ORIGIN AND GROWTH OF CYSTS OF THE JAWS

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by

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CYSTIC SWELLINGS OF the jaws appear first to have been described in 1654 by Scultetus, and it was not until 1728 that Fauchard suggested that they might be connected with the teeth. John Hunter, in his classic monograph on the anatomy and pathology of the teeth published in 1774, described a case which, as Sir Frank Colyer pointed out, was a large infected maxillary cyst, but it was annotated more as a last dreadful consequence of dental caries rather than an interesting pathological entity in itself. In 1778 three cases were described by Jourdain which appear to have been dentigerous cysts, but it was many years later that the term " dentigerous cyst " was suggested by Paget in 1853. Between 1860 and 1873 Magitot described many cases of cysts of dental origin, and an Englishman, A. W. Baker, in 1891 produced the first important monograph on their pathology, but the term dentigerous cyst still was used for all cysts of supposedly dental origin. Further discussion of their pathology took place in 1892 by Partsch, who became famous for his rational approach to treatment, more particularly that treatment by permanent decompression.

Although the dental epithelial rests were fully described by Malassez in 1885, who also intimated that they could be associated with cyst formation, it was not until 1898 that J. G. Turner produced his memorable research upon the granulomata which are associated with the roots of pulpless teeth, demonstrating the high incidence of proliferating epithelium within these lesions. He termed them " epithelial root tumours " and showed that many were the immediate predecessors of what we now term the apical or dental cyst. Research upon the derivation and nature of cystic epithelium was carried out by James and Counsell in 1926, and in 1930 Hill published a valuable investigation into the histology of apical cyst. However, the first classic experimental work into intra-cystic pressures was published in 1926 by Warwick James (with whom I had the privilege of discussing the subject of this lecture 18 months ago in this College), and this drew attention to the fact that at the stage of actual cyst formation certain factors may be introduced which will influence its growth more than those which originally effected its genesis.

INTRODUCTION

The present work is based upon clinical, histological and experimental studies over a number of years and involving a study of 300 cysts, and has

been directed towards finding a classification of cystic lesions based upon their origin rather than upon simple clinical and radiographic description. For the purpose of a broad survey of the material which has been studied, and in order to provide a type of epidemiology of epithelial cysts of the jaws, the lesions have been classified in this table (Table I) according to their provisional diagnosis at time of operation, but considerations raised by the present studies may necessitate an adjustment of certain classifications. I shall make no attempt here to describe each clinical type of cyst, but an endeavour will be made to study the nature of cyst formation in general and to relate it to the main types.

TABLE I

THREE HUNDRED CYSTS OF THE JAWS AS DIAGNOSED AT TIME OF OPERATION

Dental	*Dentigerous*	*Lateral periodontal*	*Primordial*	*Naso-palatine*	*Lateral fissural*	*Naso-labial*
202	52	5	18	17	5	1

For many years there has been considerable discussion as to whether an epithelial cyst occurs firstly as a connective tissue cavity which becomes secondarily lined by epithelium or whether the lesion arises as a primary intra-epithelial breakdown.

To illustrate the first concept I shall quote the experimental work of Powell-White (1910), who conducted a series of experiments during the course of investigation into the effects of the introduction of fatty acids and their esters into the tissues of rabbits. He found that sterile abscesses resulted from the subdermal introduction of oleic acid. If these abscesses came into chance contact with any epidermal structure such as a hair follicle, or deep rete peg, a rapid epithelialization of the cavity invariably resulted. In 1933, Ledingham performed a series of experiments to induce subcutaneous abscesses in guinea pigs with bacterial suspensions and he found that they rapidly lined with epithelium if contact was made with an epithelial structure at any point. Counsell's (1932) work suggested that chronic apical abscesses may sometimes become lined with epithelium from the overlying mucosa, via a sinus track.

On the other hand an experimental illustration of intra-epithelial cyst formation is provided by the formation of small cysts which form when autogenous skin is deliberately buried within the mesoderm. Peer and Paddock (1937) placed autogenous skin grafts subcutaneously in humans and recovered specimens at intervals up to one year; those recovered early displayed microscopic cysts, but all sections from later specimens showed no epithelium at all. Surgical experience in the human suggests that such cysts tend to disappear spontaneously (Mair, 1945). It was observed by Harkins (1945) from the results of his use of buried cutis for hernial repair that clinically significant cysts do not develop. More recent work carried out in this field by Thompson (1960) confirmed these findings.

RELATED RESEARCHES

There is certainly a process, which at least is known to occur in embryonic life, whereby unwanted enclaved epithelium is suppressed or disposed of. Most epithelial remnants from junctions of embryonic epithelial processes disappear, and only the inert, but apparently still vital, epithelial rests are left in the mesoderm. In the adult mammal, suppression of the epithelium from the sheath of Hertwig after it has done its dentoformative work is well known (the rests of Malassez), and the reduced enamel epithelium surrounding the crown of an unerupted tooth is another example. What type of vitality these cells exhibit has been uncertain, as obviously they do not undergo a life-cycle comparable with a normal epithelial cell. However, Ten Cate's (1965) recent work on the histochemistry of oral epithelial cells very elegantly demonstrates that these rests are dormant, employing an intra-cellular chemical process called the " Pentose shunt " for low energy glycolysis. Thus they would appear to be fully vital cells, many with a life-cycle as long as the remaining life of the individual and probably resting indefinitely in a pre-mitotic phase, never (ordinarily) undergoing division. The cause of the suppressed activity of unwanted cells is likely to be found in the organizers of the genetic system.

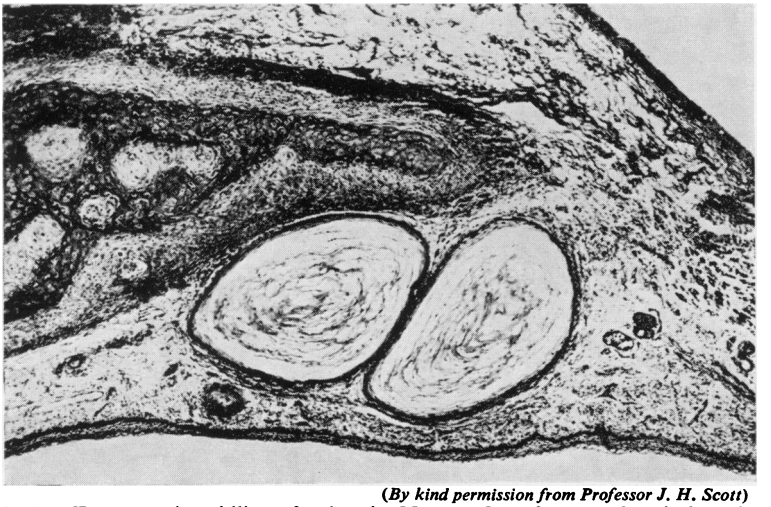
It seems that genetic suppression of epithelial rests is often delayed, as J. H. Scott (1955) demonstrated in a very significant research on human foetal material (Fig. 1). This work showed the very frequent, and probably invariable, occurrence of small epithelial cysts in mid-foetal life around the oral cavity in places where epithelial rests occur along the junction lines of embryological processes of the face. There seems to be no doubt at all that these little cysts are due to continued epithelial growth after inclusion within the mesoderm. It would appear that they have all disappeared soon after birth, and so these whole cystic units must be suppressed and absorbed in the vast majority, and only a minute number of them possibly remaining later to give rise to mature cysts of inclusive origin. Such a case could be the example quoted by Rushton (1930) as a midline palatine cyst or that of Choukas (1957).

These foetal cysts constantly show complete epithelial linings with every evidence that the contained epithelial cells have undergone a full life-cycle, ending with their desquamation filling the cyst lumen, rather like " epithelial pearls " of increasing size. It is likely that the so-called " glands of Serres " which occur in the alveolar gums of the newly born represent a comparable phenomenon. This keratinous desquamation is a notable feature in some adult oral cysts of developmental type.

It is fascinating to consider that possibly every person in this hall to-day had, at some period of development, a few small epithelial inclusion cysts about the jaws which subsequently, I earnestly hope, showed spontaneous involution and disappearance.

EXPERIMENTAL

Mr. Noel Thompson has generously provided me with histological material from his studies of buried dermis grafts in order that I could examine the life-history of cysts which may be formed in such procedures. Thus, epidermoid cysts can be recognized within one week of the burial of skin elements into human connective tissue, with early epithelial activity. At three weeks the cysts appear to be approaching their maximum size, normally not more than 1 to 2 mm. in diameter, and at six weeks there are signs of epithelial inactivity and no increase in size of the cysts can



(By kind permission from Professor J. H. Scott)

Fig. 1. Two cysts in midline of palate in 85 mm. C.R. foetus. Saggital section. ×50.

be observed (Fig. 2). At three months some epithelial activity still remains in certain cysts, but at other sites the cysts, which have not further increased in size, are showing distinct signs of intra-epithelial degeneration with failure of luminal keratinization. At five months all whole cystic units are showing thinned and degenerate epithelia, with surrounding fibrosis. At nine months the individual epithelial cells of the lining are not easily recognizable. At 12 months little epithelium can be found, although the cysts can be identified as collections of keratinous desquamation surrounded by foreign-body giant cells. At 18 months most cysts have lost all epithelial residues, and only the giant-cell lined spaces remain. The cysts are obviously showing involution and dispersing, and it is well to study the mechanism of their regression.

We know that orderly and regulated degeneration of epithelial cells plays a definite role in the formative stages of embryonic organs, but it is not known whether the same mechanisms are here employed, as the one type is under direct genetic control, while the other may be concerned with a positive rejection mechanism.

While the early experimental epidermoid cysts show marked histological similarity with very small developmental cysts of the jaws in the adult, this comparison becomes progressively less marked with time until the experimental cyst shows only signs of regression with lack of activity and with obvious signs of epithelial degeneration, while the true adult developmental cyst never seems to lose the primary attribute of continuing and positive epithelial maturation. However, I should like to draw attention to the close similarity in appearance, size and life-history of these experimentally, or rather artificially, produced lesions in the human with Scott's

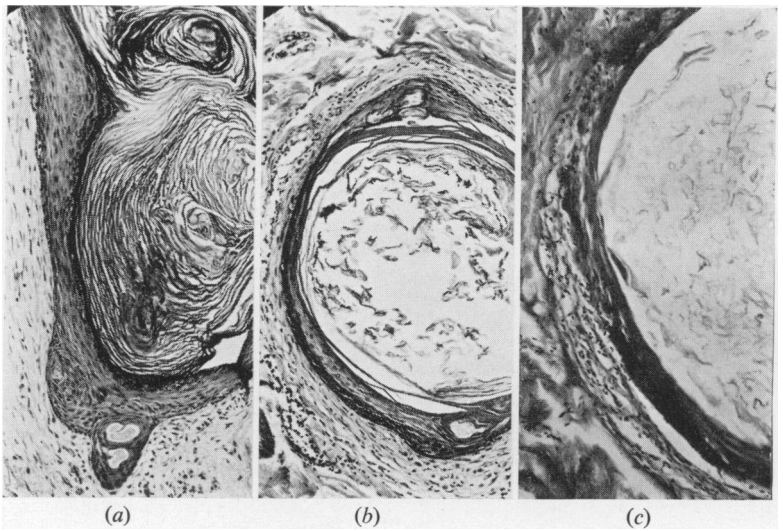


Fig. 2. Epidermoid cysts following burial of autogenous skin in the human. ×66. (*a*) At two weeks, active epithelium producing keratinous desquamation in cavity. (*b*) At six weeks, diminishing epithelial activity, commencement of surrounding fibrosis. (*c*) At 15 months epithelial cells are ill-defined and lesion becoming surrounded by giant cells. Failure of luminal keratinization.

foetal examples. Indeed, we might speculate what will happen if the suppression mechanism fails.

It is widely held that there occurs a fairly specific type of epithelial lining in a group of cysts of the jaws which have the general criteria of primordial cysts (Kramer, 1957). The basal cells of this kind of epithelium is characteristically columnar, the overlying stratum spinosum being only a few cells thick and often showing vacuolation, and surmounted by a layer of flattened cells showing parakeratosis or frank keratinization (Fig. 3). This epithelial sheet is thin, even, lacking rete pegs and unbroken.

By contrast, the characteristic lining to be found in apical and many dentigerous cysts has poorly differentiated epithelium, often with great variations in the same cyst. There is practically never any tendency to

keratinize nor to shed squames into the lumen, and the continuity of the epithelial sheet may be broken in places.

In a previous paper (Toller, 1966*a*) attention has been drawn to the occurrence of significant epithelial discontinuities in the walls of about one-third of clinically uninfected dental and dentigerous cysts. Partial absence of epithelium is observed in many cysts in which there is every reason to believe that growth is active (Fig. 4), and its significance has to be

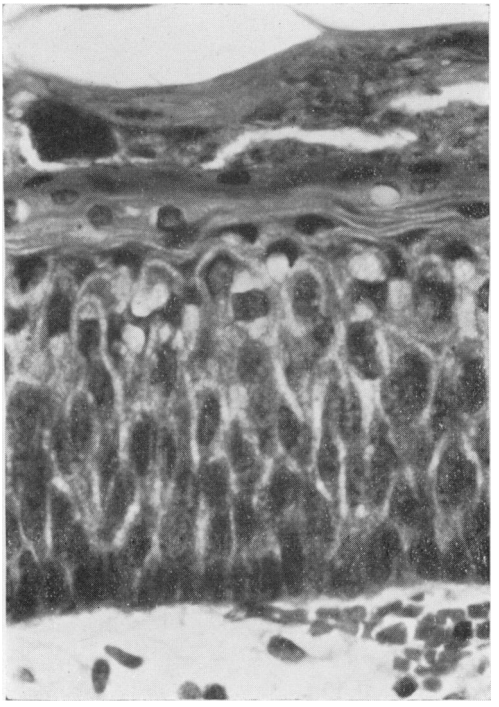


Fig. 3. High-power photomicrograph of the epithelial layer in an odontogenic keratinizing cyst. Well differentiated palisade layer of basal cells with clear stratification up to the desquamation at the surface of the cyst cavity. ×312.

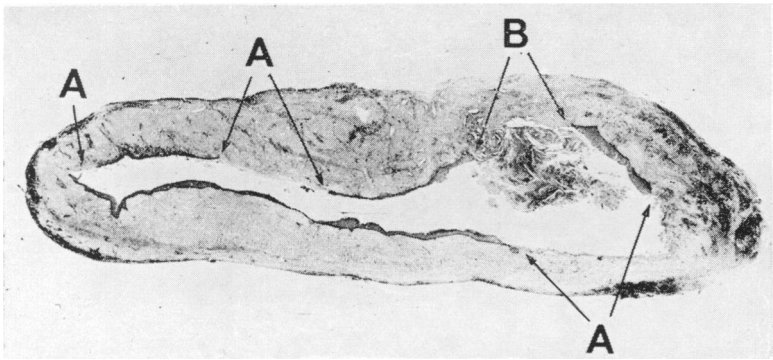
viewed against the relative permeabilities of these walls when a complete lining of epithelium is present or not, and whether significant local osmotic imbalances are present.

Radio-active tracer experiments

Owing to this observed inconstant behaviour of epithelium in dental cysts some experiments were devised to investigate certain biophysical features in these cases, particularly as the permeability of cyst walls in the undisturbed state was not known.

Firstly, a number of *in vivo* dialysis experiments (Toller, 1966*b*) were carried out in which the entire fluid was evacuated from a cyst cavity and replaced with an isotonic saline solution containing known amounts of both a radio-active crystalloid (in the form of 24NaCl) and a radioactive colloid (human serum albumen tagged with I^{131}). By means of a scintillation counter placed at intervals of time over the lesion, it was possible very accurately to study the rates of diffusion of both these substances concurrently, during the same periods of observation, and through the intact cyst walls before operation.

It was shown that the diffusion rate of the crystalloid was fairly rapid in every case but that the colloid tended to be retained (Fig. 5), whether the cyst wall was shown later by histology to be completely lined by epithelium or not.



(*By permission from the Editor of the* British Dental Journal)

Fig. 4. Section through whole mature apical cyst showing simple epithelial discontinuities at *A*, and mural cholesterol nodule at *B*, which is breaking through into the cyst cavity. Great variations in thickness of epithelial layer with failure to cover connective tissue wall in places. ×7½.

The semi-permeable properties of cyst walls *in vivo* seemed to be adequately confirmed by these experiments, since by definition a semi-permeable membrane will pass a crystalloid freely while restraining the passage of a colloid.

The principle of lymphatic access

These observations led me to believe what may indeed be a fundamental concept in the occurrence of cysts of any type, anywhere in the body. Namely, that all closed physiological cavities are in communication with the lymphatic system which regulates their fluid balance (the central nervous system having a different arrangement), but any cavity in the body which becomes separated from lymphatic access, such as a cyst cavity, may be subject to an osmotic imbalance with the surrounding tissues and may be liable to alteration in size due to pressure differences.

This principle seems directly applicable to the observed life-history of

certain intra-cranial haematomata. There is no lymphatic system in the brain and central nervous system exactly comparable with other parts of the body, but if the Virschow-Robins channels in the brain should become occluded by simple hydrostatic pressure of an intra-cranial haematoma, then it would be understandable if conditions for cyst formation should

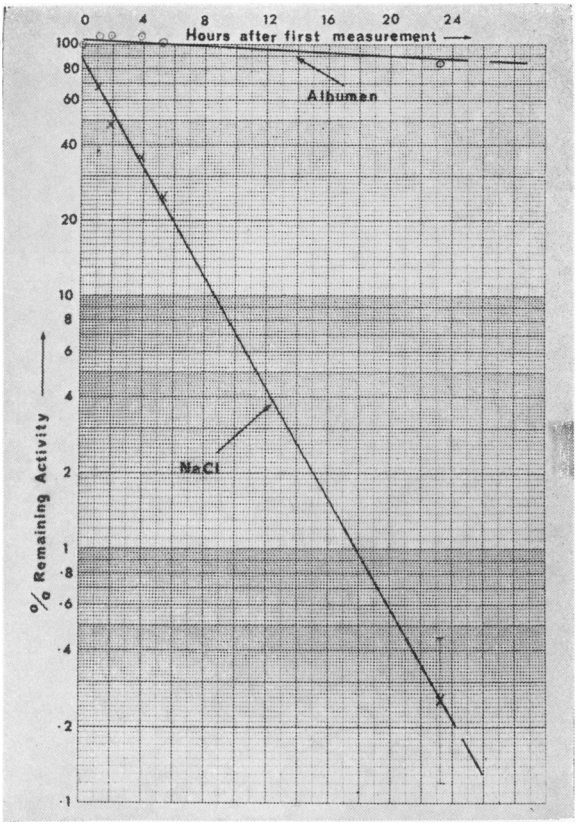


Fig. 5. Graphs obtained from double tracer experiment showing concurrent rates of diffusion of radio-iodated albumen (colloid) and radio-active sodium chloride (crystalloid) from within the lumen of a dental cyst *in vivo*. The very high rate of diffusion of crystalloid is to be compared with the slow diffusion of the albumen (molecular size 69,000).

exist upon the simple liquefaction of the clot with lysis of its red cells. This lysis of red cells can be shown after 24 hours to have raised the total osmotic pressure of such a clot. In 1932 Gardner found increasing osmotic tensions in the contents of aspirated sub-dural haematomata and this was later confirmed by Munro (1938). Such a clot would tend to increase in size by reason of osmosis if the Virschow channels remained occluded around its limits, since there would therefore be no lymphatic

mechanism for rapid removal of locally increased numbers of large molecules.

A further recently observed application of this principle may be found in a case where a sarcoma of the leg was irradiated. After radiotherapy the tumour continued to increase in size, so the leg was amputated. Morbid examination of the tumour site showed only dead tumour cells surrounding a large collection of fluid which was causing the late expansion of the area. The leg might possibly have been saved had this been known. Also, carcinomatous neck glands are known temporarily to increase in size after irradiation, possibly for the same reason, and after the malignant cells have become inactive.

A shorter formulation of this principle of lymphatic access may be expressed thus: If a region in the tissues should for any reason become isolated from lymphatic access, irrespective of whether the barrier be epithelial or not, then the condition for cyst formation exists.

It was pointed out to me by Professor Lucas that this hypothesis should be capable of objective verification, and accordingly a collateral and harmless *in vivo* experiment was devised. A certain large-moleculed dye (Patent Blue; Kinmonth, 1954) has for some years been used by my colleagues to inject into the tissues of the leg in order to identify the lymphatics during later dissection in the procedure for lymphangiography. An 11 per cent. sterile isotonic aqueous solution of this dye was introduced into seven cysts of the jaws, after aspiration, and at operation up to 24 hours afterward the dye was found to be retained within the cysts, and it was not possible to identify any of the dye in the adjacent tissues (Toller, 1966*b*). It appeared that no dye entered the lymphatics from the lumen of the cysts, and the isolation of the cyst cavities from the lymphatics seemed to be confirmed.

Vapour pressure experiments

Secondly, experiments were devised in conjunction with the isotope diffusion investigations so that a very accurate measurement of the osmotic tensions of cyst fluids could be ascertained (Toller, 1966*c*). This was done by the author's modification of Hill's thermo-electric method for comparing vapour pressures of biological fluids. It is known that the osmotic pressure of a fluid is a function of the number of particles in that solution, and by the same law, Vant Hoff's Principle, the vapour pressure of a fluid is directly related to that number. Thus, the differential rates of evaporation of fluids, which are dependent upon their vapour pressures, are related to their osmotic pressures. The rates of evaporation of two fluids can be directly compared by applying a drop of each fluid to two thermocouples. The difference in rates of evaporation of each fluid will cause a temperature difference on each thermocouple and this can be made to appear as a galvanometer deflection.

In the seven cases studied also by the radio-active tracer experiments, all fluids were found to be hypertonic to the patients' blood.

In a further series of fluids from 31 cysts of various types, 21 were significantly hypertonic and 9 were isotonic with the patients' blood plasma. Significant differences in tonicity did not appear to be related to the type or size of cyst, but there is an indication that thick cyst contents are either isotonic or nearly so.

ELECTROPHORESIS OF CYST FLUIDS

Since osmotic phenomena are necessarily related to the size and distribution of particles in solution, it seemed logical to investigate the nature of substances to be found in cyst fluids, particularly with regard to the nature of the proteins and their molecular sizes.

Electrophoresis of cyst fluids (Toller, 1966*d*) reveals that the general pattern of fluid from apical and dentigerous cysts regularly shows less of the larger protein molecules than the patients' own sera (Fig. 6*b*). The largest molecules (alpha-globulins) are either absent or present in very small amounts, while albumen which has a relatively small molecule is present in amounts comparable with blood plasma.

Thus demonstrated, the origin of the majority of cyst fluid proteins would appear to derive from without, the cyst wall acting as a dialysing membrane restraining the proteins selectively according to their molecular sizes. These findings both support and are supported by the results of the radio-active tracer experiments. The majority of cyst fluid could thus be termed a simple dialysate.

A further important finding of these investigations was the lack of all soluble proteins in fluids from keratinizing cysts (Fig. 6*c*). This is of clinical importance as it enables the fluids from this type of cyst, which present a special challenge to oral surgeons, to be readily distinguished before operation by simple electrophoretic analysis, the facilities for which are in most general pathological laboratories. This phenomenon of their extraordinarily low soluble protein content would again seem to be directly related to the extremely impermeable qualities of the typical keratinizing epithelial membrane which effectively prevents centripetal diffusion of serum proteins into the cyst fluid.

However, there seems to be an exception to every good rule, and it has been found that an appreciably large number of fluids from uninfected dental and primary dentigerous cysts, while displaying the same general background proportions of proteins, have the gamma-globulin fraction greatly increased above that found in the patients' own blood sera (Fig. 6*d*). The circumstances are such that a local or even intracystic production of this type of globulin seems likely. Recent work has shown that the three basic types of human immuno-globulins are present, and that they are immunologically reactive. Furthermore, I have recently

drawn attention to the presence of large numbers of plasma cell aggregates, or lymphoid nodules (Fig. 7), in the walls of those uninfected cysts showing raised gamma-globulin fractions. In 1957 Gorlin drew attention to lymphoid patches with actual germinal centres in the walls of 2 per cent of his series of dentigerous cysts. It is now generally accepted that human immuno-globulins are produced by plasma cells and their precursors.

Very recent investigations (yet unpublished) using immuno-fluorescent techniques at the Canadian Red Cross Hospital, Taplow, have provided evidence to suggest that the plasma cells which are found in the cyst walls are likely to be producing these antibody globulins.

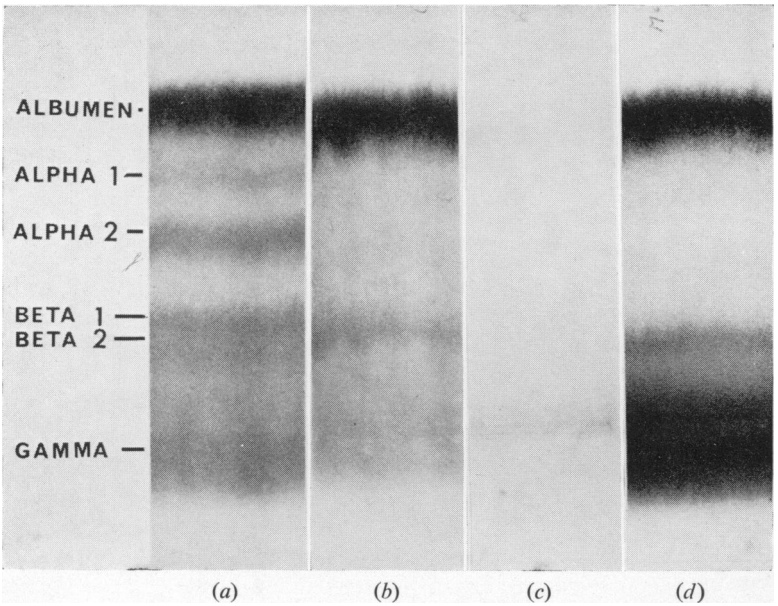


Fig. 6. Electrophoretic strips showing broad separation of proteins. (*a*) Blood serum. (*b*) Typical dental cyst fluid. Reduction or absence of the larger moleculed proteins. (*c*) Keratinizing cyst fluid. Absence of all soluble proteins. (*d*) A dental cyst fluid showing very high gamma-globulin fraction.

In the absence of infection, an antibody might be evoked by an antigenic property of the buried epithelium or its products. It is tempting here to suggest that the gamma-globulin might represent an auto-immune response to ectodermal protein, and that we are observing the mechanism whereby the body is attempting to eliminate the lesion, which in a sense is a collection of occult and active epithelium growing entirely out of context. Whatever are the biological processes which are brought into play, there may well exist a mechanism in our bodies for rejecting ectodermal protein, such as keratin, from a mesodermal context. In the normal state, one of the very functions of the basement membrane of the epithelial cells of our

skin may be to maintain isolation between mesoderm and ectodermic protein. It is possible that a failure of this function is observed in cancer.

Dr. T. Melcher, in the Department of Dental Science at this College, has recently published a valuable study concerning the ultra-structure of the basement membrane (Melcher, 1965). Its possible function as a protein-separating medium may well be of interest in the study of reactions to cyst contents.

Implanted benign epithelial cells tend to proliferate and arrange themselves into an essentially cystic formation, rather like a unit of Roman soldiers with all their interlocking shields facing outward to protect the

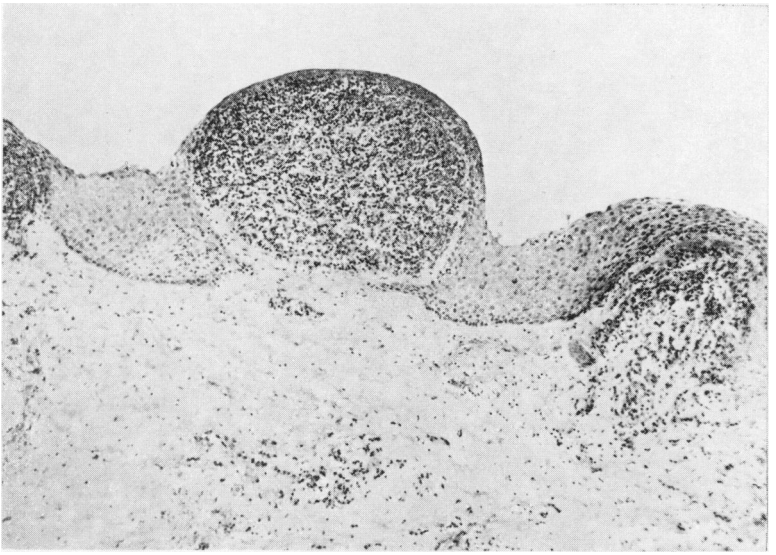


Fig. 7. Inflammatory nodules in wall of clinically uninfected residual dental cyst. The cells contain a high population of plasmacytes. ×80.

centre from attack. This can be termed an histologically rational situation, presumably deriving from the inherent polarity of epithelial basement cells.

In 1930, Hill demonstrated the occurrence of polymorphonuclear cells within the epithelial strands in apical granulomata, and he noted that their occurrence increased as the masses of epithelium became greater. James and Counsell (1932) point out that this intra-epithelial infiltration is noticeable even when the signs of obvious inflammation are absent in the adjacent tissue. Recently, Shear (1963) drew further attention to these facts and gave figures to show that the polymorphs are especially numerous in actively proliferating epithelium in very early cysts, while more or less absent within the epithelium of mature cysts, and he concludes that their presence is related to the factors causing the activation of epithelium.

However, from their position it could seem reasonable to suggest that these well-known phagocytic cells are concerned in a process whereby the epithelium is being actively destroyed by the body in its attempt to dispose of a tissue growing out of its proper habitat. This could be related to the evident fact that very few apical granulomata, nearly all of which contain epithelium (Turner, 1898; Hill, 1930), ever develop into dental cysts after extraction of the tooth.

It is possible that Ten Cate's recent work (1965) on the histochemistry of buried dental epithelium might be applied to attempt to reveal the intracellular state of lysosomes in such cells or indeed other metabolic activities. The demonstration of certain lysosome activity in these epithelial cells might well indicate whether any were in a state of being actively suppressed or destroyed, since a certain state of these organelles is known to be associated with cell involution or death, as, for instance, has been found in the orderly degeneration of cells in the disappearing tail of a tadpole or in the skin between the developing digits in the embryo.

Once an epithelial cell had found its way on to a free surface and proliferated, then a histologically rational situation would be present for it and its destruction would become unnecessary.

However, it is not yet clear why the epithelium in the dental cyst should continue to grow, albeit rather indolently, while the implanted epithelium of an experimentally induced cyst fails after a few months. It even seems possible that the hydrostatic pressure in the former tends to produce a reactionary proliferation, the stimulus being physical rather than chemical. We all know that cysts of all types regress after exteriorization and permanent decompression.

If, in a granuloma, the epithelium grows to form a complete surface of a cavity, either (1) by a primary breakdown of centrally placed cells in a large epithelial mass or (2) by spreading sideways to line the inside surface of a chronic abscess cavity, its differentiation becomes more complete and a histologically rational situation develops with the epithelium on a surface, after which the defensive or absorptive mechanism gradually subsides. If the rate of epithelial growth exceeds any antagonistic process and the central area becomes isolated from lymphatic access, then a cystic process based upon an osmotic disequilibrium (Toller, 1948) could become initiated, which would then be independent of the original infective process.

BASIC DIFFERENCES

Simple poorly differentiated epithelium, such as is found in apical or primary dentigerous cysts, breaks down centrally by true lysis of its cell components into a liquid or semi-liquid mass, resulting in an osmotic imbalance. Keratinizing epithelium does not, and here each epithelial cell matures to form an insoluble squame, its cell fluid being thrown off as a

protein-free liquid unlikely immediately to contribute to an osmotic imbalance. Figure 8 shows a small daughter cyst developing in the wall of a large primordial cyst; the mass at its centre has certainly not liquefied but appears simply to be in its final desquamatory state as would be expected by the completion of a normal life-cycle of such cells if they had been on a free surface.

The buried dermis graft investigations suggest that normal skin does not indefinitely continue to proliferate within a mesodermal context in the absence of osmotic imbalance. If a rather solid type of lesion lined by such keratinizing epithelium is shown to be increasing in size, then an abnormal epithelial proliferation is implicit.

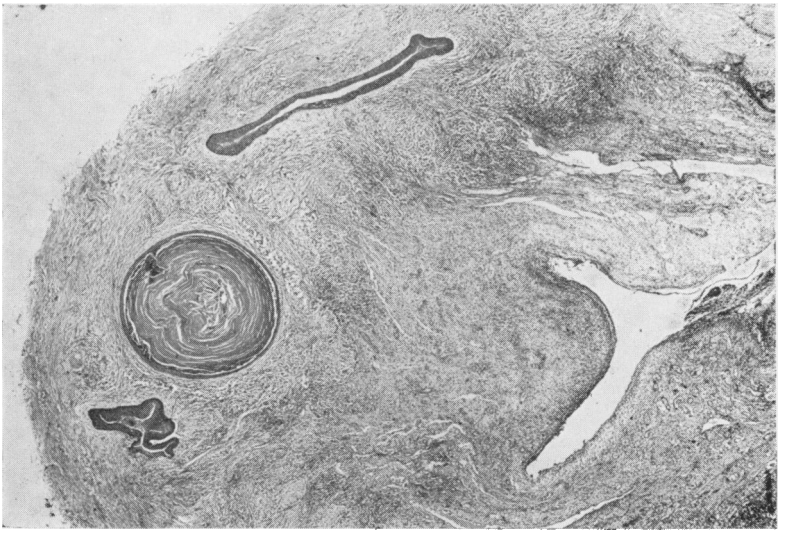


Fig. 8. Daughter cysts in wall of large primordial cyst. The main cyst cavity is at the right, and one of the small cysts is full of keratinous desquamation. ×33.

Ten Cate (1963) has very convincingly demonstrated, by his histochemical experiments, that the keratinizing response is an active one, and does not represent a degenerative change. Indeed, his recent work in this field demonstrates a strikingly different acid phosphatase activity in the superficial cells from a keratinizing cyst compared with a non-keratinizing cyst epithelium, which tends to verify these basic differences. This work was confirmed by Lutz *et al.* in 1965. This fact must surely have a very significant bearing upon the relative clinical behaviour of keratinizing and non-keratinizing cysts.

There thus appears to be a fundamental distinction between two types of cystic origins. In the one case there is true liquefaction of central cells, but not necessarily epithelial cells, which may occur in apical granuloma

and which can be said to be a degenerative process likely to be followed by a simple osmotic expansion. In the other case, there is a simple spontaneous proliferation and maturation of buried epithelial cells giving rise to cell nest formation of increasing size (Fig. 9). This process would appear to be associated with many cysts of developmental origin and may be seen most clearly in the so-called primordial cyst of the jaws. It is very important to note that the latter type of cyst seems invariably to display a keratinizing or parakeratinizing epithelium. Keratosis is not typically observed in apical cysts.

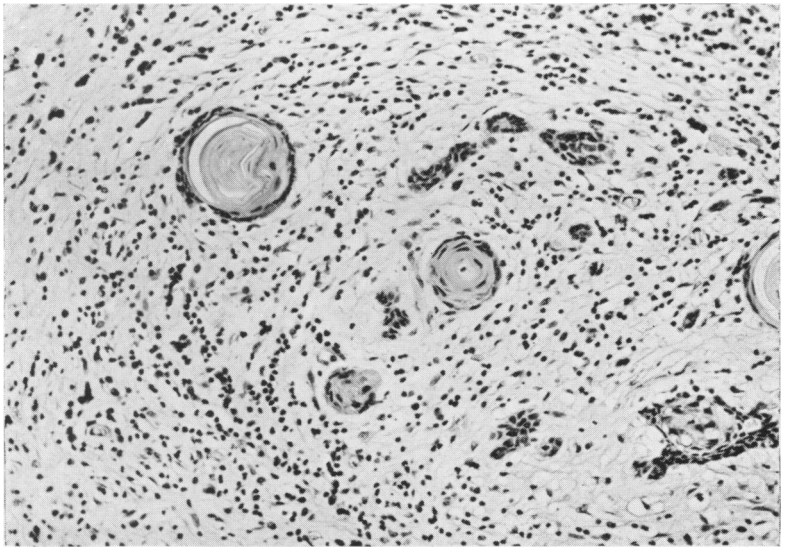


Fig. 9. Portion of connective tissue wall of an odontogenic keratocyst (primordial cyst) showing stages of intra-epithelial micro-cyst formation in the active mural epithelial strands. ×120.

There is no evidence to suggest that infection, nor any other known factor, can change a simple type of epithelium in a cyst into a keratinizing type. All recurrent cysts which I have examined histologically have recurred with the same epithelial type as was present in the original lesion whether infected or not (recurrent and previous histology examined in 14 cases).

THE APICAL CYST

While not disagreeing with the possible origin of *some* cysts in a primary epithelial breakdown, it is therefore possible to put forward the following brief description of a manner in which an apical cyst may arise and grow:

A chronic apical abscess implies a collection of dead and dying cells in the centre of a granuloma associated with a dead tooth. That granuloma often lies in an area where there exist epithelial rests, and these rests may

be aroused from their dormant condition and stimulated to proliferate along with other tissues. If an active epithelial cell finds itself on the surface of the abscess cavity it will display its natural tendency to spread over a raw surface. If the epithelium is not destroyed by the infection, or by foreign-body reaction, and succeeds in covering the entire raw surface, the mass of dead and dying tissue constituting the core of the abscess will be isolated from the tissue spaces and lymphatic drainage.

If the osmotic tension of the degenerate central area is above that of the surrounding tissues (by reason of the process of degeneration liberating more and simpler molecules than the original complex proteins) and if the infection is of such an order that an acute condition (due to complete lack of drainage) does not supervene, then fluid will be drawn into the area to attempt to bring about osmotic equilibrium. This raises the internal pressure, with a resultant slight outward pressure on the adjacent tissues. If this is above capillary pressure, the immediately adjacent capillaries are compressed. This may produce a local ischaemia, which in turn brings about further degeneration of centrally placed cells and other cells in the wall submitted to the pressure effects. The process perpetuates itself provided that the cyst wall as a whole remains a semi-permeable membrane. For this last condition to be satisfied it seems that the cells do not necessarily have to be epithelial, as this has been demonstrated by the radioactive tracer experiments. Consequently, a cyst may continue to grow whether it is entirely lined with epithelial cells or not. A complete lining of epithelial cells may, however, be necessary at the *commencement* of cyst formation to enable the original abscess contents to be walled off by the relatively greater impermeability of the epithelium, and the fact that lymphatic exchange cannot take place across an intact integument. At a later stage the layer of pressure-atrophied connective tissue itself may constitute a semi-permeable membrane.

It will be seen that an operation for the removal of the lining, or for the simple opening to the surface of the lumen of the cavity, provided that the opening is kept patent, will bring about a cure for the condition. Alternatively, the introduction of a substance which would bring about the destruction of the lining and/or allow lymphatic access to the cavity, and so render the maintenance of a raised osmotic pressure impossible, might conceivably bring about a cure. This may be the mechanism whereby haemorrhagic cysts all resolve following practically any surgical interference of any type. The occasionally observed spontaneous resolution of a cystic condition may follow the access of lymphatic drainage to the lumen following infection or trauma.

DENTIGEROUS CYSTS

A dentigerous cyst is an epithelial-lined cyst which involves the crown of an unerupted tooth in its cavity.

The term " dentigerous cyst " is an imprecise definition of a clinical

condition, and it only implies a certain physical relationship of tooth to cyst, and unfortunately gives no indication as to the true nature of such a cyst, whether its derivation is infective, degenerative, developmental or neoplastic.

The decision whether or not to surgically remove a buried tooth frequently faces the dental surgeon, and one of the facts we should like to know is the likelihood of a buried tooth giving rise to a dentigerous cyst if left within the jaw. This is not at all easy to answer. Over a two-year period at a hospital I have recently studied case-notes of 508 patients involving 1,452 buried teeth. They have been simply classified in three age groups as set out in Table II. The number of cases attending for treatment of confirmed dentigerous cyst from the same population and period is put on the same table. As can be seen, approximately one

TABLE II

Cases involving buried teeth (2-year period)			508
Total buried teeth examined with X-rays			1,452
Age	*Under 20 years*	*20–30 years*	*Over 30 years*
	330	827	295
Non-keratinizing dentigerous cysts in same population and period			
	1	3	6

dentigerous cyst was treated for every 150 buried teeth examined. The figures are far too small, and there are too many variables, to be able to suggest that one in 150 buried teeth may form a dentigerous cyst. Whereas most dentigerous cysts might have been referred to the hospital, certainly a much larger number of buried teeth were not so referred, but it may serve to draw attention to what is at risk.

In 1964 Mourshed studied a random population of 1,315 cases with reference to Stafne's statement that radiographic images of the pericoronal space of width greater than 2.5 mm. tended to show well-defined epithelial crypts which might possibly be pre-cystic. Eight out of 304 cases of buried teeth showed such dilated crypts, but only one of these was an adult in a total of 146 adult cases. This shows a curiously close correspondence to the figure I have just quoted.

It has been suggested (Thoma, 1960) that dentigerous cysts originated by a degeneration of the stellate reticulum of the enamel organ, the central type originating over the axis of the crown, the lateral type presumably starting a little later in the crown development. However, it has long been observed that teeth contained within a dentigerous cyst generally do not suffer from abnormalities of enamel.

It has been demonstrated that enamel calcification can only take place after the stellate reticulum has condensed with the fusion of the external and internal enamel epithelial layers to form the enamel epithelium. In other words, at the site of commencing calcification of the enamel of the

tooth there is no stellate reticulum whatever, and dentigerous cyst formation can only take place after the enamel epithelium has been formed. In fact, if the full thickness of enamel is always found on the contained teeth then the origin of a cyst at this site must be either by a proliferation and later cystic breakdown of the peripheral cells of this reduced enamel epithelium, or by a primary separation of this membrane from the surface of the enamel by a collection of fluid between it and the bare enamel surface, or by the involvement of the crown of a buried tooth by an adjacent cyst.

The peripheral cells of the reduced enamel epithelium in an unerupted tooth appear to be vital but quite dormant. They are therefore to be regarded as rather a special group of epithelial rests, consisting of an intact reticulum of cells which have an indeterminately prolonged life. If for any reason such a resting cell should awake from its quiescent state and undergo a normal life-cycle, it will ultimately mature or degenerate at a point close to the enamel of the buried tooth, which might therefore give rise exactly to the necessary conditions to form a microcyst.

A manner by which an epithelial rest can become active is by a failure, for unknown reasons, of the genetic inhibiting mechanism. This could account for the infrequently observed cases of multiple dentigerous cysts at various parts of the mouth (Rushton, 1941; MacGregor, 1945). It is not without interest to note that many of these cases are also associated with multiple epithelial tumours of the skin (Gorlin *et al.*, 1963), but the cysts in these cases may not primarily be follicular in nature.

A further important fact remains to be considered, great epithelial activity can sometimes be found in relation to the crowns of buried teeth, such as around this buried canine from a man aged 30 (Fig. 10). At this age the whole tooth is long completed and a more usual appearance of the crypt of a buried tooth is of a thin layer of inactive reduced enamel epithelium. Since all its cells are presumed to be fixed in the premitotic stage as rests then there is no reason for them to become active should they be left, for instance at operation for removal of the buried tooth. (This would obviously be supported by the many operations we perform on buried teeth in which the crypt may not be completely removed, but with no subsequent sign of epithelial proliferation or cyst formation.) However, it is conceivable that excessive cellular activity is associated with an abortive attempt to erupt. Thus, the mechanism of attempted eruption could be associated with dentigerous cyst formation. Ten Cate's histochemical studies have confirmed (1963) the suggestion of Weinman *et al.* (1945) that the presence of an active epithelial covering of the crown is necessary to bring about dissolution of the overlying connective tissue during eruption of a tooth. In the case of an impeded eruption it is conceivable that this epithelial activity could result in epithelial whorls and intra-epithelial cystic breakdown. Here is illustrated an example of a

minute cyst or epithelial cell-nest associated with this same buried canine tooth, and the epithelium appears to be simple stratified squamous type.

Primary dentigerous cyst or follicular cyst

Using the refined double embedding histological technique of Brain (1949), in the present series, 13 out of 15 involved crowns revealed the presence of Nasmyth's membrane. This suggests that it is most unlikely that the lesion originates by the appearance of fluid between the bare enamel surface and the tooth follicle, as was suggested by Lartschneider in 1929.

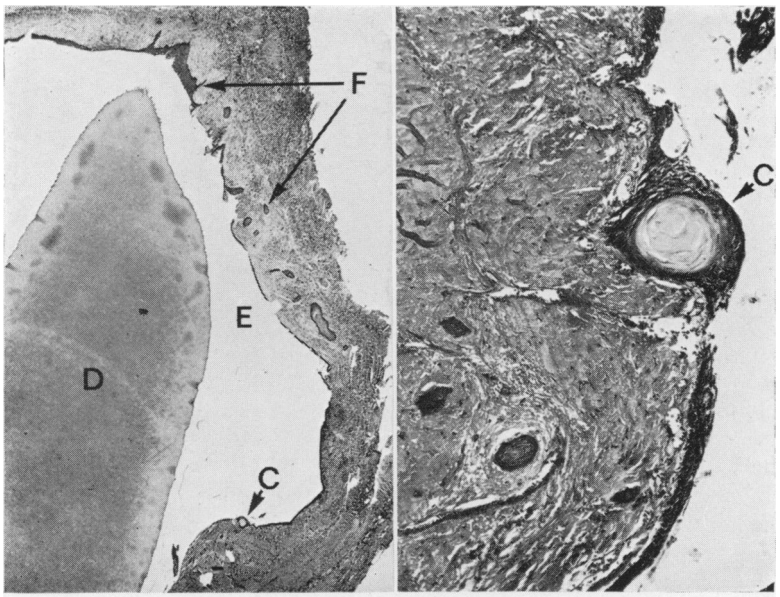


Fig. 10. (*a*) Low power photomicrograph of a buried canine tooth removed from the palate of a man aged 30 years. There is activity in the epithelial layer of the follicle (F) outside the space left by enamel (E). At C there appears to be a very early cyst formation. ×7½. (*b*) Higher magnification of microcyst (C). This may be an early dentigerous (follicular) cyst. ×75.

In a very small dentigerous cyst it is simple to demonstrate the follicular remnant, sometimes with a cellular layer intact, upon the entire enamel surface within the cavity, and this is strong evidence that the cystic origin appeared in the periphery of the elements comprising the follicle.

Should this manner of cyst formation take place outside the alveolus, just prior to eruption, then it is likely that an eruption cyst will result. In a sense, an eruption cyst is an extra-alveolar follicular cyst.

The lesion is often regarded as a dilation of the follicle around a buried tooth, and this is true provided it is remembered that an intra-epithelial

cleavage occurs, some epithelium remaining on the tooth and another layer of epithelium being carried away from it by fluid expansion.

Since this " primary " dentigerous cyst derives from an epithelial remnant which has completed its dento-formative function (comparable with Malassez's rests), then re-activation of this epithelium seems at first to provide a simple non-keratinizing type of epithelial lining, as suggested by Shear (1961). For the same reason the lateral periodontal cyst, associated with a vital tooth, carries the same simple type of epithelium. But other observations do not lend support to this suggestion of cell-type origin.

It has long been observed that both dental and dentigerous cysts, either in the mandible or maxilla, may contain various types of epithelium, stratified squamous, columnar, ciliated or mucus-secreting. Shear (1960) points out that 21 per cent of maxillary and 12 per cent of mandibular cysts of all types display the type of epithelium usually associated with the respiratory passages. Such occurrence in mandibular cysts would suggest local epithelial metaplasia, and indeed authors have been general in the employment of the term " the pluripotential nature of oral epithelium " (Gorlin, 1957).

A very interesting series of experiments was performed by Van Scott in 1961 wherein tiny groups of epithelial cells were transplanted from one type of epithelium (say, arm) to a connective tissue bed adjacent to a different epithelial type (say, mouth). The transplants were shown to acquire characteristics resembling those epithelial cells normally resident in the recipient site. This very strongly suggests that the nature of the epithelial cells was determined by the local connective tissue situation, and not by the origin type of the cell—in other words, the morphology of an epithelial cell tends to be stroma-dependent.

Epithelium is a covering tissue possessing no blood supply of its own, and its survival depends upon the supporting stroma, indeed its reaction in some measure depends upon what the stroma provides. In this context it is well to remember the experiments of Fell and Mellanby (1953) in which metaplasia in chick ectoderm was observed in the presence of hypervitaminosis A.

The moderating influence of connective tissue, specific to location, is an effect well known in embryology, and its effects may be one of the determinants of cyst epithelium type.

The finding of an epithelial state in non-keratinizing dentigerous cysts indistinguishable from that in mature apical cysts suggests a similar morphology and mode of growth, and particularly suggests that they derive from a strictly dental epithelial debris as pointed out by Shear and not from epithelium of a primordial or elementary type. Over a series of 100 tests conducted by the author, the average intracystic pressures of apical and dentigerous cysts proved to be so similar that no hydrostatic

pressure distinction was possible between them. The " epithelial attachment " of teeth contained in 10 such dentigerous cysts specially prepared to examine this feature showed no abnormality attributable to unnatural epithelial hypertrophy. The osmotic pressures of eight primary dentigerous cysts has recently been very accurately measured and in six cases was higher than that of the patient's defibrinated blood, and not dissimilar from apical cyst fluids. Neither has the protein content of cyst fluid from these two types of cyst been found to differ in any significant manner, as seen from the electrophoresis of fluids from 20 apical and 10 primary dentigerous cysts. A study of the walls of 45 such cysts revealed the same type and occurrence of discontinuities in their epithelial linings.

It is concluded that the continued growth of non-keratinizing dentigerous cysts, like apical cysts, is by an osmotic pressure expansion, and that in the majority the epithelial proliferation plays a secondary part in the mature state. However, a likely origin of what I term the primary type of dentigerous cyst seems to be concerned with the breakdown of proliferating cells of the follicle following impeded eruption. Indeed there is much merit in using the more precise term " follicular cyst " suggested by Thoma in 1950.

Secondary dentigerous cyst

A further origin must be considered if the earliest lesion in the appearance of dentigerous cysts was simply a commencement of growth, or activation, of epithelial residues of the undifferentiated dental lamina *peripheral* to the enamel organ, say in the gubernacular region between the tooth and the overlying gum, then the activity of these cells might well give rise to primary epithelial masses of which the core or cores would correspond to the final state of such cells if they were on the alveolar surface, namely keratinization, and then the cyst content would be seen to consist of a desquamatory filling like an enlarging epithelial pearl. Such an appearance is constantly found with primordial cysts. It is likely that there are some dentigerous cysts which are primordial in origin with the secondary involvement of the buried tooth. Figure 11 shows a very early cyst in what appears to be the gubernacular region, and the lining is of typical primordial type. If this cyst enlarged in size, it would not require much imagination to conceive the eruption of the tooth into this cyst with the formation of a dentigerous cyst, but with the lining of primordial type.

It is not known exactly how often a dentigerous cyst originates by inclusion of an unerupted tooth in an enlarging primordial cyst (and indeed teeth are sometimes found also in ameloblastoma), but the finding of a keratinized epithelium in many dentigerous cysts suggests that this occurs, possibly to the extent of one-quarter of all such cysts.

In a recent series of 51 dentigerous cysts treated at Mount Vernon Hospital it was found that 13 cases displayed a keratinizing epithelium

(25 per cent). In a report on 200 cases of mandibular dentigerous cysts, Gorlin (1957) noted the occurrence of keratosis or parakeratosis in 64 cysts (32 per cent).

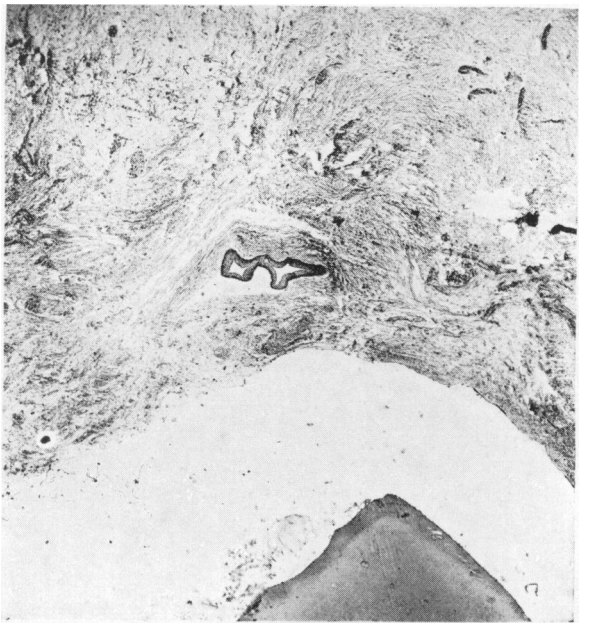


Fig. 11. Buried wisdom tooth and surrounding fibrous tissue from woman aged 24. Practically no epithelium lining the crypt around the enamel (space) can be seen, but an early epithelial cyst (extra-follicular) is present in the tissue toward which the tooth might erupt. The condition would be likely to develop into a keratinized dentigerous cyst. ×16.

NON-ODONTOGENIC CYSTS

There is a group of cysts of the jaws which are non-odontogenic. In this group lies the haemorrhagic cyst of the mandible, which has been subject to such a wide and careful study by Professor G. Howe recently (1965) that I shall not specifically deal with it here, except to say that I believe that many of the basic conceptions of cystic growth also apply to these strange lesions, especially as it is generally considered that no conventional lymphatic system exists within long bones.

In describing haemorrhagic cysts of long bones, John Hunter commented: " When the bone is opened, they are most remarkable, and appear as if scooped out. . . . I can hardly tell whether the extravasation of blood is a cause or effect. Bones will break from this kind of tumour by very slight cause, such as by turning in bed. This kind of fracture happened to the Archbishop of Canterbury."

Other non-odontogenic types, such as naso-palatine, naso-labial and globulo-maxillary cysts have been dealt with in a recent clinical survey by Fickling (1965). I regard them as inclusion cysts originating in an activation, by unknown causes, of epithelial remains in the lines of junctions of embryological processes during the formation of the face. Their mode of growth would appear to be similar to other non-keratinizing cysts, but no infective element is deemed to be related to their origin. They are true developmental cysts of the jaws, and this leads on to the most important developmental cyst of odontogenic origin, the primordial cyst.

PRIMORDIAL CYST (ODONTOGENIC KERATOCYST)

The term " primordial " means of the simplest and most undeveloped character, the primordium being the earliest discernible appearance of an organ. Thus, by definition, a primordial cyst of the jaws may be derived directly from the undifferentiated dental lamina. These cysts are therefore not directly and primarily associated with any tooth but rather with a retained portion of the dental lamina, or may be derived from any suppressed tooth anlage in the normal series, or from a sprout of the dental lamina which might give rise to a supplemental tooth.

Recently this type of cyst has been recognized as of considerable clinical importance. One of the most interesting features of the primordial cyst of the jaws is that the epithelial lining always appears to be keratinizing, or at least in a state of parakeratosis, which implies that the surface squames of keratin-like material still contain a few cells in which nuclei can be defined. In other words, the process of maturation from basal cell to squame is not quite complete in parakeratosis.

Thirty-three keratinizing cysts from the total series of 300 cysts of all types in this present study were carefully charted according to their history, clinical and radiographic characteristics, and histology, and it was found that 17 cases conformed with the full criteria of primordial cyst and all of the others could have been primordial in origin, but not all criteria were present at the time the patient was examined. In 13 of these keratinizing cases teeth were included in dentigerous relationship with the cysts.

Pindborg and Hansen (1963) were far more cautious in their excellent review of 30 cases of " keratocysts " (a good term suggested by Philipsen in 1956) and in no way attempted to relate these cases to primordial cysts, but Professor Kramer pointed out this relationship to me in 1957 and I believe this to be correct, and he also is studying this problem closely. Thus, very tentatively, I am going to group my keratinizing cysts synonymously with primordial cysts as I have yet no evidence to refute this. It is likely that the term " odontogenic keratocyst " will become adopted for this condition.

Primordial cyst was mentioned as a clinical entity by Kronfeld (1949) and by Thoma (1950) and they were considered to be simple follicular

cysts arising from odontogenic epithelium before differentiation into a mature tooth germ. Shear (1960) considered that they can arise from a cystic breakdown of the stellate reticulum, of the tooth germ, and indeed this could be so since the site and frequency of occurrence of such cysts seems to coincide with that of supernumerary or suppressed teeth. Bernier (1955) mentioned them as rare types of follicular cyst. The term " simple follicular cyst " suggested that they were like dentigerous cysts without an included tooth, but their histopathology and clinical behaviour enables them now to be grouped as a distinct class.

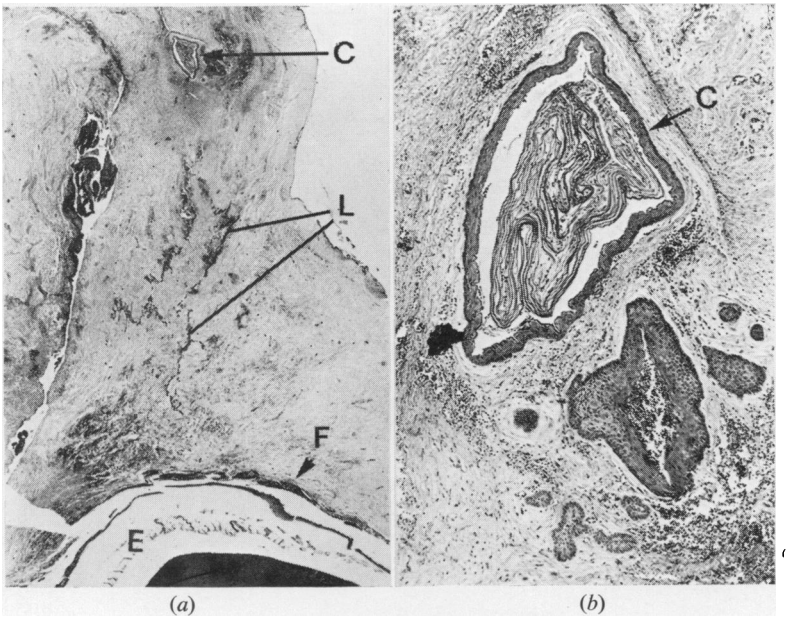


Fig. 12. (*a*) Low-power photomicrograph of an unerupted second molar tooth from a girl aged 12, with overlying connective tissue. The enamel space (E) is lined by follicular remnant (F). There are active dental lamina residues (L) in the gubernacular region. At C there is an early primordial cyst within the laminal region. ×7½. (*b*) Higher magnification of keratocyst (C). A large primordial cyst was present in the opposite side of the jaw. ×75.

It is likely that a primordial cyst can arise from any retained portion of the dental lamina which has never undergone differentiation to form a tooth structure (Fig. 12).

The primordial cyst is most frequently found in the mandible distal to the third molar, but cases have been reported involving any part of the upper or lower jaw, although the anterior maxilla is least involved. The most frequent site of occurrence is the ramus, where such a cyst may not be discovered until it has attained a fairly large size. This clinical finding suggests a slower rate of growth than some other types of cyst, but a care-

ful observation of the clinical rate of recurrence of keratinizing cysts suggests that they grow at a similar rate to other epithelial cysts of the jaws.

In 14 cases I have been able to check the patients' records to assess the times for recurrent cysts to grow to clinically significant size.

Longest time .. .. 25 years

Shortest time .. .. 1 year.

The most frequent time to recur to a clinically significant size of more than 1 cm. diameter on lateral radiograph was approximately six years. Six of these cases had recurred twice, and the rate of recurrence was similar up to each operation, and the histology of the original cysts was similar upon recurrence.

They can be multiple or bilateral, or indeed they can appear as symmetrical cysts on opposite sides of the jaw. Often the full complement of teeth is present and vital, but a primordial cyst can be associated

TABLE III

AGE OF OCCURRENCE OF PRIMORDIAL CYST

Years	*Toller*	*Shear*	*Total*
0–10	1	0	1
11–20	5	4	9
21–30	11	6	17
31–40	1	2	3
41–50	9	2	11
51–60	4	4	8
61–70	2	3	5
	33 cases	21 cases	54 cases

with the suppression of one tooth of the series or it may involve an unerupted tooth, especially so if the cyst started early in life, when it is extremely likely to become involved in dentigerous relationship with a yet unerupted tooth. It has been said (Shear, 1960) that these cysts are most frequently found in the 15–25 age group, but the present series of 33 cases suggests that the age of occurrence is widely distributed, possibly showing a peak in the 15–25 group, but also showing a peak at ages between 40 and 50 years (Table III).

Since the site of origin of primordial cysts is not necessarily intimately associated with a tooth, the early radiographic appearance tends to be a round radiolucent area in the bone within a well defined lamina-dura, but as it increases in size the relative resistance to pressure-absorption of the adjacent structures will influence its shape as in other cysts of the jaws. Where teeth are missing it may be extremely difficult to differentiate between residual apical cyst and primordial cyst, and a careful history of extractions is important. When of large size there may be a false appearance of multilocularity. However, the apparent loculi of a large primordial or dentigerous cyst are all fairly large, whereas smaller bubble-like loculi are frequently seen in ameloblastoma and giant-celled lesions.

Diagnosis is best confirmed by both aspiration and by biopsy. The cyst fluid is typically thick and milky-white or flocculent, and easily mistaken for pus. This fluid contains a high proportion of desquamated " keratin ", while cholesterol is less evident and may be absent altogether.

HISTOPATHOLOGY

In 1961 Shear annotated the main histological features as follows:

1. A regular thin lining of stratified squamous epithelium with no rete pegs (Fig. 5).
2. The presence of a keratinized layer, or parakeratosis of the surface layer, tending to desquamate into the lumen.
3. A well differentiated basal layer of columnar or cuboidal cells surmounted by only a narrow stratum spinosum of about two to five cells thick.
4. A relative absence of inflammatory-cell infiltration of the epithelium.
5. The frequent presence of desquamated keratin in the cyst cavity.

Pindborg and Hansen (1963) drew attention to the frequent vacuolation of the stratum spinosum.

In a recent study of clinical, radiological and histological aspects of 300 cysts of the jaws, at Mount Vernon Hospital and the Canadian Red Cross Memorial Hospital, 33 cases displayed these histological features together with sufficient clinical criteria to consider that they could be primordial in character.

Additional characteristics were noted:

6. A relative absence of cholesterol crystals in cyst contents.
7. Absence of mural cholesterol deposits.
8. The epithelial lining is complete.
9. The cyst contents are extremely low in soluble protein as revealed by electrophoresis of the cyst fluid.

Shear (1961) reported the occurrence of 21 cases of primordial type cyst in a group of 200 cysts of the jaws. The present finding of 33 such cases in a group of 300 cysts of all types suggests a similar incidence, namely 11 per cent. However, in an analysis of 791 cysts of the jaws, Pindborg and Hansen report that 26 were " keratocysts ", 3.3 per cent, and quote that Dechaume *et al.* reported 3.3 per cent among 300 cystic lesions of the jaws. It is possible that the series in Denmark is from a broader and more representative group than Shear's or the present series, which may show some selection of difficult cases which would have been referred to special oral surgical centres. However, the incidence of cysts with keratinizing linings over the four reported groups (1,591 cysts) is 5.7 per cent.

Shear states that the diagnosis may only be of academic interest, since he feels that they are simple in behaviour and will not recur if enucleated. Clinical research does not support this view.

The tendency of keratinizing cysts to recur was noted by Catania (1952), by Seward (1963) and, more recently, by Fickling (1965), whose clinical analyses cover many of the cases reported here. In 1963 Pindborg and

Hansen discussed some clinical features of 30 " keratocysts " occurring in 27 patients. Of these cases they were able to follow up 14 patients with 16 cysts and noted there had been a history of recurrence of 10 cysts (62 per cent of followed-up cases) or 33 per cent of their whole group.

Of 14 cases personally known by me to have received operations for recurrence of cyst of the jaws at Mount Vernon Hospital, 10 cases displayed the keratinizing type of epithelium associated with primordial cyst; or, covering the same group, of 33 cases diagnosed as primordial cyst, 19 cases (or 58 per cent) showed a history recurrence.

It may broadly be true to state that over these reported groups of cysts which had keratinizing epithelial linings the recurrence rate after surgical intervention was about 60 per cent. This is a very much higher recurrence rate than has been reported for any other type of benign cyst of the jaws and it must be regarded as significant, and as of having important implications to the surgeon.

The tendency for this condition to recur may even have a bearing upon whether the epithelial activity within or surrounding these cysts should be regarded as having some of the potentialities of a benign neoplasm. There are other conditions in the body where the distinction between excessive hyperplasia of epithelial tissue exists in such a way that disputes still arise over its precise designation. The " primary " choleastoma of the temporal bone is one such obscure condition.

Against much opposition, and in a long-standing confused field of argument, Sir Terence Cawthorne has furthered his view that there is a type of epidermoid of the mastoid, the so-called primary cholesteatoma, which is derived from embryological rests, and is not due to the centripetal invasion of an external epithelium. This condition would appear to be closely similar to the primordial cyst of the jaw, in which the spontaneous proliferation of rests, and their transition into cysts, may be more readily demonstrated. I feel this is a field which might be fruitfully explored together by both E.N.T. and oral surgeons and pathologists, and indeed Professor I. Freidman has done much work to resolve these problems.

Tytus and Pennybacker (1956) recorded 43 cases of keratinizing cysts in or about many parts of the central nervous system, where they are presumed to derive from epithelial residues of the primitive neural crest.

The calcifying epithelioma of Malherbe is generally regarded as neoplastic, but of limited growth. In the same context, the rare calcifying odontogenic cyst (Gorlin *et al.*, 1962) tends to display characteristics very close to the latter condition. In some respects the primordial cyst shows features resembling the early aspect of Gorlin's tumour, but production of ghost cells and calcification does not follow, neither is the activity of the epithelium so pronounced.

However, clinical experience would suggest that it is rare for an apical cyst to recur should a little epithelial lining be inadvertently left at opera-

tion, whereas the lining of primordial cyst seems very prone to continue to grow on its own account in the tissues, and, if incompletely enucleated, to form a recurrent cyst which will have a similar histology to the original. Alternatively, the active epithelial strands, or even small daughter cysts, which are sometimes to be found in the connective-tissue wall of a primordial cyst (Figs. 8 and 9) can easily escape complete enucleation by the surgeon, especially as the walls of primordial cysts are thin, friable and often difficult to remove.

Again this supports the view that this type of cyst is truly dependent upon the presence of epithelium for its growth, and indeed there is some reason for relating these cysts closer to the category of true benign epithelial tumours. The standard reference books on pathology usually list only papilloma and adenoma as benign epithelial tumours, and the works on oral pathology would add ameloblastoma, Malherbe's tumour and possibly certain rare pigmented tumours derived from dental formative tissues.

Sir Howard Florey (1962) pointed out that the characteristic of a neoplastic cell, as opposed to its normal homologue, is the fact that multiplication occurs in the absence of any discernible stimulus, and continues under conditions in which the multiplication of the normal cell ceases. This statement is particularly interesting in view of the contrast in behaviour between the epidermoid cyst induced experimentally from normal skin, which does not grow indefinitely, and the keratinizing cyst of the jaws and, indeed, the primary cholesteatoma of the ear, which continue to enlarge.

The early appearance of primordial cysts suggests epithelial pearls of increasing size with a well-marked keratinous desquamation filling the cavity. One might even suggest that the condition could be likened to a " papilloma turned inside out ". However, this description may be going too far, since exteriorization halts the growth of these cysts.

Although evidence suggests that osmotic pressure expansion is a factor in their growth, this probably exists in addition to a free tendency of their epithelial cells to grow on their own account in their enclosed context. Certainly with primordial cysts it is surgically important to *treat* them as benign neoplasms and that all epithelial cells should be eliminated completely and a definitive operation for marsupialization should not be practised in these cases.

It is uncommon for carcinoma to develop from a cyst lining, but owing to the apparently greater activity of epithelium in keratinizing cysts a search was made to see whether there was a greater tendency for such cysts to be the seat of these malignant lesions.

I have been able to satisfy myself on the histology of only thirteen well-authenticated cases of carcinoma developing from the wall of a cyst in the jaws, including one case which came under my own notice, but not yet published. As far as can be ascertained, seven cases were associated with

cysts lined with simple poorly differentiated epithelium, and six cysts displayed keratinizing epithelium. From this very small series, and taking into account that a keratinizing epithelium only occurs in about 6 per cent of all cysts of the jaws, it might be tentatively concluded that carcinoma arises more frequently from the wall of a keratinizing cyst. (Of a further eight similar cases reported in the literature, but where the exact history or histology is not so certainly identified, four cases were *likely* to have been keratinizing cysts.) On these small figures there would be a 15 times greater tendency for carcinoma to form in such a cyst, but it must be stressed that the occurrence of carcinoma in any cyst is fortunately extremely rare.

As a general comment, I should like to draw attention to the fact that in the more highly developed centres of civilization, where a high degree of dental health and awareness is attained, there will inevitably be a reduction in the incidence of both dental and dentigerous cysts in a community. The reduction in one case being related to better control of dental caries and apical infection and the other due to the lower incidence of teeth buried for long periods under conditions of improved orthodontic and surgical proficiency. In a sense, both dental and primary dentigerous cysts are preventable, whereas the same cannot be said of primordial (or any developmental) cyst, which latter will arise endemically. This is of some importance as the relative proportion of these cysts, which include all the keratinizing types and therefore the recurrent-prone types, will slowly increase, although the actual incidence of these cysts will remain the same in a given population. Consequently the significance of adequate pre-operative diagnosis will increase with time.

The finding of a significantly depressed total soluble protein in the fluids from a group of keratinizing cysts may prove on wider research to be a constant feature capable of being developed into the simple confirmatory diagnostic procedure of pre-operative aspiration and laboratory examination.

In the case of a suspected primordial cyst, or a large and unusual cyst, an aspiration of fluid can be carried out at the first visit together with radiology and would help to establish a diagnosis, and the extent of the operative procedure could be planned accordingly. For instance, a two-stage operation as suggested by Fickling (1965) has much to commend it in these cases when the absence of mural fibrosis and a clinically thin and delicate lining poses a special technical problem to the surgeon, and just in the situation where complete eradication of all epithelium is more than usually important. Many of us feel that a biopsy of a cystic lesion of the jaws cannot often be justified in the light of the disturbance it causes, and yet some pre-operative confirmation of diagnosis in these cases certainly is of great value.

I recommend taking a specimen of both cyst fluid and blood at the same

time. Only one drop of fluid is required for an electrophoretic estimation, so very small samples are required. Five c.c. of blood may be drawn and allowed to clot so that a little of the supernatant serum can be used. For convenience the electrophoretic strip of blood and cyst fluid can be run side by side on the same piece of paper as this will facilitate comparison and allow outstanding divergences of composition to be revealed clearly, as they will have been produced under identical laboratory conditions.

I strongly recommend that specimens from operations on all cysts should be examined histologically not only as a routine procedure but that a report upon the nature of the epithelium be supplied in considerable detail. In view of the strong possibility of recurrence, all cases which are reported as showing keratosis or parakeratosis should be submitted to a follow-up regime by the surgeon which should include radiography, and which I suggest should, if possible, take place at the end of the first, third, and seventh years.

Finally, I should like to point out that John Hunter was also concerned with early diagnosis and treatment of what seem to be keratinizing cysts. To quote: " Another type of encystic (bony) tumour [is] filled with curdy substance [and] thins the bone to a mere shell, which may suddenly give way." He then went on to say how difficult it was to treat, and how readily the whole condition became intractably infected, but, to quote again: " If known early, then perhaps exposure and sea-bathing would be the best cure."

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