise the orbital floor or the anterior wall of the antrum. Expansion of the thicker lateral wall is rare.

The lesions are better visualised using CT or MRI (Han *et al.*, 1995; Busaba and Salman, 1999). The defining criteria are complete opacification of the maxillary sinus

on CT associated with evidence of bony expansion (Fig. 15.1) (Busaba and Salman, 1999). Early lesions may show only an opacity and the overall morphology and bony margins of the antrum may be normal. At this stage, the appearance may be similar to sinusitis, although in sinusitis there is often an obvious fluid level. As the lesion develops, first the medial wall expands into the nasal passages and then there may be progressive expansion anteriorly and superiorly to raise the floor of the orbit. As the lesion enlarges there is often perforation of bone with extension into the soft tissues. With CT it may be possible to demonstrate obstruction of the ostium.

Pathogenesis

The initiating factor which leads to the development of an antral mucocoele is thought to be obstruction of the ostium resulting in accumulation of mucus and cystic growth by an osmotic mechanism (Barsley *et al.*, 1984; Meer and Altini, 2006). Often the cause of obstruction is unknown and relatively few cases are associated with a history of chronic rhinosinusitis through either infection or allergy (Marks *et al.*, 1997; Busaba and Salman, 1999). In Busaba and Salman's series, although most patients had symptoms suggestive of sinusitis, only two of 13 cases showed a history of allergy, and none had nasal polyps or evidence of disease in the contralateral sinus.

However, it seems that some form of blockage and accumulation of mucus is needed for initiation of cyst development. Barsley (1984) suggested that mucus retention increases the protein content and osmolarity of the cyst resulting in expansion by hydrostatic pressure. This is accompanied by inflammation and activation of bone-resorbing factors and osteoclasts which allow bony expansion and destruction of adjacent tissues. Such a mechanism appears plausible and is similar to those proposed for other intra-osseous cysts.

Histological features

Histologically, the appearance is of a cyst filled with mucus or mucoid material, and lined by essentially normal antral mucosa, covered by ciliated respiratory-type epithelium or flattened simple cuboidal or squamous epithelium. There may be chronic inflammation in the wall and if there is an associated allergic sinusitis then acute inflammatory cells and eosinophils may also be present (Meer and Altini, 2006).

RETENTION CYST AND PSEUDOCYST OF THE MAXILLARY ANTRUM

Retention cysts and pseudocysts are considered together because they have similar behaviour and may be indistinguishable on radiological or clinical examination. Together they are often referred to as antral cyst or mucosal cyst and many studies have not distinguished between them.

Clinical features

Frequency

These cysts are probably quite common. Myall *et al.* (1974) surveyed 1469 orthopantographs and made a radiological diagnosis of mucosal antral cyst in 75 cases (5.1%). A similar study by Casamassimo and Lilly (1980) on 4546 panoramic radiographs showed a lower frequency, 73 mucosal cysts (1.6%) having been observed in their sample. Allard *et al.* (1981b) and Allard (1982), however, demonstrated 94 examples in a series of 1080 radiographs (8.7%). The latter authors quoted the frequency in 11 other publications, which ranged from 1.4% to 9.6%. Rhodus (1990) detected 54 (4.3%) in panoramic radiographs of a sample of 1249 patients selected at random in a dental school patient population. MacDonald-Jankowski (1994) surveyed 1000 consecutive panoramic radiographs in a South London dental casualty department and found a prevalence of 'mucosal antral cysts' of 14%. All these studies used similar criteria for the definition of antral cysts. MacDonald-Jankowski (1994) and Myall *et al.* (1974) stated their criteria as 'dome-shaped' soft tissue opacities or shadows arising from the antral wall. Other authors used similar criteria, and none used complete opacification or ballooning expansion as a definition of cysts. It appears therefore that these studies did not include true mucocoeles but investigated either retention cysts or pseudocysts as defined by Meer and Altini (2006).

A similar study, using the same criteria, identified 51 lesions in 410 CT scans (12.4%) (Bhattacharyya, 2000). In this study, however, the CT scans were taken as part of the investigative procedure of patients with symptoms of chronic rhinosinusitis.

Age

The age distribution of 148 patients in the surveys of Myall *et al.* and Casamassimo and Lilly is shown in Fig. 15.2. The great majority of cases were found in patients in the age group 21–30 years.

Gender

Of the 242 cases reported by Myall *et al.*, Casamassimo and Lilly, and Allard *et al.*, 161 (68.1%) occurred in males. The proportion of males in these three studies was roughly the same.

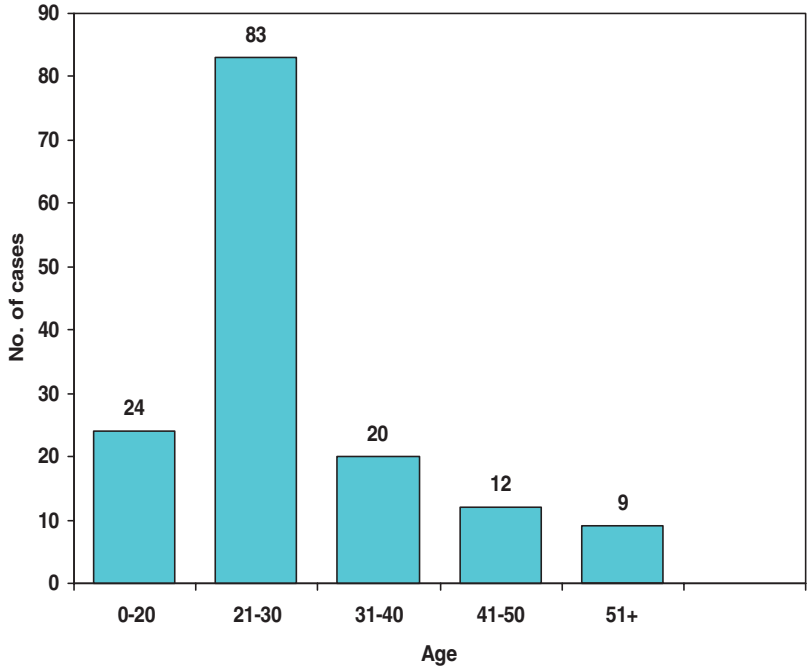


Fig. 15.2 Age distribution of 148 patients with mucosal cysts of the maxillary antrum. (Data pooled from Myall *et al*., 1974 and Casamassimo and Lilly, 1980.)

Site

In the great majority of cases only single cysts occur, but in a few instances they may be multiple and sometimes bilateral. In the study by Casamassimo and Lilly (1980), 14 of their patients (19%) had bilateral cysts. More recently, Bhattacharyya (2000) reported that nine of his 51 cases (18%) had bilateral lesions. All authors agree that the antral floor is the most common site, with 50% (Bhattacharyya, 2000) to 74% (Casamassimo and Lilly, 1980) arising in this region. Of the remaining lesions, about half arose in the lateral or medial wall with other sites only occasionally involved. Berg *et al*. (1989) found that 24 of 27 mucosal cysts originated from a rather limited area at the sharp angle between the floor and frontal or lateral aspect of the sinus cavity, close to the alveolar process.

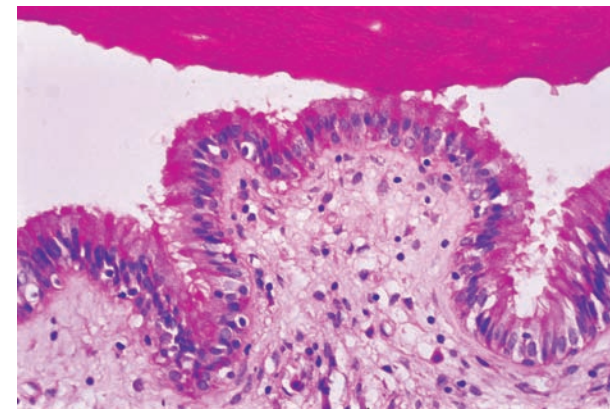


Fig. 15.3 Mucosal cyst of the maxillary antrum. The cyst is of the retention or secretory variety. It is lined by pseudostratified ciliated columnar epithelium and is filled with mucin (top) (Periodic–acid Schiff, PAS).

Clinical presentation

Retention cysts and pseudocysts present in a similar way and are most often characterised by the absence of symptoms, the lesions being discovered only in the course of routine radiological examination. Patients may complain of a wide range of symptoms such as a localised dull pain in the antral region, or fullness or numbness of the cheek, nasal obstruction, postnasal drip and a copious discharge of yellow fluid from the nostrils. These symptoms may be caused by an associated chronic sinusitis. Sometimes an antral cyst may produce a swelling. One such case from the University of the Witwatersrand files occurred in a 32 year old woman. She had a painless, fluctuant swelling of the left maxilla extending from the canine to the second molar which was noticed by her dentist during routine dental examination. She had not previously had any surgical procedure in the region. At operation, a cyst was found arising from the lateral wall of the maxillary antrum and a diagnosis of retention cyst of the antrum was made histologically (Fig. 15.3).

A number of patients have reported allergies of various kinds but it is not clear whether the frequency is higher than in the general population. Rhodus (1990) found that a substantial number of his patients with mucosal cysts complained of allergy or sinusitis or both.

A recent study has suggested an increased incidence of solitary or multiple antral cysts in patients with Fabry's disease (Baccaglini *et al.*, 2001). They examined MRI scans from 13 patients with Fabry's disease and found evidence of cysts in five (38%) cases. A further three patients had had a cyst within the past year. The authors did not distinguish between the types of cyst, but the paper appeared to describe retention cysts or pseudocysts.

Radiological features

It is on the basis of the radiological or CT features that these lesions are most clearly distinguished from antral mucocoeles. The cysts appear as spherical, ovoid or dome-shaped radiopacities which have a smooth and uniform outline (Fig. 15.4). They may have a narrow or broad base. They vary in size from minute to very large and may occasionally occupy the entire maxillary sinus (Killey and Kay, 1973), but in these cases CT will usually reveal normally aerated segments of residual antrum. Unlike mucocoeles, the lesions are not destructive and they rarely expand or resorb the bony walls of the antrum. Pseudocysts, which are often associated with odontogenic infections, are located on the floor of the sinus, but retention cysts may be located elsewhere. They are otherwise indistinguishable.

Inflammatory lesions of the sinus must be considered in the differential diagnosis as well as the apical radicular cyst, the postoperative maxillary cyst and other extra-antral lesions (Han *et al.*, 1995). Follow-up radiological examination has shown that the cyst may persist without a change in size for a long time, and may eventually disappear spontaneously. Others slowly increase in size (Gothberg *et al.*, 1976; Casamassimo and Lilly, 1980).

Pathogenesis

The pathogenesis of the mucosal cyst of the antrum has not been definitely determined but a previous infection is frequently implicated. Gardner (1984) and Gardner and Gullane (1986) regarded these lesions as focal accumulations of inflammatory exudate that lift the antral mucosa away from the underlying bone. A possible relationship between the development of a mucosal cyst of the antrum with related endodontically treated teeth or periodontitis has been considered. Casamassimo and Lilly (1980) noted a trend toward larger cysts with increasingly severe periodontal disease. Gardner (1984) considered an association with periapical infection of adjacent maxillary teeth as a distinct possibility.

Gardner (1984) regarded the cysts associated with dental inflammation as pseudocysts and made a distinc-

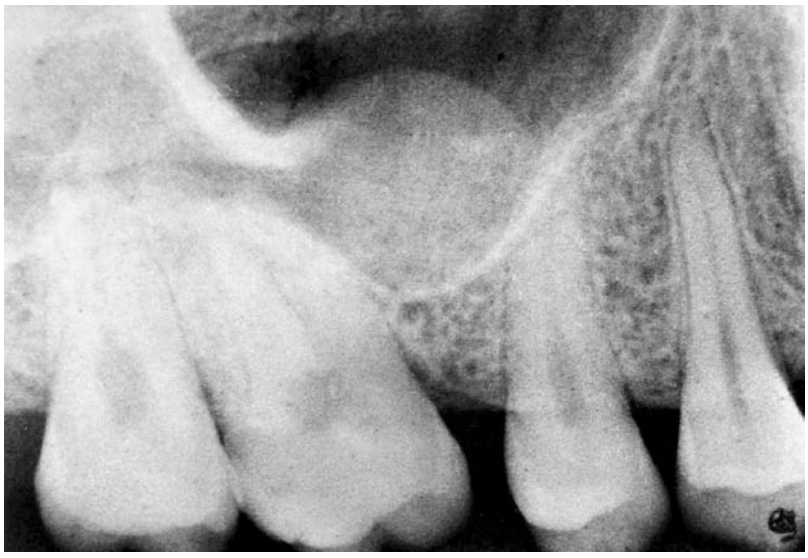


Fig. 15.4 Radiograph of a mucosal cyst of the maxillary antrum. The lesion appears as a dome-shaped radiopacity rising from the floor of the antrum.

tion from retention cysts which he suggested arose from a partial blockage of the duct of a seromucinous gland of the sinus.

Meer and Altini (2006) agreed with Gardner's interpretation and in their review further clarified the pathogenesis of these lesions. They suggested that the pseudocyst arises as a result of accumulation of inflammatory exudates below the antral mucosa, which is lifted from the underlying bone to form the characteristic dome-shaped swelling on the floor of the sinus. Thus, the lesion is formed by pools of 'mucoid' material surrounded by inflamed fibrous tissue with periosteum on one aspect. Although these cysts may be associated with chronic sinusitis, Meer and Altini supported the findings of the earlier studies (Casamassimo and Lilly, 1980; Gardner, 1984; Gardner and Gullane, 1986) and suggested that odontogenic infection of the maxillary teeth is the most common cause. They are to be distinguished from antral polyps which may be multiple, affect any part of the antral lining and are a result of inflammation and accumulation of exudates in the hyperplastic and oedematous fibrous tissue of the mucosa.

With regard to the retention cyst, it is generally agreed that these are caused by blockage of the ducts of the small mucous glands in the antral mucosa resulting in a mucus-filled cyst lined by epithelium. Most of these lesions are small and clinically silent and are found as incidental findings in thickened and inflamed antral mucosa removed for chronic sinusitis, or within antral polyps. The cause of the duct blockage may be an inspissated mucus plug or a small calculus.

Meer and Altini (2006) also suggest that some retention cysts may arise from an invagination and entrapment of normal antral epithelium into the underlying connective tissue.

Pathological features

When explored surgically, it is possible to demonstrate the intact and undisturbed cyst. It has a smooth blue surface, is thin-walled and contains mucinous material. Allard *et al*. (1981b) stated that they are almost always found in an otherwise healthy looking sinus whereas antral polyps will usually be seen in groups on inflamed oedematous mucosa.

Microscopically, a pseudocyst shows pools of mucoid material lined by inflamed fibrous connective tissue which in places may be the raised periosteum. Antral mucosa may be seen on one aspect. Ducts or seromucinous glands are not seen and the mucoid material appears to be primarily an inflammatory infiltrate because mucin stains are usually negative (Allard *et al*., 1981b; Meer and Altini, 2006).

Retention cysts are usually small and are found within an inflamed antral mucosa or an inflammatory polyp. They are lined by duct-like pesudostratified columnar epithelium, although this may become flattened to resemble a simple stratified epithelium. There may be little inflammation other than related to the associated sinusitis and the cyst is filled with mucus. A calculus or mucus plug may be evident.

Treatment

Retention cysts and pseudocysts are not destructive and usually remain static, many appear to regress spontaneously, and as they usually cause little discomfort surgical intervention is unnecessary. Allard *et al*. (198lb) indicated that only if specific or pertinent clinical features were present would they advise treatment, which, in their view, should be removal through a Caldwell–Luc approach. Hadar *et al*. (2000) limited treatment to lesions which occupied at least 50% of the sinus and used an endoscopic approach, which is now accepted as an effective treatment. In their series of 60 patients there were only two cases which recurred and there were no complications.

Pseudocysts associated with a dental infection resolve when the underlying cause has been removed.

By contrast, antral mucocoeles grow to large sizes and can be destructive. The basis of management is to decompress the cyst either by complete removal by curettage through a Caldwell–Luc approach or by an endoscopic approach through the middle meatus with marsupialisation of the cyst (Marks *et al*., 1997; Busaba and Salman, 1999).

POSTOPERATIVE MAXILLARY CYST (SURGICAL CILIATED CYST OF THE MAXILLA)

The postoperative maxillary cyst is fairly commonly encountered in Japan but appears to be a rare lesion in most other parts of the world. Its name is derived from the fact that it is a delayed complication arising years after surgery involving the maxillary sinus.

Clinical features

Frequency

In the University of the Witswatersrand department, only five cases have been diagnosed over a 32-year period (see

Table 1.1) representing 0.1% of 3498 jaw cysts, whereas Kaneshiro *et al.* (1981) reported a series of 68 patients with 71 lesions treated at the Niigata University Dental Hospital, 1967–77. Similarly, Yamamoto and Takagi (1986) reported that in their hospital the postoperative maxillary cyst accounted for 19.5% of all oral cystic lesions. They quoted similarly high frequencies in other reports in the Japanese literature. Maeda *et al.* (1981) studied 100 examples removed at their clinic over a 5-year period. Outside Japan, the only reports suggesting that the lesion may not be rare are those of Basu *et al.* (1985) and Smith *et al.* (1988) from the University of Birmingham Dental School, where 18 cases were diagnosed over a period of 3 years.

Age

The age distribution of 60 patients in the study of Yamamoto and Takagi (1986) is shown in Fig. 15.5. The great majority of their patients were in the fourth and fifth decades and their ages ranged from 21 to 72 years. A very similar age distribution was shown by Kaneshiro *et al.* (1981) whose patients ranged in age from 27 to 63 years.

Gender

There was a preponderance of males:females (2:1) amongst the patients of Kaneshiro *et al.* (1981). In the sample of Basu *et al.* (1985), there were 11 females and seven males, while there was an equal gender distribution in the series of Yamamoto and Tagaki (1986).

Site

In the study of Yamamoto and Takagi, 24 cysts occupied half of the maxillary sinus, 19 were localised in the lower portion and 17 cases occupied the whole sinus. Most cases were located in the molar and premolar regions.

Clinical presentation

Gregory and Shafer (1958) drew attention to the development of these cysts in the maxillae of patients whose maxillary sinuses had been opened surgically during a Caldwell–Luc operation. They proposed the term 'surgical ciliated cyst of the maxilla'. Publication of large series from Japan as well as other reports have confirmed the association with previous maxillary surgery. In almost all cases it is an operation for maxillary sinusitis, particularly the Caldwell–Luc procedure including a nasal antrostomy, that is responsible, but the cyst can also result from gunshot injuries, fractures of the malar–maxillary complex and mid-face osteotomies (Sugar *et al.*, 1990; Amin *et al.*, 2003).

The period between the original operation and the diagnosis of the cyst can be considerable. In the studies of both Kaneshiro *et al.* and Yamamoto and Takagi, the duration ranged from 10 to 29 years for 87% of their patients. The shortest period was 4 years and the longest 49 years, with a mean of 18.3 years.

The patients may complain of pain, discomfort or swelling in the cheek or face, or intra-orally in the palate or alveolus. Pus may be discharged.

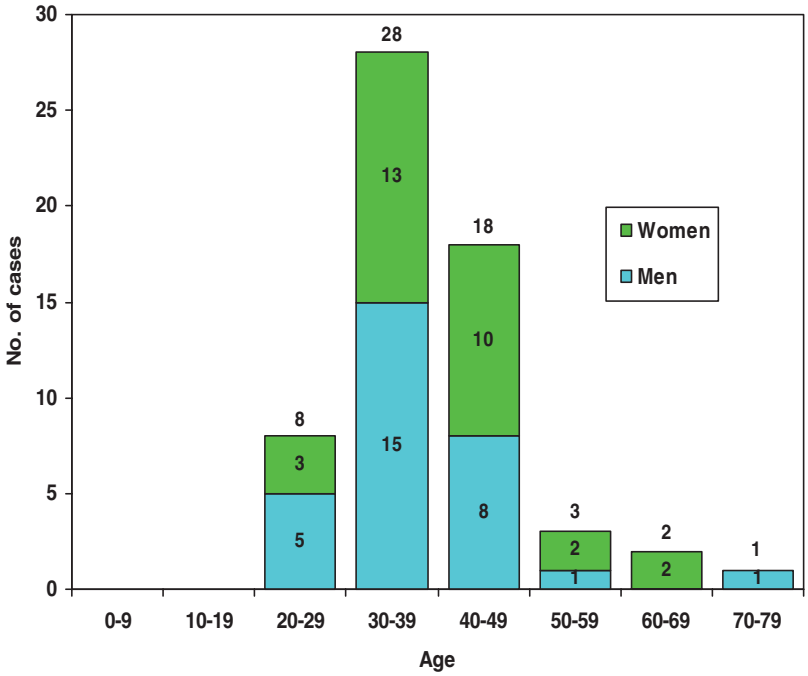


Fig. 15.5 Age distribution of 60 patients with postoperative maxillary cyst. (After Yamamoto and Takagi, 1986.)

Recently, there have been two unusual case reports of postoperative ciliated cysts arising in the mandible (Koutlas *et al.*, 2002; Bourgeois and Nelson, 2005). In both cases the patients had had simultaneous orthognathic surgery of the maxilla and mandible, and the authors speculated that the cysts arose from implantation of maxillary tissue into the mandibular operation site.

Radiological features

Radiographs reveal a well-defined radiolucent area closely related to the maxillary sinus (Fig. 15.6). In the series reported by Yamamoto and Takagi, most cases were unilocular lesions with only four of them reported as multilocular. In 42 of their 60 cases buccal cortical bone was present. Surrounding bone sclerosis was evident in at least part of the bony margin in just over half of the cases. In the study by Kaneshiro *et al.*, the bony margin was missing in the lateral, posterior or upper walls in half of their cases. They showed that the diameter of 47 radiographically well-defined cysts in the Water's position was between 21 and 30 mm in 29 cases, less than 20 mm in 11 and over 31 mm in seven cases. Occasionally, the cystic area appears to encroach on the sinus itself but lack of communication between the two has been demonstrated by injecting the sinus with a radiopaque material (Shafer *et al.*, 1983). In the early lesions no destruction of bone is evident but as they enlarge the sinus wall becomes thinned and eventually perforated (Gardner and Gullane, 1986), and may resemble a malignant neoplasm (Basu *et al.*, 1985). Gradually, the cyst expands beyond the original boundaries of the sinus.

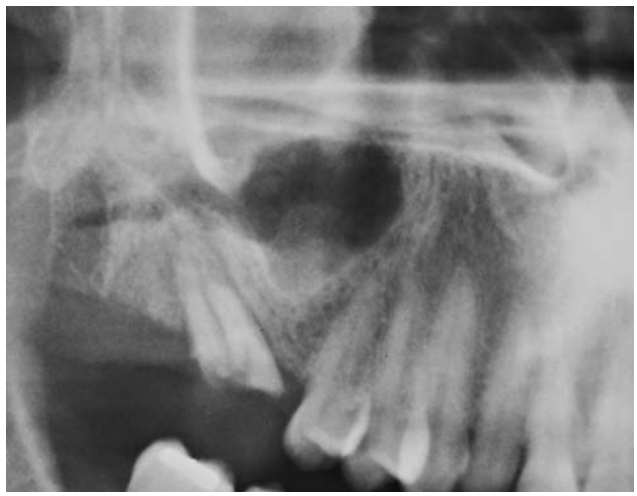


Fig. 15.6 Radiograph of a postoperative maxillary cyst. The lesions presented as a well-defined radiolucency at the site of a previously extracted tooth.

Pathogenesis

The high frequency of postoperative maxillary cyst in Japan has been attributed to the large number of cases of maxillary sinusitis that occurred in Japan during and just after the Second World War which were treated by the Caldwell–Luc procedure because antibiotics were not available. There are few reports of this lesion since the last edition of this book in 1992, and there have been no further large series from Japan. This suggests that the frequency of the postoperative cysts is now declining. This is probably caused in part by conservative management of sinusitis and to the increasing use of endoscopy to treat antral disease as an alternative to the Caldwell–Luc procedure.

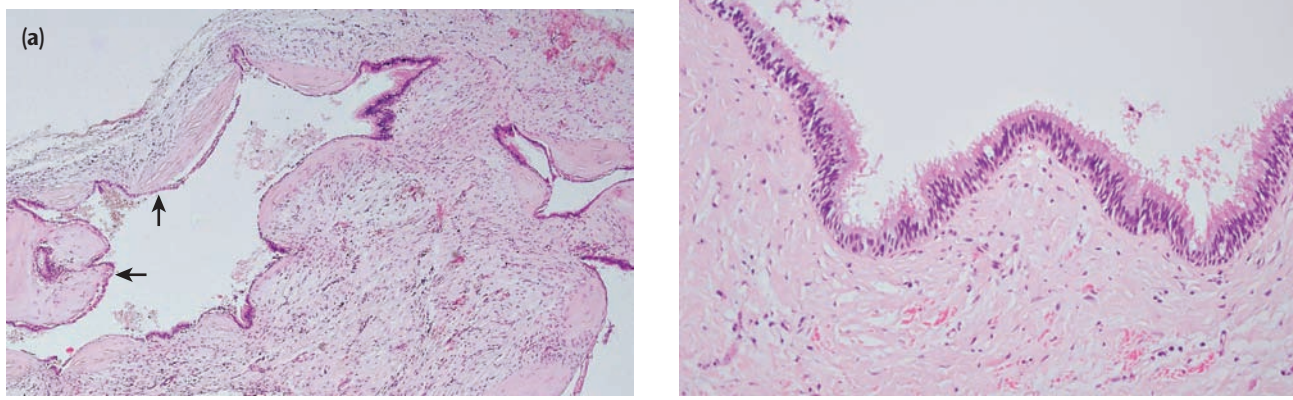


Fig. 15.7 Histology of the postoperative maxillary cyst. (a) The cyst wall is irregularly folded to form a multilocular appearance. The lining is composed of pseudostratified ciliated columnar epithelium but with areas of flattened simple stratified epithelium in areas of inflammation (arrows) (H & E). (b) Higher magnification of part of lining illustrated in (a) showing typical respiratory-type epithelium (H & E).

Gregory and Shafer suggested that the cysts are derived from the epithelial lining of the maxillary sinus which is trapped in the wound during closure of the Caldwell–Luc incision, and subsequently begins to proliferate. By forming a closed sac which is unable to drain through the ostium into the nose, it constitutes a cyst or mucocoele which enlarges and may resorb the bony walls of the antrum (Gardner and Gullane, 1986).

Histological features

Histologically, the cysts are lined by pseudostratified ciliated columnar epithelium, with squamous metaplasia in chronically inflamed areas (Fig. 15.7). Combinations of ciliated, cuboidal and squamous epithelium with varying numbers of mucous cells may be seen. Ciliated epithelium is the type most commonly encountered (Maeda *et al.*, 1981). The epithelium may be ulcerated in parts. The underlying connective tissue may be cellular or fibrotic (Gardner and Gullane, 1986). Foam cells, cholesterin clefts, haemosiderin and foci of calcification may be present.

Basu *et al.* (1985) described a well-defined acellular layer in the capsule, below and parallel to the surface, which was either hyaline or mucoid in appearance. Occasionally, a cellular layer of fibrous tissue was interposed between this layer and the epithelium.

Basu *et al.* (1985) found wide variations in the protein levels of the cyst fluids, thus precluding any valuable preoperative information from this source for diagnostic purposes. However, in another study by the same group on the analysis of glycosaminoglycans in the fluid aspirate (Smith *et al.*, 1988), they demonstrated a characteristic electrophoretic pattern of hyaluronic acid and heparin sulphate, with lesser amounts of chondroitin-4-sulphate. This was different from the pattern they had previously shown in odontogenic cyst fluids (Smith *et al.*, 1984), and might therefore be of diagnostic value. The presence of hyaluronic acid and chondroitin-4-sulphate in the fluids of this cyst was also demonstrated by Suzuki (1988). He concluded that hyaluronidase in the cyst fluid acts on the hyaluronic acid in the cyst wall which then passes into the cyst fluid.

Treatment

Sugar *et al.* (1990) have suggested that in most cases enucleation through an approach appropriate to the site is the treatment of choice, but marsupialisation for uniloc-ular cysts with a thin wall and extensive bony perforation was proposed by Yoshikawa *et al.* (1982). In the experience of Kaneshiro *et al.* (1981), recurrences may occur if the cyst is infected or if the wall is very thin and there is perforation of the bone, making enucleation difficult because of tight adhesion of the cyst to adjacent tissues.

16
Cysts of the Salivary Glands

MUCOCOELES

Mucous extravasation cysts and mucous retention cysts are often referred to collectively as mucocoeles. Our practice has been to use the term 'mucous extravasation cyst' for those lesions in which mucus has extravasated into the connective tissues and in which there is no epithelial lining. The term 'mucous retention cyst' is employed to describe mucocoeles that result from dilatation of the ducts and which are lined by epithelium.

Clinical features

Frequency

Mucocoeles of the mouth are very common. Their true incidence is difficult to determine as many patients endure them without seeking treatment, and of those diagnosed a large number are not surgically excised and do not reach a pathology department. Series of cases of mucocoeles of the mouth have been reported by Bhaskar *et al.* (1956b), Standish and Shafer (1959), Gardner *et al.* (1963), Robinson and Hjørting-Hansen (1964), Cohen (1965), Cataldo and Mosadomi (1970), Southam (1974), Harrison (1975), Eversole (1987), Yamasoba *et al.* (1990) and Oliveira *et al.* (1993). Over a 20-year period our own department collected 180 mucocoeles in 179 patients. Of these, 147 (82%) were extravasation and 33 (18%) were retention cysts. This represents a higher proportion of retention cysts than in the series reported by Cataldo and Mosadomi (4.0% of 594), Standish and Shafer (6.2% of 97), Cohen (9% of 80), Southam (5.1% of 236 mucocoeles), Eversole (6.2% of 1380 mucocoeles), Yamasoba *et al.* (2.9% of 70 mucocoeles of the lower lip) and Oliveira *et al.* (7.54% of 112); but similar to those of Chaudhry *et al.* (1960) (16.5% of 66) and Robinson and Hjørting-Hansen (17.6% of 125).

Age

The age of the patients at diagnosis in 151 of our South African cases is shown in Fig. 16.1. The youngest patient was 8 months and the oldest 88 years, with a peak frequency in the third decade. Other studies have shown a peak frequency in the second decade and have included more cases in children up to the age of 9, but all agree that most cases are seen before the age of 50. One example recorded by Standish and Shafer was present at birth and Poker and Hopper (1990) reported one which occurred in the tongue of a 10 week old girl. In the large series of 594 cases reported by Cataldo and Mosadomi (1970), 16 (2.7%) were in infants less than 1 year old. Southam found that all but one of the 12 retention cysts in his series were in patients over 50 years. Harrison analysed 400 mucocoeles including 47 of his own cases and the remainder from the literature. He pointed out that extravasation cysts occurred most often in younger patients (84% in the first four decades), whereas retention cysts occurred more frequently in older patients (85% older than 40). In our own sample, 20 of 30 patients with retention cysts were older than 40 (67%). This would probably account for the bimodal trend seen in Fig. 16.1.

In Eversole's sample of retention cysts (sialocysts) cases were rare before the third decade when there was a peak frequency, with a second peak in the seventh decade. His samples of reactive oncocytoid and mucopapillary sialocysts occurred in older patients.

Gender

In our material, the distribution was 95 males (52%) and 88 females (48%). In most studies there has been an equal gender frequency. Retention cysts are found somewhat more frequently in women than in men.

Site

The great majority of mucocoeles are found in the lower lip. In our material, 83 cases (54%) occurred in this site. By comparison, very few occurred in the upper lip (5%). The distribution of the remaining cases is shown in Table 16.1 and is similar to those in other reported series. In Harrison's study, 72% of extravasation cysts were found

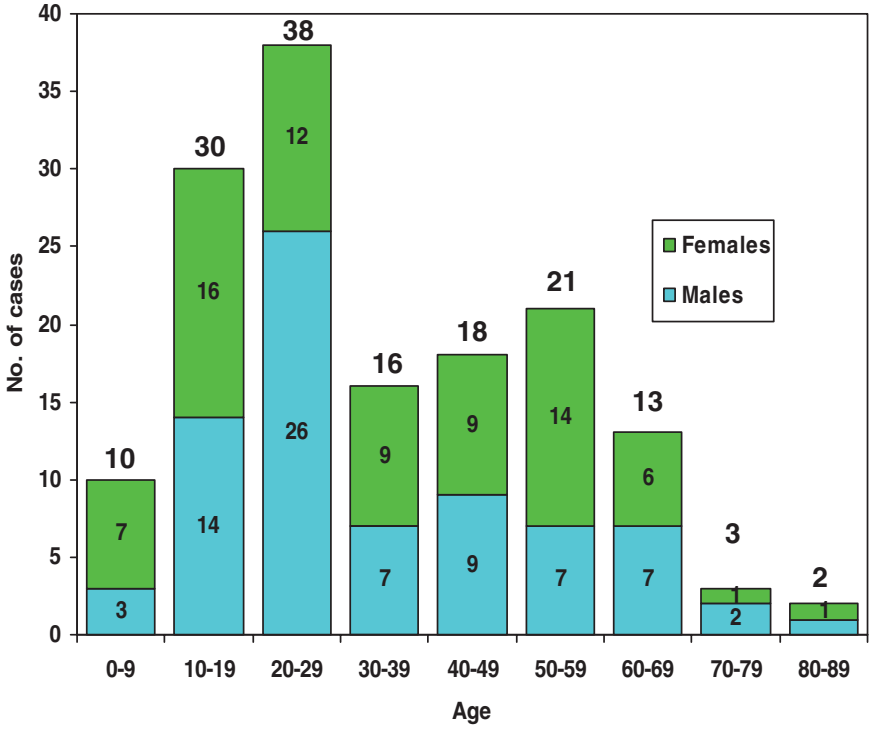


Fig. 16.1 Age distribution of 151 patients with oral mucocoeles.

Table 16.1 Site distribution of 155 mucocoeles.

Site	Number	Percentage
Lower lip	83	53.5
Upper lip	8	5.2
Floor of mouth and ventral tongue	30	19.4
Palate	17	11.0
Buccal mucosa	14	9.0
Retromolar	3	1.9
Total	155	100

in the lower lip, whereas 39 of 40 retention cysts occurred elsewhere in the mouth. The same was found in Eversole's sample where the retention cysts were most often found in the floor of the mouth followed by buccal mucosa, lower lip, palate, tongue and upper lip. Extravasation mucocoeles have been reported in the anterior ventral aspect of the tongue associated with the glands of Blandin and Nuhn (Sugerman *et al.*, 2000). Jinbu *et al.* (2003) reported a series of 26 cases representing 10% of 263 mucocoeles received in their department over a 10-year period.

Clinical presentation

Patients with mucocoeles usually complain of a painless swelling which is frequently recurrent. They may have been present for only a few days but some patients tolerate them for months or even years before seeking treatment. The swelling may develop suddenly at mealtimes

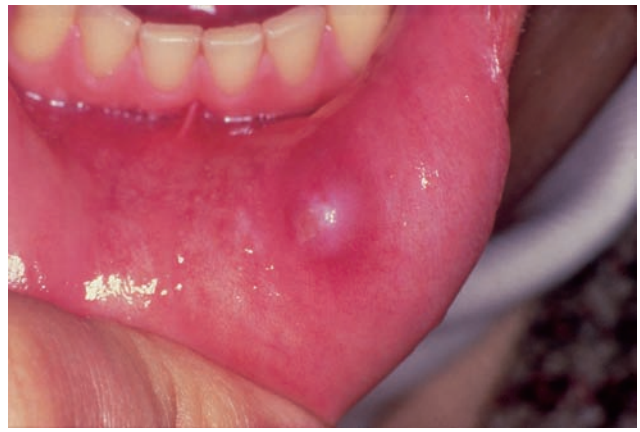


Fig. 16.2 Mucocoele of the lower lip.

and many drain spontaneously at intervals. Some 10% of patients are able to relate the development of the cyst to trauma. The mucocoele may be only 1–2 mm in diameter but it is usually larger, the majority being between 5 and 10 mm in diameter. The ranula is invariably larger than this. The swellings are round or oval and smooth (Fig. 16.2). The superficial lesions are blue and fluctuant while the deeper lesions are the colour of normal mucosa and are firmer. Superficial cysts give few diagnostic problems but deeper firmer lesions may be confused with a fibro-epithelial polyp or a small salivary gland tumour. A firm well-demarcated lesion of the upper lip is more likely to be a salivary gland tumour than a mucocoele. Some have been diagnosed as lipomas.

Occasionally, mucocoeles may be very superficial and lie just below the epithelium and resemble a subepithelial vesicle (Eveson 1998). Superficial mucocoeles seem to have a predilection for females and often present as multiple blister-like lesions on the palate and buccal mucosa (Bermejo *et al*., 1999; Mandel 2001). Distinction from a vesiculo-bullous disorder, particularly pemphigoid, may be difficult on clinical grounds alone.

Mucocoeles associated with the glands of Blandin and Nuhn have a characteristic presentation on the anterior ventral aspect of the tongue (Fig. 16.3). They are usually less than 10 mm in diameter, and usually appear as polypoid or pedunculated swellings (Sugerman *et al*., 2000; Jinbu *et al*., 2003). Occasionally, they may reach a large size and cases of 3 cm or greater have been reported (Poker and Hopper, 1990; Andiran *et al*., 2001). At this site large lesions may be alarming and may interfere with normal feeding or may compromise the airway.

Pathogenesis

The pathogenesis of the mucocoele has excited a great deal of interest. For many years it was generally believed that obstruction of a salivary duct led to its dilatation proximal to the obstruction, with the formation of an epithelial-lined retention cyst. This concept was questioned by Bhaskar *et al*. (1956a) who carried out experimental obstruction of the excretory ducts of the submaxillary–sublingual glands in mice over periods ranging from 6 days to 9.5 months. They found that mucocoeles did not develop although they did find microcyst-like spaces which they believed represented 'tangential cuts through the tortuous dilated ductal elements'. This study was followed by another series of experiments in which the right submaxillary excretory ducts of five young mice and six young rats were exposed and severed. The animals were sacrificed at intervals of from 1 to 9 days postoperatively and the glands were studied grossly and microscopically. They found that in six of the nine animals, severing of the duct produced typical mucocoeles which were comparable to human lesions. In the early stages there was an accumulation of mucus in the connective tissue and with continuous pooling of saliva a clearly demarcated cavity developed which had no epithelial lining. They concluded that their experiments, when considered with the fact that mucocoeles are found most frequently in areas exposed to trauma, such as the lower lip, indicated that a cut or a traumatic defect of a salivary duct was responsible for the production of mucocoeles.

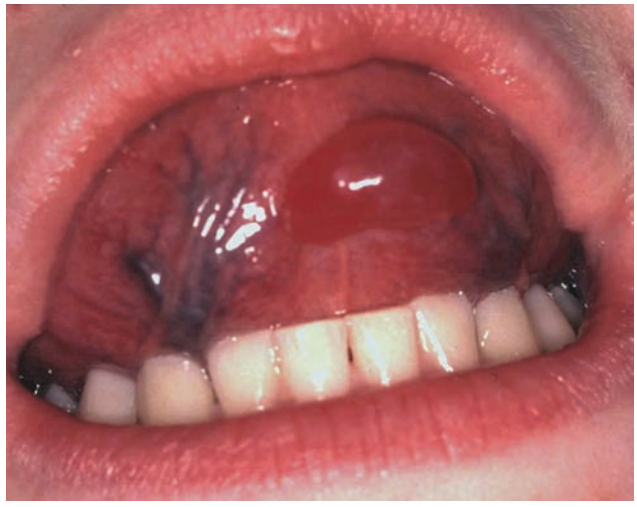


Fig. 16.3 A mucocoele on the ventral aspect of the tongue, associated with the glands of Blandin and Nuhn. (By courtesy of Professor J. Eveson.)

The failure to produce mucocoeles following acute ligation of the main excretory ducts of the submaxillary and sublingual glands was confirmed experimentally by Standish and Shafer (1957). However, they did find that when both the ducts and the arterial blood supply to the glands were ligated, thin-walled dilated ducts of cystic proportions occurred in some 8-, 12- and 16-week animals and appeared to be of submaxillary duct origin. In a later paper, Standish and Shafer (1959) reinforced their view that the vast majority of so-called mucous retention cysts represented an extravasation phenomenon in which a ruptured duct allowed the ready egress of mucus in the adjacent connective tissue. The smaller number of epithelial-lined mucocoeles represented a partial retention phenomenon which was seen as a dilatation of the excretory duct and smaller lobular ducts with concomitant rupture and escape of mucus into the surrounding tissues.

Chaudhry *et al*. (1960) also concurred with these views but felt that complete severance of the minor salivary gland ducts seemed an impracticable aetiological factor in the development of human mucocoeles and that pinching of the duct seemed to be a more likely explanation for their formation. Their own experimental studies indicated that when the submandibular gland duct of the rat was cut or pinched with a haemostat, mucocoeles may be formed by the escape of mucus into the surrounding tissues from the traumatised duct.

Experimental work carried out on cats (Harrison and Garrett, 1972) has produced results that required that the effects of duct ligation be reappraised. These workers were at pains not to damage the chorda tympani and hence to avoid impairing the parasympathetic nerve supply to the glands. They therefore investigated the effects of duct ligation of the sublingual salivary gland of the cat. This gland secretes spontaneously, as do the minor salivary glands of humans where mucocoeles are most frequently found, and has a duct which may readily be tied

anterior to the lingual nerve. They found that extravasation of mucus occurred in all glands up to 20 days after ligation. Ruptured acini were often observed in the first few days, but the ducts were not dilated and ductal ruptures were not seen. Ruptured acini were found only very occasionally after 2 days.

These findings were reinforced in a later study by Harrison and Garrett (1975a). They suggested that following obstruction of the sublingual gland duct of the cat, continuing secretory activity in the gland resulted in rupture of acini and extravasation. If the macrophage and fibroblast reactions induced by the extravasated mucin were sufficiently intense in the first few days after ligation, then extension of the extravasated mucin and mucocoele formation did not occur and the secretory acini become atrophic. However, if the extravasation was too great to be contained in this way, a mucocoele formed and the secretory acini remained active. Ultimately, a balance appeared to be achieved between the rate at which the secretions reached the mucocoele and the rate of removal of fluid from the cavity of the mucocoele. The fact that the minor salivary glands of humans, like the cat sublingual gland, secreted spontaneously may be of significance in the pathogenesis of mucocoeles of the oral mucosa. A similar conclusion was reached by Prætorius and Hammarström (1992) based on a study of 200 mucocoeles. They were of the opinion that trauma to the secretory acinar cells led to their rupture and the formation of a pool of mucus, and that there need not necessarily be any rupture of the excretory ducts. They suggested that a mucocoele formed in this way be termed the 'parenchymatous' type.

Mucocoeles in humans may therefore follow trauma to a duct which is either pinched or severed; or trauma to the secretory acini, leading to the extravasation of mucus. Alternatively, complete ductal obstruction may lead to the development of a mucous retention cyst. The rarer mucous retention cyst that is lined by epithelium may possibly, from the very little evidence available, arise in some instances by partial or complete obstruction of the excretory duct by a salivary calculus, by congenital atresia of submandibular duct orifices (Hoggins and Hutton, 1974), by spontaneous dilatation (Southam, 1974) or by extraluminal causes such as periductal scar formation as a result of trauma. Factors that can lead to dilatation of the duct can also cause its rupture. The possibility of a different aetiology and pathogenesis for some retention cysts compared with the extravasation cysts was that more of the former appeared to occur in an older age group, in females and in sites other than the lower lip.

The presence of eosinophilic oncocyte-like epithelial cells lining some retention cysts of the oral mucosa has led Southam (1974) to postulate that, in the absence of any evidence of duct blockage, these cysts may develop spontaneously in a duct lined by oncocytes. Alternatively, he suggested that they may represent a cystic type of papillary cystadenoma.

A further possibility is that some cysts are associated with persistent sialadenitis of the minor glands of the lips or buccal mucosa. Such lesions have been termed cheilitis glandularis and stomatitis glandularis, respectively (Williams and Williams, 1989; Cannel *et al*., 1997; Musa *et al*., 2005). The lesions usually presented as multiple suppurating cysts, and histologically showed mucous extravasation as well as cystic spaces lined by ductal epithelium which had often undergone oncocytic metaplasia.

Pathology

Mucocoeles are usually received in the laboratory excised with associated salivary gland and frequently a portion of oral mucosa is present on the superficial surface of the lesion. When the specimen is cut, the cyst may be discrete, bound by a lining and filled with a gelatinous material. It may also be diffuse and have more liquid mucinous contents.

Histological features

Microscopically, three distinct morphological patterns of mucocoele have been defined by Robinson and Hjørting-Hansen (1964). The first two represent mucous extravasation cysts and the third mucous retention cysts. Those designated 'poorly defined cysts' consisted of irregularly shaped, poorly defined pools containing faintly eosinophilic mucinous material and numerous vacuolated macrophages which are sometimes called 'muciphages'. Some of these cysts were small and others extended widely into the connective tissue. There may be communication between the cyst and a duct. Those designated 'well-defined' cysts comprised two groups. Both were sharply circumscribed but they differed in that the periphery of the one consisted of granulation tissue or condensed fibrous tissue or both, and was infiltrated by vacuolated macrophages, lymphocytes and polymorphonuclear leucocytes, including eosinophils (Fig. 16.4). One or more dilated ducts may be present and sometimes a breach may be seen in a duct. The second group of well-defined cysts may be partially or completely lined by epithelium. The epithelium varied. It may consist of one or two layers of flattened cells or may be stratified squamous or the lining may be of one or two layers of cuboidal cells or a thicker pseudostratified columnar epithelium (Fig. 16.5).

Robinson and Hjørting-Hansen were able to demonstrate continuity between a cyst and a duct in 31 of their 150 cases (20%). Granular eosinophilic oncocyte-like cells may be seen in the epithelial linings (Southam, 1974).

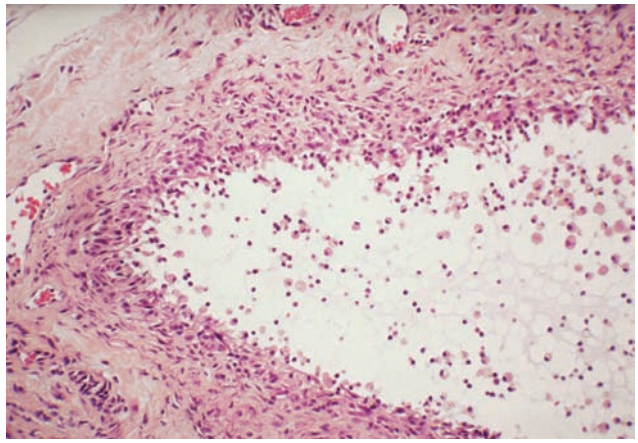


Fig. 16.4 A mucous extravasation cyst lined by inflamed fibrous connective tissue with many muciphages which are also seen in the lumen (H & E).

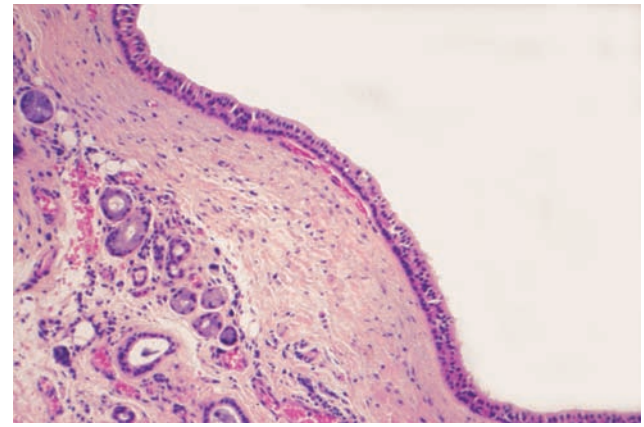


Fig. 16.5 A mucous retention cyst lined by two layers of cuboidal epithelium (H & E).

Eversole (1987) has carried out a detailed histological study of epithelial-lined mucocoeles which he preferred to call sialocysts. He classified his sample of 121 cases into three subgroups: mucous retention cysts (58%), reactive oncocytoid cysts (34%) and mucopapillary cysts (8%). The microscopic criteria that he used for the diagnosis of the mucous retention cyst were the presence of a unicystic or multicystic cavity lined by non-oncocytic ductal epithelium with luminal mucous retention, no evidence of intraductal calcification and minimal inflammation in the wall. Of this subgroup, 82% were unilocular while 18% exhibited a tortuous or multicystic pattern. The lining epithelial cells were solely cuboidal in 52% of examples, a combination of cuboidal and columnar cells in 22%, cuboidal or columnar with mucous cells in 17%, while in the remaining 9% there were combinations of the above with foci of non-keratinising stratified epithelium. None of these cysts recurred following excision.

Diagnosis of the reactive oncocytoid variety required the presence of oncocytoid metaplasia. They could be unicystic or multicystic and the lining cells were high columnar, often pseudostratified, with pronounced cytoplasmic eosinophilia. Seventy per cent were unicystic and the others showed multiple cystic foci. The adjacent minor salivary glands displayed mild sclerosing sialadenitis with ductal ectasia. Extralobular ducts were commonly lined by columnar oncocytes. In most cases, the linings of the cysts were smooth but in about one-quarter of this group small papillary projections were present and the lesion then resembled the papillary cystadenoma. None of these cysts recurred following excisional biopsy.

Tal *et al.* (1984) described a condition which they called 'multiple mucous retention cysts of the oral mucosa'. They reported two cases in which numerous minor salivary gland ducts, in one case more than 100, had dilated to form cysts. Histologically, there were numerous cysts and extensive ductal ectasia. Most of the small dilated ducts were lined by cuboidal and columnar oncocytes while the larger ones were lined by pseudostratified columnar epithelium containing mucus secreting cells and many oncocytes. The duct orifices were dilated. In some areas there was a severe chronic inflammatory cell infiltration and the minor salivary gland tissue was replaced by fibrous tissue. The histological features in these cases closely resemble those of the reactive oncocytoid cyst but the extent of glandular involvement was remarkable. In some cases these multiple cystic lesions probably represented examples of stomatitis glandularis.

There were 10 examples of the mucopapillary variety in Eversole's study. These were the rarest of the three varieties, and were large, tortuous and multicystic. They were lined by cuboidal and columnar epithelial cells with focal areas of squamous epithelium alternating with regions showing mucous metaplasia. Papillary projections lined with mucous cells protruded into the cyst cavities. Follow-up of this series ranged from 1 to 9 years and none recurred following complete local excision. These lesions have been described by a number of authors as papillary cystadenomas. Eversole disputed this diagnosis, which implied that the lesions were neoplastic. Nevertheless, his interpretation of this lesion as a simple cyst must be regarded as controversial.

Treatment

Small mucocoeles may require no surgical treatment provided that the patients find them no hindrance. Larger lesions require surgical removal, usually through a small vertical incision. The cyst and its associated lobules of salivary gland should, whenever possible, be removed together and intact.

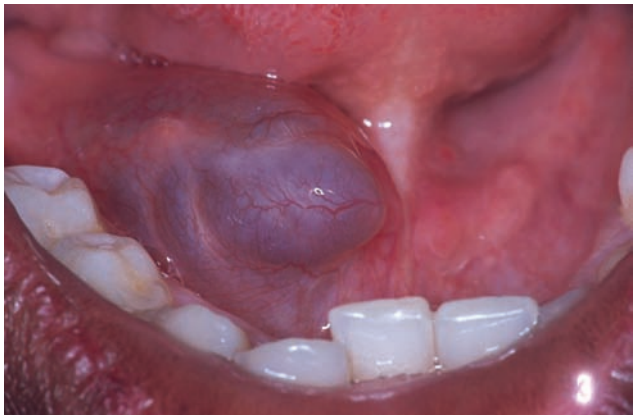


Fig. 16.6 Ranula.

RANULA

The term 'ranula' is used to describe those mucocoeles occurring on the floor of the mouth (Fig. 16.6). They are usually unilateral and because they produce a translucent blue swelling were likened to a frog's belly; from this the term 'ranula' was derived.

Ranulas have been classified as either superficial or plunging. The superficial variety may develop as a retention or extravasation phenomenon associated with trauma to one or more of the numerous excretory ducts of the sublingual salivary gland. Its pathogenesis and pathology are no different from those of the mucocoeles elsewhere in the mouth. Significantly, the majority of these ranulas have no epithelial lining (Fig. 16.7).

In a recent large review of 580 cases (Zhao *et al*., 2004), 395 (68%) were superficial oral lesions, 119 (20%) were plunging and only 67 (12%) were mixed. In other words, from a clinical viewpoint, most plunging ranulas arose in the deeper submandibular tissues without evidence of an intra-oral swelling. The peak age of presentation was in the second decade and there was a slight predilection for females (56.5%). Most lesions, whether plunging or not, were 2–3 cm in diameter.

The pathogenesis and treatment of the plunging ranula have been controversial subjects. Roediger *et al.* (1973) provided evidence to indicate that they are mucous extravasation cysts of sublingual gland origin which ramify diffusely into the neck. A deficiency or hiatus between the anterior and posterior parts of the mylohyoid muscle has been reported to be fairly common and herniated projections of the sublingual gland through these perforations may permit mucus extravasation into the submandibular space and the tissues of the neck. Nathan and Luchanski (1985) found such perforations of the mylohyoid muscle in 65 (43%) of 150 cadavers which they examined, and in 17 (11%) cases the defect was bilateral. Ectopic sublingual glands superficial to the

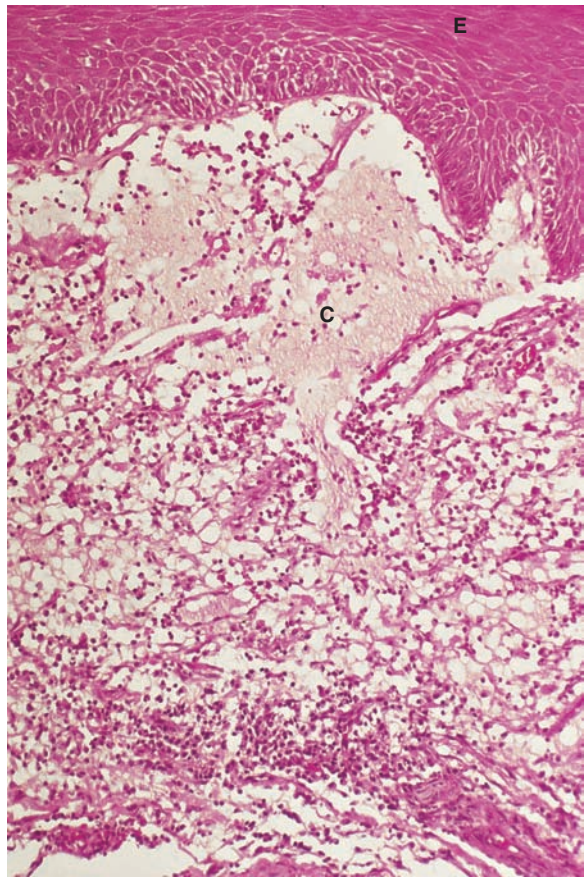


Fig. 16.7 Ranula. In this example the cyst (C) is ill defined and has a wall of granulation tissue containing inflammatory cells and extravasated mucin. E, epithelium of floor of mouth (H & E).

mylohyoid may also provide a source for the extravasation (de Visscher *et al*., 1989). The mucus may extend deep into the cervical tissues and occasionally into the thorax (Pang *et al*., 2005).

Surgical management may be extremely difficult and hazardous and is the subject of an extensive literature which is well covered in more appropriate surgical texts. Overall, most agree that surgical removal of the sublingual gland through the mouth without any cervical approach is the initial form of treatment. This removes the secreting source, thereby preventing recurrences, and also avoids the problem of a difficult neck dissection. In the large series of Zhao *et al*. (2005), only 1% of lesions recurred if the sublingual gland was removed compared with 58% if the ranula was excised alone and 67% following marsupialisation only. Baurmash (2003) considers that removal of the sublingual gland can be hazardous and argues for conservative treatment in some cases. He pointed out that some ranulas may be superficial, arising from the small ducts in the sublingual fold or at the opening of the submadibular duct. For these lesions he advocates marsupialisation and has described a number

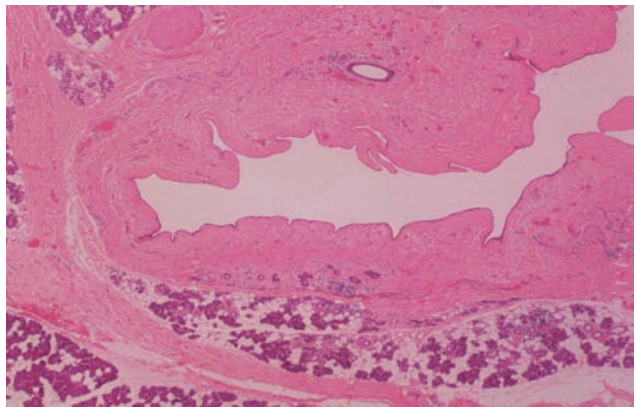


Fig. 16.8 A salivary duct cyst of the parotid gland; an irregular cyst wall lined by ductal epithelium.

of cases where treatment was successful (Baurmash, 2001).

Recently, plunging ranulas have been treated with the sclerosing agent OK-432 (Rho *et al*., 2006). This substance only appears to have been used in Asia and is a sclerosing and immune system stimulating agent derived from lyophilised *Streptococcus pyogenes*. Rho *et al*. (2006) treated 21 patients and found total resolution in seven (33.3%) cases and near-total or marked shrinkage in most of the remainder. They propose that sclerotherapy using OK-432 is a safe and potentially curative substitute for surgery.

Congenital sublingual cysts may occur as a result of atresia of the submandibular duct orifices. In the two cases reported by Hoggins and Hutton (1974), it was possible to demonstrate that the cysts were, in fact, dilated submandibular ducts.

SALIVARY DUCT CYSTS

Mucous retention cysts arising in the parotid gland are usually referred to as salivary duct cysts (Batsakis and Raymond, 1989). They are similar in pathogenesis and histopathological features to retention cysts of minor salivary glands. Patients most commonly present in the fifth decade and although duct obstruction appears to be the cause, the source of the obstruction is often not apparent. Most lesions are slowly enlarging painless swellings affecting a single gland. Belli *et al*. (2004) reported a case of bilateral lesions in a 75 year old female which resulted in large voluminous masses. In this case, bilateral obstruction of the parotid ducts by a mobile denture was thought to be the cause.

Histologically, lesions are usually unilocular cysts lined by ductal epithelium, which may be cuboidal or columnar and may occasionally show mucous or oncocytic metaplasia (Fig. 16.8). Occasional lesions may be multilocular or papillary and must be distinguished from cystic neoplasms.

LYMPHOEPITHELIAL CYSTS

Lymphoepithelial cysts arise in the parotid gland or within the oral cavity, usually the floor of the mouth. In the parotid gland they are similar to branchial cleft cysts but while it is possible that a first branchial cleft defect may affect the parotid gland, most lymphoepithelial cysts at this site probably arise as a result of cystic change in intranodal salivary gland inclusions. Intra-oral lymphoepithelial cysts probably arise in association with oral tonsils, although an origin from the epithelium of minor salivary gland ducts, especially in the floor of the mouth where tonsillar tissue is scarce, is a possibility. Branchial cysts and intraoral lymphoepithelial cysts are discussed in Chapter 17.

Lymphoepithelial cyst of the parotid gland

Lymphoepithelial cysts in the parotid gland are uncommon; Camilleri and Lloyd (1990) indicated that about 70 cases had been reported in the literature and few not associated with human immunodeficiency virus (HIV) disease (see p. 178) have been reported since. The age range was 16 to 69 years and there was a male: female ratio of 3:1. It is important that this lesion be differentiated from neoplasms, particularly cystic low-grade mucoepidermoid carcinoma and from cystic types of benign lymphoepithelial lesion (Weidner *et al*., 1986). The latter authors reported five cases. All their patients consulted a doctor because of nodules in the parotid gland.

Histologically, all consisted of epithelial lined multilocular cystic spaces enclosed by dense lymphoid tissue composed of small lymphocytes, plasma cells and normal germinal centres (Fig. 16.9). No subcapsular or medullary lymphatic sinusoids were seen. In three cases the epithelium appeared ‘muco-epidermoid’, being composed of variable mixtures of cuboidal cells and mucin-producing columnar cells. In these cases, the epithelium was either stratified or composed of a single layer of cuboidal cells. In a few areas invagination of the epithelium into adjacent lymphoid or fibrous stroma formed small epithelial nests that were both solid and microcystic. In other areas the epithelium was papillary. In two lesions the epithelial component was entirely squamous and contained intercellular bridges. Mitotic figures were rare. All their patients were treated by superficial parotidectomy.

HIV-related bilateral lymphoepithelial cysts of the parotid gland associated with cervical lymphadenopathy

Holliday *et al.* (1988) reported an association between lympho-epithelial cysts of the parotid, cervical lymphadenopathy and infection by HIV. Their series consisted of 18 male patients ranging from 22 to 53 years, of whom 10 were homosexual and eight were intravenous drug users. All patients had painless facial swellings and in four cases these were bilateral. CT scans showed that 15 patients had multiple cysts in the parotid and in 14 of them the lesions were bilateral. All patients had multiple enlarged cervical lymph nodes. Eleven of 13 patients tested had antibodies to HIV, and two of the others later developed AIDS. Fine needle aspirates showed benign lymphocytes and squamous or cuboidal epithelial cells. Histologically, the lesions consisted of cysts lined by cuboidal and squamous epithelium surrounded by lymphoid tissue with prominent germinal centres. The authors warned that the CT findings of multiple parotid cysts and cervical adenopathy may indicate, before the onset of opportunistic infections, that the patient is infected with the HIV virus. The patients should be referred for HIV testing and parotidectomy should be deferred.

Shugar *et al.* (1988) reported the same syndrome in nine homosexual males. CT and MRI revealed that all but one of the patients had bilateral multiple intraparotid cysts and all had cervical lymphadenopathy. Fine needle aspirates were consistent with benign cysts and histological examination showed multiple cysts lined by epithelium suggestive of dilated salivary gland ducts. These were surrounded by a lymphoid hyperplasia containing enlarged germinal centres. In some specimens there was a uniform follicular hyperplasia. It would appear that the primary lesion was a lymphoid hyperplasia, as occurs in the cervical lymph nodes. Partial obstruction of salivary gland ducts within the hyperplastic parotid lymphoid tissue led to the development of the cysts.

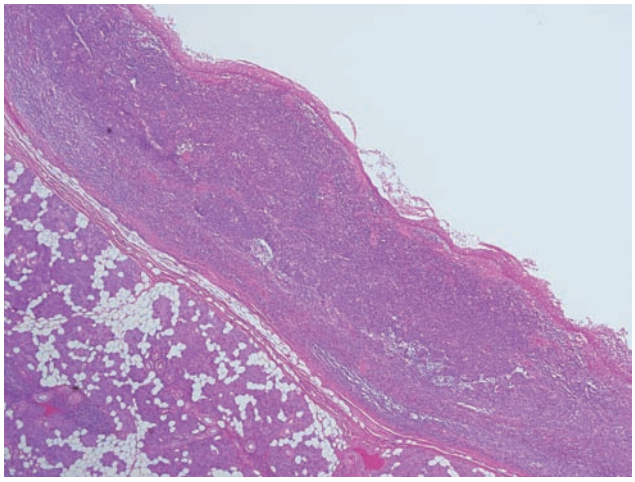


Fig. 16.9 Parotid lymphoepithelial cyst is lined by thin epithelium overlying dense lymphoid tissue (H & E).

Elliott and Oertel (1990) reported 14 lymphoepithelial cysts of the salivary glands, 13 from the parotid, which were diagnosed in 11 patients. Thirteen of the cases had occurred within the past 6 years. Five patients were tested for evidence of HIV infection, and all were positive. Six patients had varying degrees of lymphadenopathy. The cysts were lined by stratified squamous epithelium and occasionally by cuboidal epithelial cells. Multinucleate giant cells with abundant eosinophilic cytoplasm were found in four cases in the lumen of the cyst or just below the epithelial lining or in the lymphohistiocytic infiltrate. Atrophy of surrounding salivary gland parenchyma with lymphocytic infiltration of the ductal epithelium suggested cell-mediated immune destruction of the epithelial cells of the ducts in response to infection by the virus.

Histologically, HIV-associated lymphoepithelial cysts may be similar to cystic change in lymphoepithelial lesions of the type seen in Sjögren's syndrome. However, lesions in HIV patients are associated with diffuse infiltrative lymphocytosis syndrome (DILS) (Mandel and Hong, 1999; Tripathi *et al.*, 2004) in which there is a CD8 lymphocytosis and infiltration of predominantly CD8 positive lymphocytes in the salivary glands. In lymphoepithelial lesions, the lymphocytes are predominantly of the CD4 subset. Although HIV patients are at risk of lymphoma development, HIV-associated lymphoepithelial cysts are not regarded as pre-lymphomatous and do not appear to progress to MALT-type lymphomas as seen in Sjögren's syndrome related lesions. Another distinguishing feature is the presence of multinucleated giant cells in HIV-associated lesions (Fig. 16.10). These have been shown to contain p24 (HIV-1) protein in immunocytochemical studies (Vicandi *et al.*, 1999).

POLYCYSTIC (DYSGENETIC) DISEASE OF THE PAROTID GLANDS

Seifert *et al.* (1981) and Batsakis *et al.* (1988) have drawn attention to this condition which is probably of developmental origin. Its pathogenesis has been compared with the embryonic sequence of disturbances that lead to cystic malformations in other viscera such as the lung, pancreas, kidney and liver, although no such associated lesions have yet been reported in relation to the parotid gland lesion.

Although rare and only a few cases have yet been recorded, a consistent pattern has emerged. Clinically, it has occurred only in females; there was almost always bilateral parotid involvement; there was a history

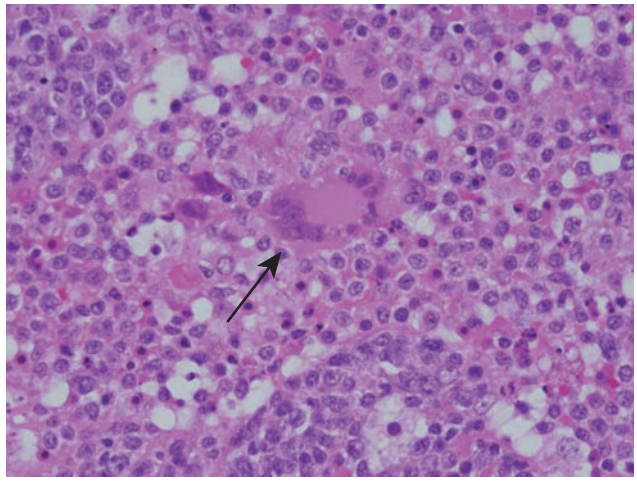


Fig. 16.10 A multinucleated giant cell (arrow) is seen within the dense lymphoid infiltrate of an HIV associated lymphoepithelial cyst (H & E).

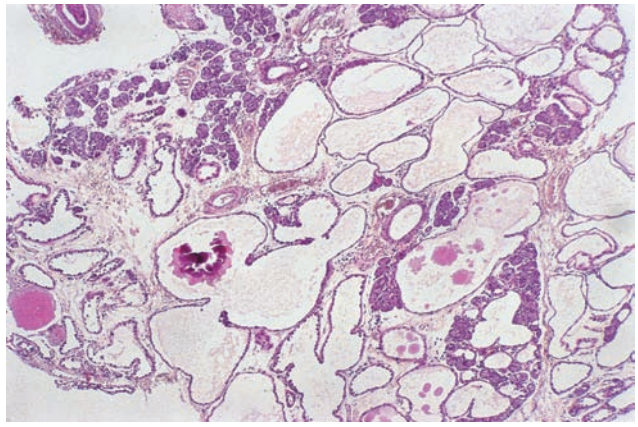


Fig. 16.11 'Honeycomb' appearance of polycystic disease of the parotid. (By courtesy of Dr K. Donath.)

of fluctuating, non-tender parotid gland swelling for several years; overt clinical signs were delayed; and sialograms showed cystic alterations without involvement of the main parotid duct (Batsakis *et al*., 1988). Smyth *et al*. (1993) reported two cases with a familial background in which a mother and daughter were affected.

Histological study of the series of cases reported by Batsakis *et al*. showed that the functional acinar parenchyma of the glands was almost completely replaced by a honeycombed latticework-like multicystic lesion (Fig. 16.11). Inspissated proteinaceous secretions were present in the cyst spaces. Small clusters of serous acini and occasional ducts lay in the intercystic fibrous septa. Often the cystic spaces appeared almost devoid of an epithelial lining because the cells were flattened and attenuated. Elsewhere the lining cells were cuboidal and often showed regressive hydropic changes and sloughing into the cysts. There was no squamous metaplasia and there was no evidence of inflammatory cells.

Familiarity with this disease should obviate the histological diagnosis of carcinoma. No surgery is necessary except for diagnosis and for cosmetic reasons if required.

SCLEROSING POLYCYSTIC ADENOSIS OF MAJOR SALIVARY GLANDS

This disorder is not primarily a cystic lesion but it is included in this chapter for completion and to ensure that it is properly distinguished from polycystic disease of the parotid gland. Sclerosing polycystic adenosis was first described in 1996 (Smith *et al*., 1996) as a reactive fibrosing pseudoneoplastic lesion in the major salivary glands. Since that time about 40 cases have been described (Gnepp *et al*., 2006). Almost all cases have arisen in the

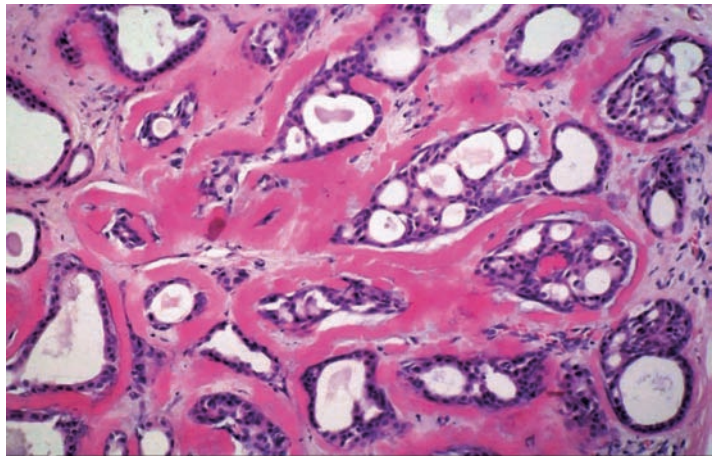


Fig. 16.12 Sclerosing polycystic adenosis. (By courtesy of Professor J. Eveson.)

parotid gland with only two cases in minor salivary glands and three in the submandibular gland. Lesions have affected males and females equally with an age range of 9–75 years. Clinically, the lesions present as solitary tumour-like masses.

Histological study of the lesions has shown unencapsulated masses of sclerotic and fibrosed collagenous connective tissue containing accumulations of hyperplastic ductal and acinar epithelial elements. Ductal ectasia to form cystic spaces is a consistent feature (Fig. 16.12). The epithelium lining the cysts may show a cribriform pattern and areas of apocrine metaplasia.

About half of cases have shown features of epithelial dysplasia or even carcinoma *in situ* in the ductal epithelium (Gnepp, 2003; Gnepp *et al*., 2006). However, no cases have been shown to progress to malignancy and the significance of these findings remains to be determined.

17
Developmental Cysts of the Head and Neck

Developmental cysts of the head and neck are rare. Most neck masses are caused by lymph node enlargement of one sort or another, with neoplastic disease being more likely with increasing age. Of cystic neck lesions metastatic carcinoma is, overall, probably the most common lesion encountered in adults. In children, developmental cysts are the most frequent cause of cystic masses of the head and neck and, of these, thyroglossal duct cysts are the most common, comprising about 70%. Branchial cleft cysts are the next most common, with most other lesions being very rarely encountered. The relative frequency and developmental anatomy of these lesions has recently been reviewed (Luna and Pfaltz, 2001).

DERMOID AND EPIDERMOID CYSTS

Dermoid and epidermoid cysts may occur on the floor of the mouth. Dermoid cysts are developmental cysts arising from entrapped midline ectodermal tissue lined by epidermis with skin appendages present in the fibrous wall. Epidermoid cysts are similar cysts lined by epidermis, but without appendages. In considering these lesions we make a clear distinction from common inclusion cysts of the skin which are often loosely and synonymously (and wrongly) called sebaceous cysts, milia, epidermal cysts, epidermoid cysts or trichilemmal cysts. The terms sebaceous cyst and milia are used clinically and no longer have any pathological connotation. Epidermal cysts and trichilemmal cysts are different entities with characteristic clinical and pathological features. These are summarised later in this chapter, but readers are referred to standard dermatopathology texts for details of these common lesions.

Clinical features

Frequency

Valuable reviews of these cysts have been written by Meyer (1955), Seward (1965), Allard (1982) and King *et al.* (1994). They quoted statistics from the Mayo Clinic which indicated that of 1495 'dermoid' cysts seen in an adult population over a 26-year period, 1910–35, 103 (6.9%) occurred in the head and neck region and only 24 (1.6%) were found in the floor of the mouth. In a sample of 514 cases from the same source during the period 1936–61, Taylor *et al.* (1966) reported a higher frequency of 6.5% in the floor of the mouth. Of the 184 (36%) lesions found in the head and neck, 19% were in the floor of the mouth. Allard (1982) found 11 cases in the files of the Oral Pathology Department of his hospital out of a series of 8000 surgical specimens collected over 10 years. In the Sheffield series, Jones and Franklin (2006a) found that only 19 dermoid cysts had been reported from a total of 44 007 adult head and neck specimens over a 30-year period. The lesion was slightly more common in children but, even then, of 4406 specimens only eight cases (0.02%) of dermoid cyst were identified (Jones and Franklin 2006b). Howell (1985) traced five sublingual cases from three oral surgical units in England treated over a 9-year period. King *et al.* (1994) added a further three cases and reviewed 195 cases of dermoid cysts of the floor of the mouth reported up to 1995.

Age

Although they may be present at birth (Yoshimura *et al.*, 1970; Yeschua *et al.*, 1977) and in elderly patients, the majority occur between the ages of 15 and 35 years. In a series of 76 oral cases collected from the literature, Allard (1982) found that 71% occurred by the age of 30 years and 91% by the age of 45 years. The duration of symptoms varied from 0 to 31 years.

Gender

Fifty-nine per cent of Allard's sample were found in males and 41% in females. In their study, King *et al.* (1994) recorded a similar male predilection with 61% of lesions in males and 39% in females. Longo *et al.* (2003) reported 16 new cases with a male : female ratio of 3 : 1.

Site

For oral lesions, the midline of the floor of the mouth is the most common location of these cysts (Fig. 17.1), which may also cause a swelling in the midline of the neck. In Allard's sample, 71% occurred there of which about half had appendages in their walls (dermoid cysts) and half did not (epidermoid cysts). The remaining 29% were evenly distributed in different parts of the mouth including four in the tongue which were all epidermoid cysts. Only two cases in this series were reported in the lateral part of the floor of the mouth.

Seward (1965) believed that dermoid and epidermoid cysts of the midline of the floor of the mouth always originate above the mylohyoid muscle, but may penetrate it. Some authors have differentiated between a sublingual or genioglossal type which is located between the geniohyoid muscle and the oral mucosa, and a geniohyoid (submental) type which is positioned between the geniohyoid and mylohyoid muscle (Allard, 1982). The rare lateral type, which is smaller, is located in the premolar–molar region and lies in the gutter formed by the mandible laterally and the genioglossal and geniohyoid muscles medially. It lies in the plane between the oral mucosa superiorly and the mylohyoid muscle inferiorly (Allard, 1982). In the review of King *et al.* (1994), 52% of cases were recorded as sublingual, 26% as submental and 6% as submandibular. The remaining cases (16%) occupied more than one space.

Issa and Davies (1971) have recorded an exceptionally rare example of a dermoid cyst that occurred in the coronoid region of the mandible in a 26 year old woman. Another example of an intra-osseous dermoid cyst was described by Craig *et al.* (1980). It occurred in the midline of the mandible in a 28 year old man. The authors carefully assessed the possible pathogenesis of the lesion and concluded that it was of non-odontogenic origin. They suggested that an intra-osseous dermoid cyst should be considered in the differential diagnosis of midline cystic lesions of the mandible.

Dermoid cysts also occur on the face. In a series of 231 cases in children, about three-quarters were located above the shoulders (Pollard *et al.*, 1976). The orbital and periorbital region was the area of the body most frequently involved, with 87 cases (37%). Interestingly, the left eyebrow (50 cases) was affected very much more often than the right (20 cases). Similarly, in the large series from the Mayo clinic (Taylor *et al.*, 1966), the most common site for head and neck lesions was the lateral aspect of the eyebrow. The neck, scalp, ear and nose were the other sites involved.

Clinical presentation

The intra-oral swelling lifts the tongue (Fig. 17.1) and may lead to difficulty in speaking, eating, breathing or closing the mouth. Deeper lesions between the geniohyoid and mylohyoid muscles produce a submental swelling in the neck giving the patient a 'double-chin' appearance. The swelling may feel doughy or fluctuant. The cysts tend to be small in infancy and enlarge during adolescence.

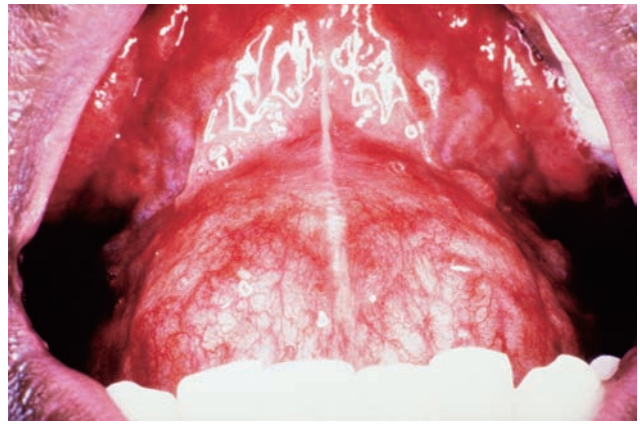


Fig. 17.1 Dermoid cyst of the floor of mouth.

Pathogenesis

The origin of dermoid and epidermoid cysts of the floor of the mouth, like other developmental cysts, is controversial. Having examined and discarded a number of concepts, Seward (1965) suggested that the most likely site for their origin is anteriorly between the contributions from the mandibular arches to the tongue. The problem with postulating an origin from contributions of mandibular arches to the tongue or from the first pharyngeal pouch is that it implies endodermal derivation. This seems unlikely for a structure that contains skin adnexae. On the other hand, Hamilton and Mossman (1972) stated that by the 32nd day of intra-uterine life, the endoderm of the floor of the mouth can no longer be distinguished from stomodeal ectoderm and there is probably a considerable amount of intermingling of the two epithelia. The boundary line is, however, behind that part of the epithelium of the mandibular process that gives origin to the teeth.

Implantation keratinising epidermoid cysts may occur in other parts of the mouth as a result of trauma (Ettinger and Manderson, 1973). These cysts are of limited size and remain small over many years. A definite history of trauma to the area 11 years before was recorded in a case of a midline cyst of the lower lip (Papanayotou and Kayavis, 1977).

Abrams *et al.* (1977) described an implantation epidermoid cyst which occurred in the mandibular condyle following surgical treatment in the region 2 years previously.

Histological features

Both dermoid and epidermoid cysts are lined by keratinised stratified squamous epithelium resembling epidermis. Occasional cases may have areas of pseudostratified ciliated columnar epithelium but cysts of the floor of the mouth lined predominantly by secretory epithelium are probably of salivary duct origin (Sadeghi and Bell, 1980). The dermoid cyst is characterised by the presence in the wall of one or more dermal appendages such as hair follicles, sweat glands or sebaceous glands (Fig. 17.2). Hair is very rarely found. The lumen is usually filled with keratin.

Sewerin and Praetorius (1974) described the occurrence of keratin-filled epidermoid cysts of the vermilion border of the lower lip which they believed represented dilated excretory ducts of the sebaceous glands. Serial sectioning of material from their cases revealed an orifice which formed a direct connection between the cystic cavity and the surface. Consecutive sections also showed a sebaceous gland in the wall at one level and not at another and they emphasised that serial sectioning is necessary before one attempts to label a cyst as either dermoid or epidermoid. In view of the ubiquity of sebaceous glands (Fordyce spots) in the oral mucosa, Allard (1982) speculated that some so-called dermoid cysts are in fact epidermoid cysts with the fortuitous presence of Fordyce spots in the wall.

Olsen *et al.* (1988) described a rare case of steatocystoma simplex in the maxillary buccal vestibule of a 65-year old man. Histologically, the lesion consisted of a submucosal cyst lined by a thin, stratified, squamous epithelium containing sebaceous gland acini. No dermal appendages were found in the cyst wall.

There are a number of reports of simultaneous occurance of dermoid cysts in association with another type of developmental cyst. These appear to arise in the floor of the mouth as well as at other sites including the pancreas, spleen and mediastinum. Presumably, the entrapment during development of pluripotential cells may allow for different pathways of differentiation at the same site. In the floor of the mouth, dermoid cysts have been described in association with gastrointestinal cysts (Eppley *et al.*, 1985; Arcand *et al.*, 1988; Crivelini *et al.*, 2001; Ho and Crean, 2003), bronchogenic cysts (Obiechina *et al.*, 1999; Gleizal *et al.*, 2006) and lymphoepithelial cysts (Ahn *et al.*, 1996; Epivatianos *et al.*, 2005). In most reports there have been at least two distinct cystic lesions with different types of lining although occasionally two types of epithelial lining have been shown to co-exist in the same cyst (Crivelini *et al.*, 2001).

Occasionally, cysts may be encountered that have elements derived from ectoderm, endoderm and mesoderm. These are termed *teratoid cysts* and are the most rare of the developmental cysts of the oral cavity. Harada *et al.* (1995) reported a case and reviewed four cases which had been reported up to 1995. Bonilla *et al.* (1996) added a further case to the literature. The lesions arise in the floor of the mouth and are congenital, usually presenting in neonates, although the case of Ohishi *et al.* (1985) occurred in a 5 year old boy. The cysts were lined by keratinising stratified squamous epithelium, gastrointestinal epithelium or respiratory type epithelium, and sebaceous glands, sweat glands and cartilage were present in the wall. Smooth muscle, striated muscle, neural tissue or bone may also be found in the wall. Another rare variety of cyst was described by Miller and Houston (1989) in the cheek of a 26 year old man. Histological examination showed that it was an ectopic apocrine cyst. The cyst was lined by stratified squamous epithelium but in parts there were rows of secretory cells of variable height showing 'decapitation' secretion of the apocrine type.

A case has been reported of an epidermoid cyst in the mucosa of the cheek which contained in its wall an intradermal naevus and structures identical to Meissner's tactile corpuscles (Gutmann *et al.*, 1978).

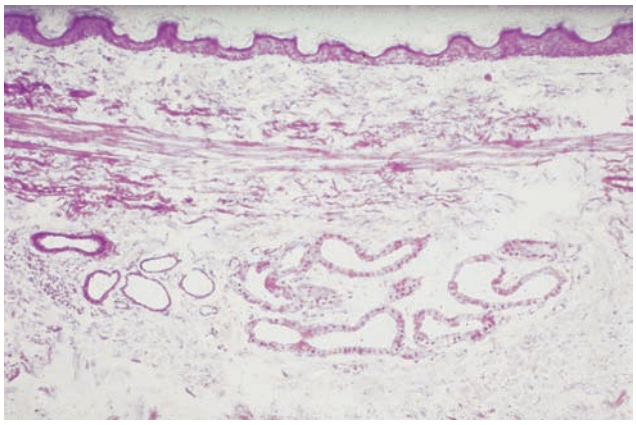


Fig. 17.2 Dermoid cyst lined by keratinised stratified squamous epithelium, with dermal appendages in the wall (H & E).

Treatment

Treatment of epidermoid and dermoid cysts of the soft tissues is by surgical excision.

KERATINOUS CYSTS OF THE SKIN

Keratinous cysts may occur on the skin of the face, neck and scalp. These cysts are often loosely referred to by a number of names including sebaceous cysts, epidermoid cysts and milia. However, they are distinct from dermoid and epidermoid cysts as described above and only two varieties can be distinguished histologically. The most common type is the epidermal cyst. These are often produced by traumatic implantation and hence are most

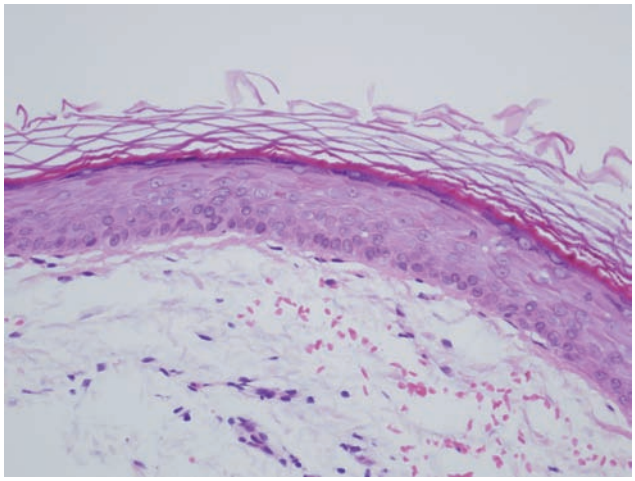


Fig. 17.3 Epidermal cyst of the skin. There is a prominent stratum granulosum (H & E).

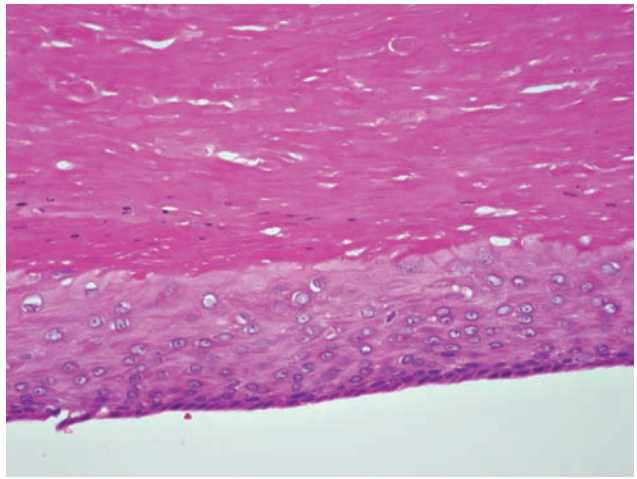


Fig. 17.4 Trichilemmal (pilar) cyst of the skin, showing the swelling of the superficial epithelial cells and transition to keratin which fills the lumen. There is no stratum granulosum (H & E).

frequently found on the hands and fingers although their occurrence on the skin of the face is quite common. They are lined by keratinised stratified squamous epithelium with a prominent stratum granulosum (Fig. 17.3). When part of the cyst lining ulcerates, a chronic inflammatory cell infiltration and foreign body type multinucleate giant cells are seen in the cyst wall.

The less common variety of keratinous cyst is the trichilemmal (pilar) type. These usually occur on the scalp, but rarely may be seen on the face, neck, trunk and extremities. They are lined by a stratified squamous epithelium but no stratum granulosum is formed (Fig. 17.4). The superficial epithelial cells are swollen. The cornified layer of the epidermal cyst has a lower cystine content than stratum corneum of the skin and, moreover, citrulline is present. The trichilemmal cyst content is low in sulphur-containing amino acids and differs in this respect from hair cortex (Rosai, 1981).

BRANCHIAL CLEFT ANOMALIES

True branchial cleft cysts arise as a result of a developmental anomaly of the branchial arches, clefts and pouches in the lateral neck. Because of their histopathological features, they are often also referred to as lymphoepithelial cysts. Cysts with similar histological features may be found within the parotid glands or in the oral cavity, but their developmental origin may be different. In this new edition we have drawn a distinction between true branchial cleft cysts arising from the branchial apparatus and those lymphoepithelial cysts arising within the parotid gland or intra orally. Parotid lymphoepithelial cysts are considered in Chapter 16.

BRANCHIAL CLEFT CYSTS

Branchial cleft anomalies may present as cysts, sinuses or fistulas or combinations of these defects. They arise from the branchial apparatus which comprises four pairs of arches, separated by four pairs of grooves and, internally, by four paired pharyngeal pouches. The arches give rise to most of the important structures of the head and neck with the important stages of development and differentiation occurring between the third and seventh embryonic week (Luna and Pfaltz, 2001). Ninety per cent of all anomalies arise from the second branchial arch, approximately 8% from the first and 2% from the third arch. Lesions arising from the fourth arch, although theoretically possible, are virtually unknown. The most common lesions are cysts, but sinuses and fistulas may also develop, most commonly in association with first arch defects. In these cases, a sinus may open onto the skin in the preauricular region or towards the angle of the mandible.

The most widely accepted view of the pathogenesis is that the branchial cyst develops from incomplete obliteration of the branchial clefts with entrapment of epithelial remnants. Bhaskar and Bernier (1959) postulated, however, that the neck cyst is not of branchial origin but that about 96% of them in reality represent cysts in cervical lymph nodes. The cystic change occurs in salivary gland epithelium which is trapped in the nodes of the neck during embryogenesis. Thus, they proposed that the lesion should be called 'lymphoepithelial cyst'. Rickles and Little (1967) concluded that several structures may give rise to the epithelium lining the cysts that occur in the neck. The few cysts found in the upper neck region could develop from either salivary gland inclusions in parotid lymph

nodes or from epithelial remnants of the upper portion of the branchial apparatus. The majority of cysts found in the midneck region could develop from epithelial remnants of the cervical sinus and/or the branchial pharyngeal pouches, both of which are part of the branchial apparatus. The cysts found in the lower neck region may develop from remnants of the thymic duct or from the lower portion of the branchial apparatus.

Many authorities still regard branchial cleft cysts and lymphoepithelial cysts as synonymous. While the issue is not completely resolved, we would agree with Rickles and Little and regard lymphoepithelial cysts of lymph nodes or within the parotid gland as different entities from true developmental cysts arising from the branchial apparatus. Although the histology may be similar, the former type of cyst probably arises from salivary inclusions within lymphoid tissue and is described in Chapter 16.

Because most branchial cysts arise from the second arch, the most common location is superficially in the neck, close to the angle of the mandible, anterior to the sternomastoid muscle. They occur at all ages with a fairly equal distribution from the first to the sixth decades according to Rickles and Little (1967), but most commonly in the third decade according to Allard (1982). However, most consider branchial cysts to be rare over 40 years of age. In this older age group, cystic degeneration in a metastatic carcinoma in a cervical lymph node is more common than a branchial cyst. Because the two lesions may be histologically similar, the diagnosis of branchial cyst in an elderly person should be one of exclusion. There is no gender predilection.

The neck lesions vary in size from small to very large (about 10 cm diameter). The most frequent symptoms are swelling, which may be progressive or intermittent, and pain. Sometimes attention is drawn to the lesions or they enlarge in response to a dental or upper respiratory tract infection. In view of their thick wall and fluid contents, they impart, on palpation, a sensation similar to that of a partly filled hot water bottle. They are demonstrable by ultrasound (Earl and Ward-Booth, 1985). Occasionally there may be a sinus or fistula which opens onto the skin at the anterior aspect of the sternomastoid muscle towards the lower third (Luna and Pfaltz, 2001).

Cysts associated with the first arch are most frequently found in a preauricular location although occasional lesions may be found within the parotid gland. Third arch cysts rarely present superficially but are found deep in association with the laryngeal ventricle or deep to the internal carotid artery.

Histological features

In a summary of the histological features of 689 branchial cysts of the neck reported in the literature, Allard (1982) found that in 96% the cyst was lined by stratified squamous epithelium. Occasional cysts are lined by respiratory-type epithelium or by a combination of both. In virtually all cases the wall contained lymphoid tissue which usually contained normal germinal centres (Fig. 17.5).

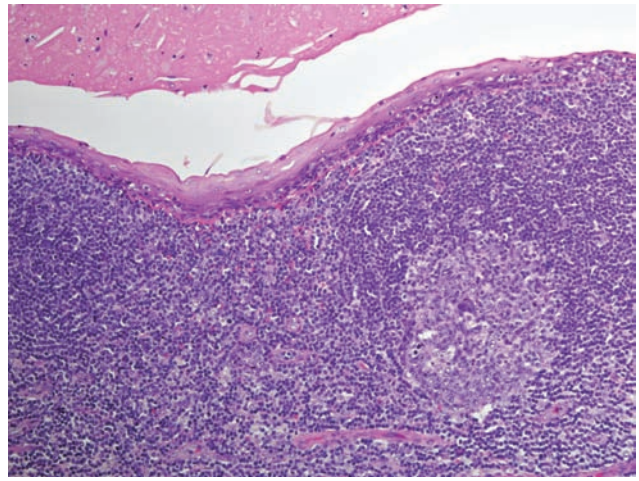


Fig. 17.5 Branchial cyst from the lateral neck. The cyst is lined by keratinised squamous epithelium, with prominent and normal lymphoid germinal centres in the wall (H & E).

INTRAORAL LYMPHOEPITHELIAL CYSTS

Intraoral lymphoepithelial cysts affect mainly the floor of the mouth and the tongue. Bhaskar (1966) reported a series of 24 intraoral lesions, 15 of which were in the floor of mouth and nine in the tongue. Most of the tongue cases involved the lateral margin. The age range was 15–65 years. No case occurred in the first decade and the majority were found in the third, fourth and fifth decades. Males (17 cases) were involved more frequently than females (seven cases). The cysts usually appeared as non-ulcerated, freely movable masses which had been present for periods ranging from 1 month to many years. Schiødt and Friis-Hasché (1972) reviewed the literature and their findings were essentially the same as Bhaskar's. Giunta and Cataldo (1973) reported a series of 21 of their own intraoral cases. The age of their patients ranged from 7 to 65 years. There were 12 females and nine males. Seventeen of the cases (80%) involved the floor of the mouth, two were in the soft palate and one each in the retromolar area and the mandibular labial vestibule. They ranged in size from 3 to 15 mm in greatest diameter, with an average of 6 mm. More than half of the cases were diagnosed clinically as mucocoeles. All were treated by surgical removal without recurrence.

An analysis of 38 intraoral examples from their own files was performed by Buchner and Hansen (1980). Their

patients ranged in age from 14 to 81 years with most being in the third (nine cases), fourth (10 cases) and sixth (eight cases) decades. Twenty three of their patients were males (61%) and 15 were females (39%). As in other series, the most common location was the floor of mouth (50%) followed by the ventral and the posterolateral surfaces of the tongue, each with 18.4%. The remaining examples were found on the soft palate, anterior palatine pillar and buccal vestibule.

Allard (1982) carried out an extensive review of the literature and found 105 cases, to which he added three of his own. The youngest reported patient was 7 years and the oldest 81 years, with a peak frequency of 42% in the third decade. Males were involved in 64% of cases and females in 36%. The floor of the mouth was involved in 69% of cases, the tongue in 23%, and other locations such as soft palate, buccal vestibule and anterior pillar of fauces in the other 8%.

Most of the reported lesions were symptomless and were detected on routine examination, but a few patients complained of swelling or discharge. Their size ranged from 1 to 10 mm. The usual observation was of a round or oval swelling of the oral mucosa of normal colour except when large when they were yellow or white. The masses were submucosal and freely mobile. Some were described as firm, others as soft. The clinical diagnosis was frequently incorrect, many being described as mucocoeles, lipomas or 'irritation fibromas'.

Occasional cases have been reported which coexist in the floor of the mouth with epidermoid cysts (Ahn *et al*., 1996; Epivatianos *et al*., 2005). In these cases the epithelial lining of both cyst types was similar, but in the epidermoid cysts the wall lacked a lymphoid infiltrate.

With regard to pathogenesis, Bhaskar (1966) believed that as the oral cavity contains foci of lymphoid tissue, it is possible that ectopic glandular epithelium within these foci can undergo cystic change and form the lymphoepithelial cyst of the oral cavity. Support for this view came from Vickers and von der Muhll (1966) who performed surgical autogenous transplants of hamster cheek pouch epithelium into the submandibular lymph nodes. In seven of nine experimental animals, inclusion cysts lined by keratinised stratified squamous epithelium formed within the lymph nodes.

Knapp (1970a,b) described what he called 'oral tonsils' and the possible role of these structures in the pathogenesis of the intraoral lymphoepithelial cyst. These oral tonsils are normal structures in the oral mucosa and resemble the tonsils in Waldeyer's ring. They are 1–3 mm in diameter and are found in varying numbers on the soft palate, ventral surface of tongue and floor of mouth. Knapp postulated that lymphoepithelial cysts are in fact pseudocysts that develop in oral tonsils in which the crypt opening becomes plugged. Accumulation of retained material leads to formation of the pseudocyst. Buchner and Hansen (1980) were of the opinion that this pathogenesis was tenable in some, but not all lymphoepithelial cysts. Continuity between cyst and surface epithelium can be demonstrated in only some specimens, even in serial sections. It seems possible that both pathogenetic mechanisms may play a part in the development of intraoral lympho-epithelial cysts.

The studies of Toto *et al*. (1982) supported the view that the intraoral lesion is a pseudocyst and that the epithelium could be of tonsillar crypt or of salivary duct origin. An origin from salivary duct epithelium, especially in the floor of the mouth where tonsillar tissue is scarce, is a possibility. Nair and Schroeder (1987) undertook a number of studies of the anatomy of the minor salivary glands in the monkey and described aggregates of normal lymphoid tissue embracing the ducts of minor glands close to the orifices. Such tissue was termed duct associated lymphoid tissue (DALT) and was thought to be analogous to similar tissues in the lungs or gastrointestinal tract. As described below, some lymphoepithelial cysts communicate with the oral cavity via a duct-like opening. Alpaslan *et al*. (1993) suggested that this association indicated that the lymphoid tissue in the wall was derived from DALT tissue.

To summarise, it is probable that intra-oral lymphoepithelial cysts arise through a number of mechanisms. Some may arise from epithelial inclusions within oral lymphoid tissues but others are probably pseudocysts arising as a result of cystic dilatation of tonsillar crypts or superficial ducts of minor salivary glands.

Histological features

The lymphoepithelial cyst in the mouth shows similar histological features to the branchial cyst (Fig. 17.5). It is usually lined by stratified squamous epithelium devoid of rete ridges and which may be keratinised (Figs 17.5 and 17.6). The keratotic layer is usually parakeratinised and only occasionally orthokeratinised (Buchner and Hansen, 1980). Occasional cysts are lined by ciliated or non-ciliated pseudostratified columnar epithelium which may contain goblet cells and a few have a lining of simple cuboidal or flat epithelium (Buchner and Hansen, 1980). Areas of ulceration occur. In some cases the lumen of the cyst communicates with the oral cavity through an epithelial-lined tract. The epithelium is closely enveloped by lymphoid tissue. In most cases the lymphoid tissue encircles the entire cyst (Fig. 17.6) but in a few it is present in only part of the wall. In the majority of cysts the lymphoid tissue shows typical germinal centres (Fig. 17.5) but in others only a diffuse, dense infiltrate of lymphocytes may be present. The lumen contains mainly desquamated parakeratotic cells and debris.

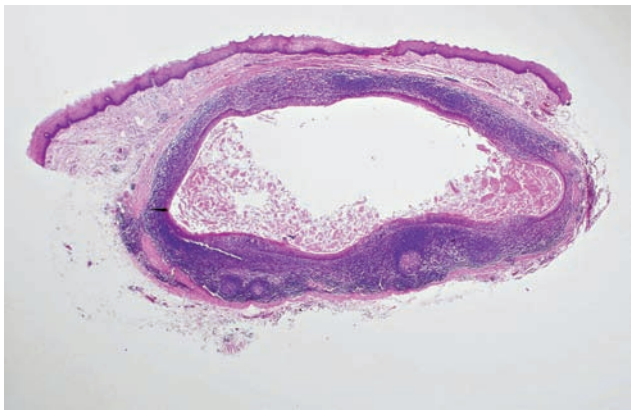


Fig. 17.6 Lymphoepithelial cyst of floor of mouth. The cyst lies just below the oral epithelium (H & E).

Treatment

The treatment of choice for branchial cleft cysts and oral lymphoepithelial cysts is complete surgical excision. The precise technique and surgical approach depends on the location of the cyst and is beyond the scope of this book.

THYROGLOSSAL DUCT CYST

The anlage of the median lobe of the thyroid gland develops at about the fourth week of intrauterine life from a site at the base of the tongue which is recognised later as the foramen caecum. A hollow epithelial stalk, known as the thyroglossal duct, extends caudally and passes ventral to the hyoid bone to the ventral aspect of the thyroid cartilage where it joins the developing lateral lobes. The thyroglossal duct disintegrates by about the 10th week, but cysts may form from residues of the duct at any point along its line of descent. The aetiology of the cyst is not known but inflammatory conditions which lead to reactive hyperplasia of the lymphoid tissue adjacent to the remnants of the thyroglossal tract and may stimulate the epithelial remnants themselves have been mentioned, as has a blocked thyroglossal duct with an accumulation of secretion (Allard, 1982).

The thyroglossal duct cyst is the most common of the developmental cysts of the neck, accounting for about 70% of such lesions overall, and for up to 90% of congenital abnormalities in the neck in children (Luna and Pfaltz, 2001; Koch 2005). Allard (1982) undertook an extensive review of the literature, which garnered 1747 cases, and found an equal gender distribution. In a slightly smaller sample of 1316 cases for which patient ages or decades were available, 32% were younger than 10 years, 20% were in their second decade, 14% in their third and 35% were older than 30 years.

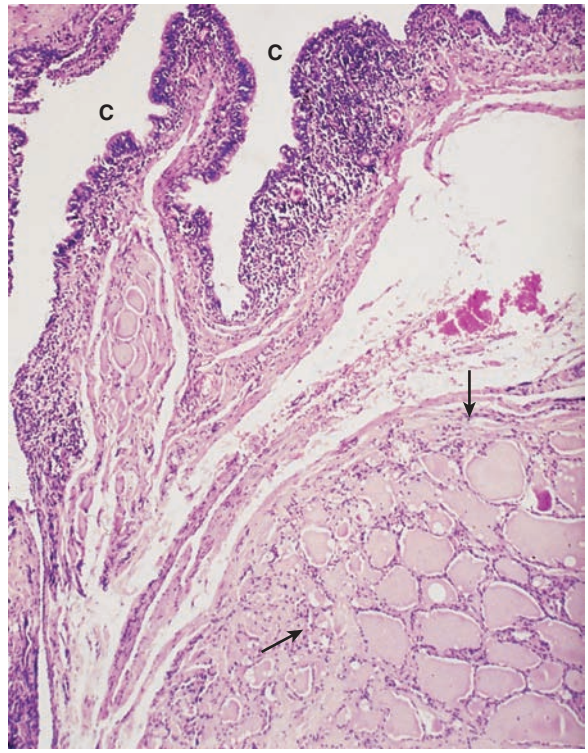


Fig. 17.7 Thyroglossal duct cyst (C) lined by pseudostratified columnar epithelium. Thyroid tissue (arrows) is present in the wall (H & E).

The cysts are most commonly located in the midline of the neck in the area of the hyoid bone. Only about one-quarter of lesions are found above the hyoid and only 2% are located in the mouth. Intra-oral lesions arise either in the floor of the mouth or at the foramen caecum. A proportion of thyroglossal duct cysts have an associated fistula. The cysts are usually in the midline and produce soft, movable, sometimes fluctuant, sometimes tender swellings. Occasionally, they may be located laterally. Classically, they lift when the patient swallows or protrudes the tongue. If they are located high in the tract they may cause dysphonia or dyspnoea.

Histological features

Thyroglossal duct cysts are lined by a pseudostratified columnar epithelium which may be ciliated, or by a stratified squamous epithelium. The latter type of epithelium is seen particularly in cysts close to the mouth. Thyroid tissue may be seen in the fibrous wall (Fig. 17.7) but is only found in up to 40% of lesions, even after examination of serial sections (Luna and Pfaltz, 2001). Mucous cells may be present in the cyst lining and seromucous glands in the wall (Wampler *et al*., 1978), particularly if the cysts are located in the lingual area. In the same region lymphoid tissue with

prominent germinal centres may also be seen. Malignant change has occasionally been observed and it is reported that thyroid carcinoma may arise in approximately 1.5% of lesions (Patel *et al*., 2002). A review of the literature on the subject also revealed nine cases in which squamous cell carcinoma had developed (Lustmann *et al*., 1989).

Treatment

Surgical excision is usually advised for the treatment of thyroglossal duct cysts. The Sistrunk operation involves removal of a 1 cm block of tissue surrounding the duct and a 1–2 cm portion of the central part of the hyoid bone. The thyroglossal tract should also be traced down to the pyramidal lobe of thyroid gland and to the foramen caecum at the base of the tongue (Wampler *et al*., 1978). Reporting on a series of 16 thyroglossal duct cysts in patients over the age of 30 years, van der Wal *et al*. (1987) stated that there were no recurrences in eight patients who had been treated with the Sistrunk operation. The other group of eight were not treated for various reasons. Follow-up of these patients showed that the cyst had remained unchanged in one case, decreased in size in three and disappeared completely in the remaining four.

DEVELOPMENTAL CYSTS OF FOREGUT ORIGIN

The developing foregut arises from the primitive stomatodeum at about the 20th day of intrauterine life. At day 22 a ventral bud gives rise to the laryngotracheal tube which eventually forms the lungs and bronchial tree. The dorsal aspect of the downgrowth gives rise to the alimentary tract as far as the duodenum. Developmental anomalies of the foregut are relatively common and form a spectrum of disorders referred to as *foregut duplications* (Azzie and Beasley, 2003). Duplications may present as cysts, diverticula or pouches. Overall, cysts are most common, and most lesions are encountered within the thorax. Cysts in the head and neck are rare. The actual mode of presentation of foregut anomalies depends on the anatomic level of the defect, but a defining feature of all cysts is a lining of gastrointestinal or respiratory epithelium, the presence of smooth muscle in the wall and an attachment to the foregut.

In the neck and oral cavity, lesions have been described under a number of terms, including heterotopic gastrointestinal cyst, oral alimentary tract cyst, anterior median lingual cyst, bronchogenic cyst and foregut duplication cyst. It is difficult to define each as a distinctive entity because the mode of presentation is similar but the histological findings are variable. Reports usually define the cyst type by the histological nature of the lining, whether it be wholly or predominantly of gastrointestinal or respiratory type epithelium. The anatomic level of origin may determine the precise nature of the lesion. Cysts in the oral cavity are almost exclusively found in the tongue and their origin from the early bud of the foregut or close to the ventral and dorsal division may result in a lining of pluripotential epithelium which may differentiate into respiratory or gastrointestinal epithelium or both (Allard, 1982; Constantinides *et al*., 1982; Manor *et al*., 1999). Cysts developing at deeper levels will either be dorsal or ventral and become lined by gastrointestinal or respiratory epithelium, respectively. Ventral cysts arising from the laryngotracheal groove are termed bronchogenic cysts and may present in the neck. Lesions arising from the developing alimentary tract are more often duplications or diverticula.

LINGUAL CYST OF FOREGUT ORIGIN

The term lingual cyst is a useful descriptive term for cysts of foregut origin that arise within the tongue, which is overall the most common site for these lesions in the oral cavity. Lesions reported in the literature appear to encompass bronchogenic cysts lined by respiratory epithelium, and gastrointestinal cysts lined by gastric or intestinal epithelium. Among the latter group particularly, are many reports of lesions in which the lining was composed of both types of epithelium. Manor *et al*. (1999) reviewed 53 lingual cysts reported in the English language literature between 1942 and 1997 and added a single case of their own. Of the 53 reported cases, 29 were reported as 'alimentary tract' cysts and 24 as of foregut origin. However, they found much confusion with regard to terminology. For example, authors often reported lesions with respiratory epithelium as of alimentary origin, or cysts with both types of epithelium as of 'foregut origin'. Manor *et al*. considered that both types of cyst had a common embryological origin, arising from embryonal rests of foregut origin that become entrapped between the parts of the developing tongue. For this reason and because of the overlap in clinical and histological features they felt that the clear differentiation between lingual cysts of foregut origin and lingual alimentary cysts that was used in the third edition of this book could no longer be justified.

They proposed that the simple descriptive term *lingual cyst* was more appropriate with an added description of the type of epithelium – lingual cyst with respiratory epithelium, lingual cyst with gastrointestinal epithelium or lingual cyst with respiratory and gastrointestinal epithelium.

Clinical features

Lingual cysts are rare lesions. Manor *et al*. (1999) recorded 53 cases up to 1997 and added a case of their

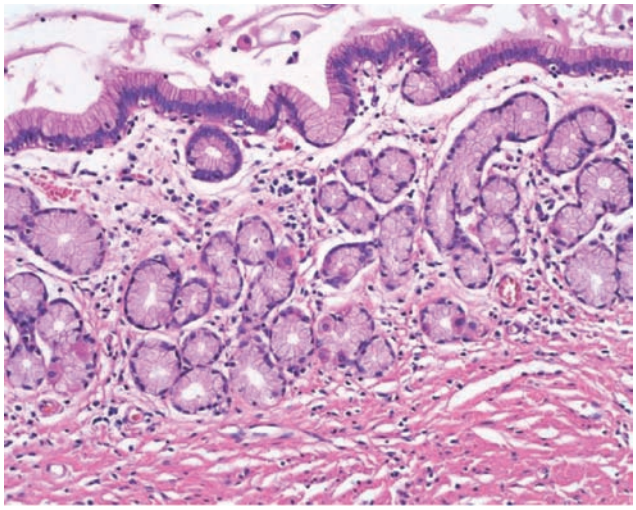


Fig. 17.8 A lingual cyst lined by gastric type epithelium (H&E). (By courtesy of Dr J. Hille.)

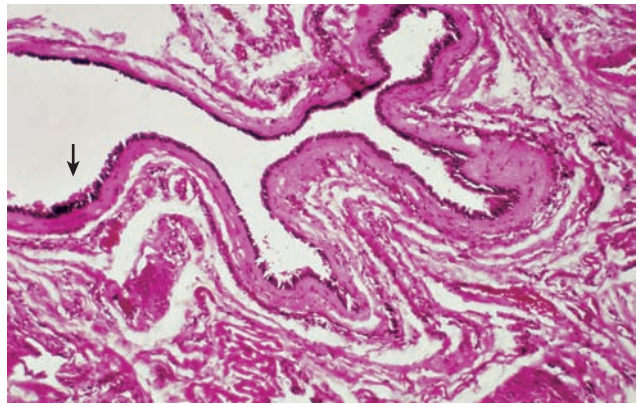


Fig. 17.9 Anterior median lingual cyst (intralingual cyst of foregut origin) lined in part by cuboidal epithelium and in part by ciliated pseudostratified columnar epithelium (arrow) (H & E).

own. Since then, a further 17 cases have been reported, six by Eaton *et al.* (2001), two by Said-el-Naief *et al.* (1999) and one each by Morgan *et al.* (1996), Kim *et al.* (1998), Obiechina *et al.* (1999), Ćorić *et al.* (2000), Mandell *et al.* (2002), el-Bitar *et al.* (2003), Kong *et al.* (2004), Benhammou *et al.* (2006) and Gleizal *et al.* (2006).

Most cases have occurred in infants and young children. Allard (1982) reviewed 18 cases from the literature; 12 patients were in the first year of life, three were between the ages of 2 and 11 years, and in two of the three adult patients the lesions had been present since childhood. The male:female ratio was 3:1. Manor *et al.* (1999) reported an age range of 0–42 years with a mean age of 5.5 years and median age of 6 months. The male:female ratio was 1.6:1.

The most frequent clinical presentation is an asymptomatic lingual swelling covered by clinically normal mucosa. Of the 54 cases reviewed by Manor *et al.* (1999), only five recorded any disturbance in tongue function, eating or speaking. Lesions were most often found in the anterior midline of the tongue and presented dorsally. Only six cases were located in the ventral tongue and a further three extended into the floor of the mouth. Five cases involved the posterior tongue. Allard (1982) recorded eight cases in the anterior part of the tongue, two in the posterior part and three in the floor of the mouth. The cysts may be enclosed entirely within the tongue or floor of mouth or may communicate with the surface.

Occasional lesions with similar histology and probably of similar origin may present in the lateral tongue or in the neck. Allard (1982) found two cases in the anterior part of the neck and two in a submandibular salivary gland.

Histological features

The cysts are lined by respiratory epithelium, gastric epithelium, intestinal epithelium or combinations of two or three of these types. In 52 of the cases reported by Manor *et al.* (1999), only 12 contained mainly respiratory epithelium, 25 contained mainly gastrointestinal epithelium and 15 were mixed respiratory and gastrointestinal. Said-el-Naief *et al.* (1999) reported two cases lined by mixed epithelium with stratified squamous elements and respiratory epithelium, but with only small focal areas of gastric epithelium. Their examples also contained salivary elements and smooth muscle in the wall. This example illustrates the problems of terminology, because despite the relative paucity of gastric epithelium, these authors published their cases as 'oral gastrointestinal cysts'. The 'foregut duplication cyst' reported by Kong *et al.* (2004) was lined only by gastric mucosa.

When lined by gastric mucosa, the epithelium is of the type seen in the body and fundus of the stomach (Fig. 17.8). Both parietal and chief cells may be found. Gastric glands may be present. Some cysts have a muscularis mucosa. The cyst reported by Gorlin and Jirasek (1970) was lined with intestinal mucosa and Paneth cells, goblet cells and argentaffin cells were demonstrable. Another interesting feature of their case, which occurred on the floor of the mouth, was the presence of a tube which extended from the floor of the mouth into the cyst. The tube was lined by stratified squamous epithelium and adjacent sebaceous glands emptied into it.

In a case of ours from the University of the Witswatersrand, the cyst occurred on the tongue of a 2 year old girl and had been present since birth. It was lined by cuboidal and respiratory epithelium (Fig. 17.9).

Constantinides *et al.* (1982) described two cases of congenital lingual cysts which displayed the same histological features as our own and that of Kong *et al.* The first occurred in a newborn infant boy who had a large, tense cystic swelling within the anterior half of the tongue. It did not interfere with breathing but made feeding difficult. At operation, after this cyst was removed, further dissection revealed a second cyst embedded in the base of the tongue extending into the neck. The authors considered that the lesion was in fact an hourglass-shaped cyst. Histological examination of both their cases revealed that the cysts were lined by stratified squamous epithelium and ciliated and non-ciliated cuboidal 'respiratory type' epithelium.

In the floor of the mouth, developmental lingual cysts have been described in association with dermoid cysts as discussed previously in this chapter (Eppley *et al.*, 1985; Arcand *et al.*, 1988; Obiechina *et al.*, 1999; Crivelini *et al.*, 2001; Ho and Crean, 2003; Gleizal *et al.*, 2006).

Treatment

Treatment consists of surgical excision. Recurrences are rare but have been reported.

BRONCHOGENIC CYST

Bronchogenic cysts are lined by respiratory epithelium and are derived from the primitive foregut at a point below the level of the ventral extension of the laryngotracheal tube. They are found most frequently within the thorax, but may rarely be encounterd in the neck. Occasionally, cysts within the tongue have been reported as bronchogenic cysts (Obiechina *et al.*, 1999; Benhammou *et al.*, 2006; Gleizal *et al.*, 2006) but these lingual lesions have been included as lingual cysts of foregut origin and have been discussed in the previous section.

Bronchogenic cysts in the neck appear to arise lower down the developing tracheobronchial tree and are thus lined entirely by respiratory epithelium. Most lesions are encountered in the suprasternal notch region and over 70% are in the midline (Ustundag *et al.*, 2005). When present at a lateral site they may be found overlying the clavicles or at the anterior border of the sternomastoid muscle. In a review of 70 cases of the head and neck region reported up to 2005, Ustandag *et al.* (2005) found only five lesions above the hyoid bone, three of which were submental and two in the tongue. Two cases were in the submandibular region, one of which was deep and towards the floor of the mouth and a second which was subcutaneous and mimicking a lymph node. Other sites in the upper neck were overlying or just lateral to the thyroid gland, or just lateral to the larynx or epiglottis. Most lesions are located in the skin and immediate subcutaneous tissues.

Cervical bronchogenic cysts are found in males with a ratio of about 3:1 (Luna and Pfaltz, 2001; Ustandag *et al.*, 2005) and become clinically apparent just after birth. In the series of Ustandag *et al.*, the age range was from 0 to 54 years but only 12 cases were found in adults. They usually present as symptomless masses which slowly increase in size. Lesions may communicate with the skin through a sinus tract.

Histological features

Histologically, the cyst is lined by respiratory-type epithelium (Fig. 17.10) although simple stratified epithelium may be present especially if the lesion has become infected. The wall may contain smooth muscle and seromucous glands. Thoracic lesions typically also contain cartilage, but this is only rarely seen in cervical lesions.

Treatment

Treatment consists of complete surgical excision along with the sinus tract if one is present.

CYSTIC HYGROMA

The cystic hygroma is a developmental abnormality in which there is progressive dilatation of the lymphatic channels. The lesion is more correctly designated as a

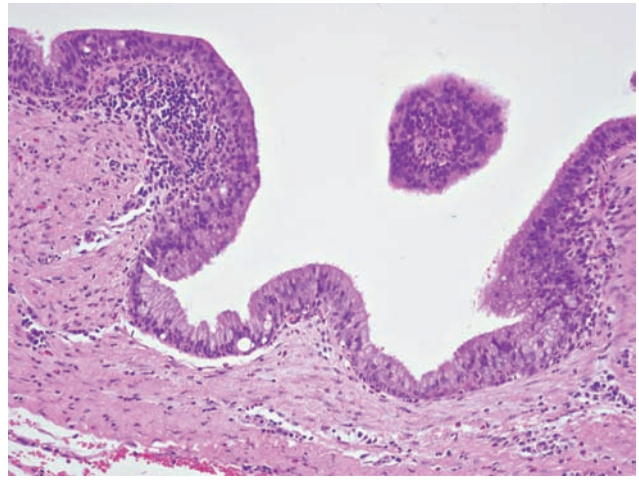


Fig. 17.10 A bronchogenic cyst which arose in the subcutaneous tissues of the lateral neck. The cyst is lined by pseudostratified ciliated epithelium with mucous cells (H & E). (By courtesy of Dr C. Ades.)

cavernous type of lymphangioma but cystic hygroma is a commonly used clinical term. It most frequently involves the face and neck although it can occur anywhere in the body.

It is often present at birth and most cases are diagnosed before the age of 2 years (Bayer and Hardman, 1976). In the head and neck region, lesions produce a swelling, often painless and usually compressible. The lesion is usually unilateral but the entire side of the neck and lower face may be involved. The overlying skin may be blue and the swelling transilluminates. There may be a history of gradual or sudden enlargement.

Histologically, the cystic hygroma consists of dilated cystic spaces lined by endothelial cells.

Treatment should aim at complete surgical removal of the mass. In a review of 44 cases treated in their own department, Charabi *et al.* (2000) followed patients for up to 36 years and found that 50% had recurrent or residual lesions and 44% reported some degree of morbidity including impaired speech or swallowing. The authors describe the use of intralesional injections of OK-432, which has been developed in Japan (Rho *et al.*, 2006), and suggest this may be a promising alternative to surgery. Burezq *et al.* (2006) suggest that aspiration alone is a suitable and reliable form of treatment.

NASOPHARYNGEAL CYSTS

Nasopharyngeal cysts are rare clinical entities which have been reviewed by Nicolai *et al.* (1989). They may be classified as congenital or acquired, and midline or lateral. Retention cysts are the most frequent among midline cysts and are usually attributed to coalescence of the median recess of the pharyngeal tonsil. They are lined by ciliated or non-ciliated columnar epithelium with areas of squamous metaplasia in response to inflammatory stimuli. Lymphoid follicles are present in the wall. The cyst cavity is packed with epithelial debris.

Congenital midline cysts may arise either from the pharyngeal bursa (Tornwaldt's bursa) or from Rathke's pouch. Their clinical and histological features are similar to those of the retention cysts. Cysts arising from Rathke's pouch are exceedingly rare. They have a median base attached to the nasopharyngeal vault and lie anterior to the usual site of origin of the retention and pharyngeal bursa cysts. They are lined by stratified squamous epithelium, in keeping with their ectodermal origin.

Lateral nasopharyngeal cysts are usually of branchial cleft origin, and have been discussed previously.

THYMIC CYSTS

Thymic cysts are rare clinical entities which arise in persistent thymic tissue which may occur in any location between the angle of the mandible and the midline of the upper neck to the sternal notch (Carpenter, 1982). They are most often encountered on the left side of the neck and males are affected twice as often as females (Luna and Pfaltz, 2001). About 70% present in the first decade and the remainder are usually diagnosed before the age of 30 years. Histologically, the cyst is lined by squamous and cuboidal epithelium and thymic tissue may be present in the wall.

18
Parasitic Cysts

Parasitic cysts occur in the mouth although they are rare. Valuable reviews have been published by Allard (1982) and Hansen and Allard (1984). Most of the reported cases of parasitic cysts in the mouth have been caused by the class Cestoidea (flatworms and tapeworms). These include the genera *Echinococcus* and *Taenia*. There are four species of *Echinococcus*: *E. granulosus, E. vogeli, E. oligarthus* and *E. multilocularis*; and two species of *Taenia*: *T. solium* and *T. saginata*. The class Nematoda (roundworms) produce oral lesions only exceptionally rarely. They include the genera *Trichinella, Gongylonema* and *Ascaris* with their respective species, *T. spiralis, G. pulchrum* and *A. lumbricoides*.

HYDATID CYST

Hydatid cysts occur in hydatid disease or echinococcosis. Hydatid disease is caused by the larvae of *E. granulosus*, the dog tapeworm, which resides in the intestinal tract of the dog. Its ova are excreted in the faeces and may be ingested by the intermediate hosts, cattle, sheep and pigs. Humans are also a susceptible intermediate host and, as dogs are common household pets, may accidentally ingest the ova.

The ingested ova hatch in the upper gastrointestinal tract from where the small embryos permeate the intestinal mucosa and are dispersed through the blood vessels and lymphatics to all parts of the body. The great majority of cysts are found in the liver, but others are found in the lungs, bones and brain. Hydatid disease is common in sheep-raising countries such as Australia, New Zealand, Argentina and South Africa, but only about 2% of cases affect the oral and maxillofacial regions. Between 20% and 30% of patients will have multiorgan involvement, which always affects the liver as well as other sites. Oral lesions are usually the subject of occasional case reports.

Bouckaert *et al.* (2000) reported two cases from South Africa and reviewed 20 cases which had been reported in the English language literature up to 1999. A further case was reported in the maxillary sinus of a 6 year old boy by Ataoglu *et al.* (2002). Of the total of 23 reported cases, there were 11 cases in males and 12 in females with an age range of 6–54 years and mean age of 24 years. The most common sites of presentation were the salivary glands and the pterygopalatine or infratemporal fossa areas with seven cases at each site. In the salivary glands, four cases affected the parotid and three the submandibular gland. Other reported sites included the tongue, buccal mucosa, maxillary sinus and the subcutaneous tissues of the neck.

The first case reported by Bouckaert *et al.* (2000) arose in the submandibular gland in a 20 year old female and presented as a 4-cm diameter submandibular swelling which also elevated the floor of the mouth. The cyst contained clear fluid and showed numerous vesicular projections or brood capsules on the inner layer. The second case presented in the buccal mucosa of a 6 year old boy. This lesion was necrotic on examination and had been subjected to trauma.

Perl *et al.* (1972) described a case in an 18 year old black South African woman who complained of a painless swelling on the right side of the tongue which had been present for 3 months and was increasing in size. An intact unilocular cyst was removed which, when cut in half, revealed the presence of brood capsules. Nandakumar and Shankaramba (1989) described a case in which a cyst had formed in the angle of the mandible of a 16 year old male. The cyst was diagnosed at operation when the contents were accidentally spilled during enucleation and the presence of opaque, milky white particles were observed.

Histological features

The hydatid cysts are initially of microscopic dimensions, but enlarge progressively. The mature cyst consists of three layers: an outer layer of host origin and two inner layers of parasitic origin. The host layer consists of fibrous tissue in which there is an infiltrate of chronic

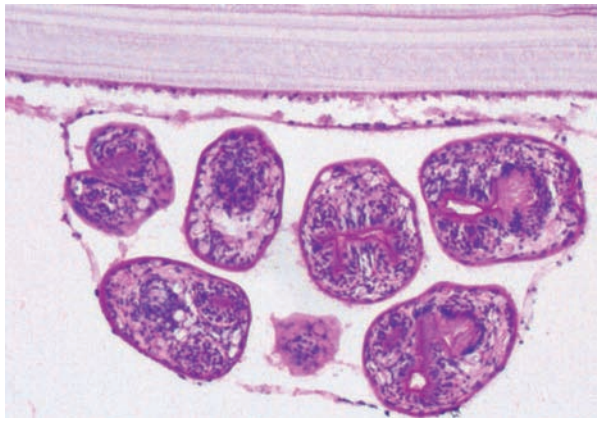


Fig. 18.1 Hydatid cyst. Intermediate non-nucleated layer (top) with germinative layer forming brood capsules on its inner aspect. The scolices are formed in these brood capsules (Courtesy of Professor JJ Hille).

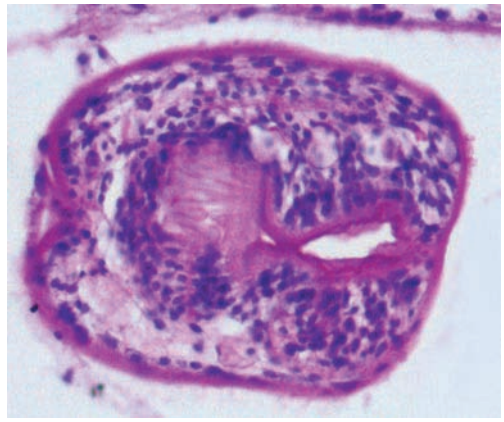


Fig. 18.2 Higher power view showing detail of a scolex in the brood capsule of a hydatids cyst (Courtesy of Professor JJ Hille).

inflammatory cells, eosinophils and giant cells. The intermediate layer is white, non-nucleated, and consists of numerous delicate laminations. It usually shrinks away from the outer fibrous layer when the tension within the cyst is relieved. Finally, there is the inner, nucleated germinal layer (Figs 18.1 and 18.2). The cyst fluid is relatively clear, albumin-free and contains the so-called 'hydatid sand' consisting of brood capsules and scolices. These brood capsules or daughter cysts develop originally as minute projections of the germinative layer which develop central vesicles and become minute cysts. Scolices of the head of the worm develop in the inner aspects of the brood capsules. It is when they separate from the germinative layer that they form the 'hydatid sand'.

CYSTICERCUS CELLULOSAE

Humans develops cysticercosis through the larval form, *Cysticercus cellulosae*, of the pork tapeworm *Taenia solium*. They can act as both the intermediate and the definitive host. The adult worm may be ingested in inadequately heated or frozen pork. Alternatively, humans may ingest the cysticerci themselves from infested pork and these develop into the adult worm. This lives attached to the wall of the small intestine where, fully grown, it may reach a length of 7 metres. Gravid proglottids containing the eggs begin to drop off and are passed in the faeces. In this way they may be ingested by humans through contaminated food or from their own dirty hands, or they may be regurgitated into the stomach. In the stomach their covering is digested off and the larval forms are hatched. These penetrate the intestinal mucosa and are then distributed through the blood vessels and lymphatics to all parts of the body, where they develop into cysticerci, thus completing the life cycle. In humans, cysticercosis may be aquired by ingestion of infected pork or directly by ingestion of eggs by the faecal–oral route. This explains the occasional cases reported in vegetarians (Jay *et al.*, 2005).

There are few reports of cysticercosis of the oral regions. Saran *et al.* (1998) reviewed the literature and found only 43 cases reported up to 1995. They added a further five cases of their own. Of the total of 48 cases, the male : female ratio was 1 : 1 with an age range of 3–70 years and mean age of 22 years. The most common site, where 25 of the lesions presented, was the tongue, followed by buccal mucosa and lips. Eight of the 48 cases had multiple oral lesions. Almost all cases presented as asymptomatic swellings covered by normal appearing mucosa.

Subsequently, a further 24 cases have been reported: eight by Mazhari *et al.* (2001), seven by de Souza *et al.* (2000), six by Nigam *et al.* (2000), and one each by Pinswasdi and Charoensiri (1997), Elias *et al.* (2005) and Jay *et al.* (2005). In these more recent lesions only two occurred in the tongue. Of the eight cases reported by Mazhari *et al.* (2001), four arose in the buccal mucosa, two in the lip, one in the tongue and one in the gingival. Nigam *et al.* (2000) reported three cases each in the buccal mucosa and lip. The patient reported by Jay *et al.* (2005) had multiple lesions in the buccal mucosa associated with a subcutaneous lesion on the wrist and multiple lesions in the brain.

Timosca and Gavrilită (1974) recorded five cases in Romanian patients. Two occurred subcutaneously in the neck, two deep to the cheek mucosa and one had multiple lesions involving the lip, cheek and skin. Three cases

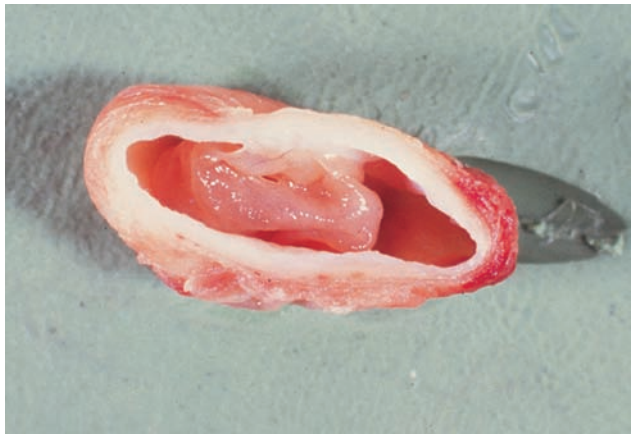


Fig. 18.3 Gross specimen of *Cysticercus cellulosae* removed from tongue.

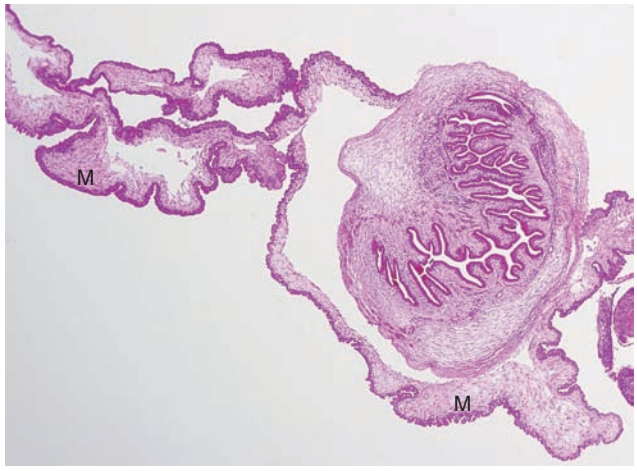


Fig. 18.4 *Cysticercus cellulosae* containing the larval form of *Taenia solium*. M, double layered membrane (H & E).

from the files of the oral pathology department at the University of the Witswatersrand have been reported by Ostrofsky and Baker (1975). One occurred as a swelling of the dorsum of the tongue in a 7 year old child; another in the tongue of a 70 year old man. The third was a firm mass 10 mm in diameter in the right cheek. Another two cases from the University of the Witswatersrand have been reported by Lustmann and Copelyn (1981). One occurred in the tongue of an 11 year old boy and one in the tongue of a 25 year old man. Hansen and Allard (1984) described four of their own cases: three in the lips and one in the cheek. Their literature review identified 30 cases.

All the specimens examined in our laboratory have been intact cystic masses which, when cut, contained clear watery fluid and a coiled white structure apparently attached to the inner aspect of the cyst (Fig. 18.3).

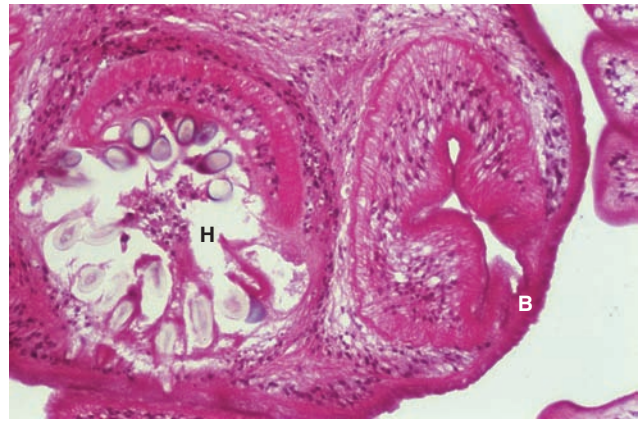


Fig. 18.5 Scolex of larval form of *Taenia solium*. B, bothria; H, hooklets. (H & E)

Histological features

Histological examination of *Cysticercus cellulosae* shows a dense fibrous outer capsule which is derived from host tissue. This contains a fairly dense inflammatory cell infiltrate consisting predominantly of lymphocytes, plasma cells and histiocytes. On the inner aspect of this fibrous capsule, the nature of the infiltrate is different and consists of a dense aggregation of eosinophil and neutrophil polymorphonuclear leucocytes. A few foci of dystrophic calcification are present in this capsule, and some of these are concentrically laminated. Within the fibrous capsule is a delicate double-layered membrane consisting of an outer acellular hyaline eosinophilic layer and an inner, sparsely cellular layer. This membrane has a loose attachment to the fibrous capsule and is readily torn away from it. The cyst lies within this membrane and contains the larval form of *T. solium* (Fig. 18.4). At the cephalic extremity of the larva, the scolex with rostellum, bothria (suckers) and hooklets may be identified (Fig. 18.5). Caudal to the scolex is the duct-like invagination segment lined by a homogeneous anhistic membrane.

Although *Cysticercus cellulosae* is harmless in the oral tissues, localisation in the brain, heart valves and orbit occurs and produces important functional derangements. They may remain alive for many years. After their death a granulomatous reaction forms around the parasite, and calcifies.

TRICHINOSIS

Trichinosis is caused by *T. spiralis*, a roundworm parasite of rats and pigs. The reviews of Allard (1982) and Hansen

and Allard (1984) revealed only two cases, one of which produced a tumour-like enlargement of the gingiva and the other a radiolucent area on the crest of the alveolar ridge. Microscopic examination showed an encysted form of *T. spiralis*. These reviews also identified two similar cases of oral lesions caused by the roundworm *G. pulchrum*. No further oral cases have been reported in humans since that time.

Index

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