TUMOURS AND TUMOUR-LIKE CONDITIONS OF THE ORAL MUCOSA

A clinical and histological study of seventy five cases

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SUMMARY

The following investigation on tumours and tumour-like lesions of the oral cavity is based on a series of 75 cases. Most of the lesions were in patients presenting for treatment to the Dental Department of the Royal Adelaide Hospital. A smaller number were referred by dental and medical practitioners of South Australia.

A review of the literature indicated little difference of opinion in respect to malignant tumours of the oral mucosa. However, as far as benign tumours and tumour-like lesions in this region are concerned it was apparent that a great deal of confusion exists, particularly with regard to terminology. An attempt has therefore been made in the present investigation to arrive at a definite terminology for these lesions. For the above reasons, and as there were only two malignant lesions in the series, greater emphasis has been placed on the benign soft tissue outgrowths throughout the investigation.

The purpose of the investigation was to determine the nature and relative frequency of tumours and tumour-like conditions of the oral cavity. It has already been indicated that there is a great deal of confusion regarding these conditions. Therefore it was considered that the investigation would make some contribution to knowledge in the field of Oral Surgery and Pathology.

Clinical findings, together with a histological report of each case of the series were carefully recorded by the writer.

Analysis of the results showed that in excess of 75 per cent of the lesions were in the nature of fibro-epithelial or fibrous hyperplasias, most of which could be related to some form of chronic irritation. However, in addition to the 2 cases of malignancy, there were 17 cases showing some dyskeratosis, including 10 cases in females showing a peculiar form of dyskeratosis characterized by the formation of hyaline bodies in the more superficial layers of the epithelium. The only benign tumours that occurred in the series were two cases of papilloma.

In most of the lesions, a definite diagnosis could not be made on clinical evidence alone. The investigation therefore emphasizes the importance of histological examination of all proliferative lesions of the oral mucosa.

This thesis is submitted in fulfilment of the requirements of the degree of Master of Dental Surgery, University of Adelaide. The qualifying examination of a standard equivalent to the Honours degree, which is required of all candidates proceeding to the Master of Dental Surgery degree by thesis, was passed in November 1963 the subject being General Pathology.

I hereby certify that to the best of my knowledge, the text of this thesis is entirely my own composition and that the findings reported herein are the result of my own investigation, excepting where due reference is made. Furthermore, no part of this work has been previously submitted for a degree in this or any other University.

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CHAPTER I

INTRODUCTION

Neoplastic growths, either benign or malignant, are not uncommon in the oral cavity. In the United States, SARNAT and SCHOUR (1950) have estimated that malignant growths of the oral cavity constitute 4.8 per cent of all malignancies in men and 1.2 per cent in women. On the other hand, KRUGER (1959) also in the United States, estimates that carcinoma of the mouth accounts for 5 per cent of all malignancies, and in Denmark, oral cancer accounts for 2 per cent of cancer deaths (HERTZ, 1956). These neoplasms may arise either from the more superficial tissues such as the oral mucosa, or from the deeper tissues within the bone of the jaws.

Many so-called tumours of the oral mucosa have been incorrectly named and a large percentage of these are in the nature of inflammatory hyperplasias probably arising as the result of chronic irritation, either traumatic, or infective, or both. While true tumours of the oral mucosa are not uncommon, GORLIN (1957) is of the opinion that it is difficult to ascertain the incidence of various types of benign tumours of the oral mucosa because of the problems encountered in defining these growths and because of the lack of accurate data on their incidence in unselected groups. He divides papillomatous lesions into true and false. In the former category he places squamous cell papilloma and true fibroma, while in the latter he places the fibro-epithelial lesions or "irritation" fibroma, and the denture hyperplasia or epulis fissuratum.

SALMAN and LANGEL (1954) state that 90 per cent of malignant tumours of the oral cavity are epithelial in nature while the majority of benign tumours arise from the connective tissues. These authors therefore conclude that the chances of benign neoplasms under-going transformation to frank malignancy are extremely slight. However, SARNAT and SCHOUR (1950) and SHARP, BULLOCK and HAZLET (1956) are of the opinion that all benign tumours are abnormal and can at any time undergo malignant change if exposed to prolonged irritation. They suggest that benign tumours of the oral cavity should be watched carefully or preferably be excised.

ROBINSON (1957), in a discussion on precancerous lesions comments that the word "precancerous" has different meanings for different people. "To the bench pathologist it may mean only that the lesion shows dyskeratotic changes in microscopic section; to the clinician it may indicate that the lesion falls within a group of changes loosely associated with possible malignant growth; to the patient it may signify the doom of death."

In general, tumours are classified as benign and malignant on a histogenetic and a prognostic basis (PEREZ-TAMAYO, 1961). However, WILLIS (1960) in discussing the supervention of malignancy in benign tumours writes as follows:-

'The over-emphasis which has been placed on the distinction between innocence and malignancy has arisen because of the prognostic value of this distinction. The clinician's first demand of the pathologist who examines the tumour he has just removed is, "Is it innocent or malignant?" This habitual query

has engendered the notion that every tumour must be either innocent or malignant. A more enlightened modification of the question, and one which pathologists should encourage clinicians to ask is "How innocent or malignant is this tumour?"'

It is in the classification of benign tumours and tumour-like growths of the oral cavity that the greatest confusion exists. This state of affairs is to a large extent caused by uncertainty in terminology, but also by some clinicians who attempt a histopathological diagnosis based solely on the clinical picture of a particular lesion. Furthermore, purely descriptive terms such as "polyp" and "epulis" while apparently clarifying the issue by not attempting a histopathological diagnosis, in practice do little to reduce the confusion.

It is agreed by most authorities that a great percentage of soft tissue outgrowths of the oral cavity have an inflammatory basis (FIGI, 1930; DARLINGTON, 1933; BRADLEY, 1944; BERNIER, 1949 and 1959; KERR, 1951, COOK, 1951; BOYLE, 1954; COLBY, KERR and ROBINSON, 1961). On the other hand, McCARTHY (1941), while not defining neoplasia, is of the opinion that fibroma outnumbers any other type of growth of the oral cavity. Furthermore, many writers while differentiating between hyperplastic and neoplastic outgrowths, agree that fibrous hyperplasias of long standing may be indistinguishable from true fibromas (BRADLEY, 1944; SHAFER, HINE and LEVY, 1958; TIECKE, STUTEVILLE and CALANDRA, 1959; THOMA and GOLDMAN, 1960). Apparently, many of these lesions have in the past been labelled as tumours simply because they are manifested as swellings, but in modern terminology could not be regarded as being true neoplasms. BLOODGOOD (1933) however, concluded that these lesions lie between inflammation and neoplasia.

It seems possible therefore that true fibroma is related to fibrous hyperplasia since it is often difficult to distinguish between them. SHAFER et. al. (1958) point out that in few situations is the distinction between hyperplasia and neoplasia as poorly defined as it is here and conclude that it may be possible for the true oral neoplasm to arise as a result of chronic irritation. On experimental evidence this possibility is now regarded as being unlikely (PEREZ-TAMAYO, 1961).

It requires only a superficial study of the literature on this subject in order to arrive at the conclusions reached by COOKE, (1952b) that different terms are used by different authors, but these terms are not always clearly defined. For example, a polyp is defined by COOKE as a pedunculated swelling of mucous membrane, and this definition is the generally accepted one (DORLAND, 1959). The statement by SALMAN and LANGEL (1954) that the fibrous polyp may also have a sessile base, must therefore add in no small measure to the confusion.

The literature dealing with giant cell epulis, for example, is also clouded by controversial and contradictory statements. Thus, some authors agree that the lesion is inflammatory in origin (WILLIS, 1949; COOKE, 1952a; STONES, 1962), while AMIES (1951) states definitely that it is a true neoplasm. BLUM (1931) and DARLINGTON (1933) describe three varieties of epulis namely, fibrous, vascular or pregnancy epulis, and giant cell epulis. Other authorities however, are of the opinion that these three histological types of epulis may represent different stages of the same growth (ANDERSON, 1939; EULER, 1953). Some authors emphasize the possible relationship between

the fibrous and the giant cell lesion (STONES, 1941; BROWN, DARLINGTON and KUPFER, 1956). Furthermore, it may be difficult to differentiate between fibrous epulis and a pregnancy tumour undergoing regression (TIILILÄ, 1962). On the other hand, GESHICKTER and COPELAND (1936) are of the opinion that giant cell epulis is in some way associated with the shedding of the deciduous teeth. This is questioned by BROWN et. al. (1956) who show that these outgrowths are not uncommon at sites not included in the area of the deciduous dentition.

The further possible inter-relationship of all these lesions is mentioned by KERR (1951) in a paper on granuloma pyogenicum, which is a lesion closely resembling pregnancy tumour histologically. He states that in the advanced stages of healing of this condition there is produced a dense fibrous connective tissue with only a few residual vascular spaces. Histologically this may resemble a fibro-epithelial hyperplasia. ASH (1961) is also of the opinion that granuloma pyogenicum may grow rapidly then remain static or undergo fibrosis to become indistinguishable from a dense fibrous epulis. It is interesting to note that ASH places giant cell epulis, fibrous epulis, and granuloma pyogenicum in the group of neoplastic-like conditions, and yet goes on to say that unlike true neoplasms they have a tendency to "burn themselves out".

That treatment and prognosis are dependant on diagnosis is a general statement which is particularly applicable to the lesions under discussion. An accurate clinical diagnosis can often be made of the pedunculated papilloma but an exact diagnosis of the sessile outgrowths is difficult, if not impossible, without histological examination (COLBY et.al. 1961). Two

lesions from the present investigation clinically appeared to be most innocuous, but histological examination in both cases, and subsequent behaviour in one case, proved them to be malignant tumours, thus reminding the writer of the importance of routine histological examination of all specimens of soft tissue removed from the oral cavity. Furthermore, since pain is not an important symptom of malignant lesions, the danger of allowing those which appear benign to remain untreated cannot be minimized. It is therefore important, particularly for those to whom the oral cavity is an area of special interest, to have a clear understanding of these conditions.

Aims of the investigation

From the preceding discussion it is apparent that there is considerable confusion in the literature on benign tumours and tumour-like conditions of the oral mucosa, and as a thorough search revealed that the literature on this subject was not extensive, a separate formal review of it has not been included in the investigation.

Thus the investigation has been concerned almost exclusively with benign tumours and tumour-like conditions of the oral cavity. Malignant tumours are discussed only with regard to their possible relationship to benign conditions and only when they occurred in the present series as clinically resembling benign conditions. The main aims of the investigation were as follows:-

1. To clarify the existing terminology of these lesions based on histological findings.

2. To determine, within the limitations imposed by the small number in the series, the relative frequency of the various

lesions, as determined by histological examination. At the same time the incidence with regard to age, sex, and position of the lesions in this series has been recorded.

3. To relate, where possible, the various lesions to their duration and apparent aetiology.

CHAPTER II

STRUCTURE AND FUNCTION OF THE ORAL MUCOSA

A sound knowledge of the histology of the soft tissues of the oral cavity is a most important pre-requisite for an understanding of disease occurring in this region. A brief description of the oral mucous membrane together with its regional variations is pertinent to the present investigation and is for this reason included.

The term "mucous membrane" is defined by DORLAND (1959) as a membrane covered by epithelium, lining canals and cavities which communicate with the exterior of the body. The oral mucous membrane consists of a fibrous lamina propria and a covering of stratified squamous epithelium separated by a basement membrane. The mucosa is firmly attached to the underlying bones and muscles by the sub-mucosa.

In the normal mucosa the strata of the epithelium are clearly defined. From below these layers are as follows:-

1. The basal layer, or the stratum germinativum, which consists of a layer of regularly aligned cuboidal cells. The basement membrane adjoining is a complex of argyrophilic reticulum, the meshes of which contain the cytoplasmic processes of the basal epidermal cells thus furnishing an anchorage for the epidermis (MONTAGNA, 1956).

2. A layer of large polyhedral cells of variable thickness which adjoins and is called the stratum spinosum or prickle cell layer. These terms are applied because the cells appear connected to each other by means of small intercellular bridges or spines. The cells of this layer are larger, and the intercellular bridges are less conspicuous in non-keratinizing epithelium (SICHER, 1962).

3. The stratum granulosum. The cells of the more superficial layers of the stratum spinosum gradually become flattened and in some areas may contain fine basophilic granules. These granules, which were once thought to be the precursors of keratin, are referred to as keratohyalin granules and the layer of cells which contains them is called the stratum granulosum. Since keratinization is not the rule in the oral cavity, this layer is not generally present (SICHER, 1962).

4. The surface layer of oral epithelium is formed either by a layer of keratin or by a layer of flattened cells which retain a pyknotic nucleus. These latter cells are referred to as parakeratotic cells. The epidermis of the palms of the hands and soles of the feet contains, above the stratum granulosum, a conspicuous hyaline layer which is called the stratum lucidum. This layer is seldom seen in thinner epidermis and, as a rule, is missing from the oral mucosa (MONTAGNA, 1956). This fact is substantiated by LEVER (1961) who is also of the opinion that where there is no horny layer in the mouth, the epithelial cells, in their migration from the basal layer to the surface, first become vacuolated then shrink and finally desquamate. According to WELSH (1955) the cells of the stratum lucidum no longer contain keratohyalin granules but instead have acquired a substance called eleidin.

Since keratin is one of the toughest of fibrous proteins, PILLSBURY, SHELLEY and KLIGMAN (1961) have stated that the stratum corneum is to the skin what the bark is to a tree.

The lamina propria of the oral mucosa is a layer of connective tissue of variable thickness which lies below and supports the epithelium. The lamina propria may be divided into the papillary layer, which is the upper layer extending between the epithelial ridges, and the remainder, which is called the reticular layer (BHASKAR, 1962; SICHER, 1962).

Below the lamina propria lies the sub-mucosa which attaches the mucous membrane to underlying structures. This layer contains the larger blood vessels and nerves, and the various minor salivory glands. In the sub-mucosa the vessels and nerves divide and sub-divide to enter the lamina propria.

The structure of the oral mucous membrane while following a basic plan, shows some regional variations which are to a large extent determined by the functions of the specific region. Thus the gingival tissues and the hard palate, when subjected to heavy masticatory stresses are keratinized, whereas the protected membrane of the floor of the mouth is relatively thin and non-keratinized. Fig. 1.

ORBAN and WENTZ (1960) classify the oral mucous membrane on a functional basis as follows:-

A. Masticatory mucosa -
   1. The gingivae.
   2. The mucous membrane of the hard palate.

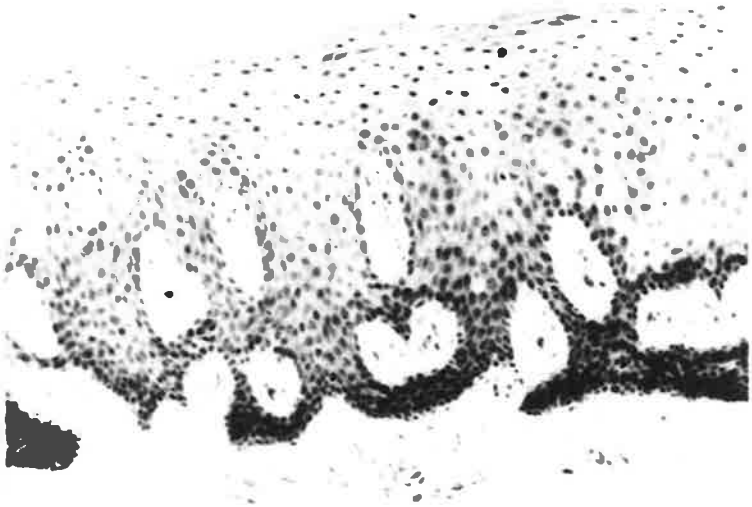


Fig. 1

Palatal mucosa from 12 year old female showing thin layer of keratin. (H. and E. X 100)

B. Lining mucosa which covers -

1. The cheeks and lips.
2. The inferior surface of tongue.
3. The floor of mouth.
4. The vestibule of the mouth.

C. Specialized mucosa of the tongue.

As far as the epithelial covering is concerned it is only the masticatory mucosa which normally becomes keratinized. The remaining mucosal epithelium is fairly uniform, and differences between the various mucosae are related to those occuring in the lamina propria and the sub-mucosa. The soft palate, for example, shows a lamina propria composed of loose connective tissue, whilst in the hard palate the lamina propria consists of dense collagen which sends long papillae into the epithelium. The mucosa of the tongue and cheek presents a good example of adaptation to functional demands. In these areas the mucosa is firmly attached to the underlying muscles, this attachment preventing trauma to it during mastication.

CHAPTER III

NOMENCLATURE AND TERMINOLOGY

In the preceding chapter, the histological structure of normal oral mucosa together with functional variations has been briefly reviewed. It is however, the histological structure found in abnormal states that is of special interest in the present investigation.

It has already been stressed that lack of uniformity in terminology has been an important cause of the confusion surrounding the conditions under discussion. For this reason, in this chapter an attempt will be made to define the terms used to describe the more common of these conditions, so that terminology and nomenclature can be standardized as far as it is possible to do so.

1. Tumour.

In its ancient and general sense the word "tumour" was applied not only to true neoplasms but also to inflammatory and reparative masses, hyperplasias, simple cystic swellings and malformations producing swellings. In its restricted modern sense the word has become synonymous with neoplasia or new growth. PEREZ-TAMAYO (1961) is of the opinion that in the present state of knowledge the best definition is merely descriptive and that it is most difficult to propose a definition of neoplasia which applies to all tumours and is free of criticism. A widely accepted definition is that of WILLIS (1960).

"A tumour is an abnormal mass of tissue, the growth of which exceeds and is unco-ordinated with that of normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change."

From their behaviour, tumours are separated into benign and malignant groups. A benign tumour generally grows slowly, does not invade neighbouring structures, and interferes with the patient's well-being mainly because of its position or its internal secretions. A malignant tumour on the other hand, generally grows rapidly, invades neighbouring structures, produces metastases, and if untreated will finally end the patient's life. Nothing qualitatively different exists in a biological sense between a benign and a malignant tumour; basically, they are both disturbances of cellular growth and differentiation. Clinically, however, the differences are very great (PEREZ-TAMAYO, 1961).

2. Hyperplasia.

This is an increase in the number of cells constituting a tissue. In the skin, hyperplasia may result when a pathological stimulus upsets the equilibrium between division of the basal cell layer and death at the skin surface. A new equilibrium is reached but this is not progressive as is the case with neoplasia (FLOREY, 1958).

3. Hypertrophy.

This refers to an enlargement of a tissue which is due to an increase in the size of its component cells. According to PEREZ-TAMAYO (1961), the term was introduced to the nomenclature in the pre-microscopic era to indicate increase in size of a part. This connotation has been sanctioned by

usage and conditions such as gingival hyperplasia are still referred to as an hypertrophy.

The end result of hyperplasia and hypertrophy is an increase in the amount of living protoplasm. In general, the total mass of functioning protoplasm may increase in response to either exaggerated hormonal stimulus or to greater functional demands (PEREZ-TAMAYO, 1961). BERNIER (1959) believes that it is probably not completely realistic to attempt a definite separation between hyperplasia and hypertrophy. It is his contention that both conditions are present to some degree in all proliferative reactions of the oral cavity and that no reaction is ever purely hyperplastic or hypertrophic to the exclusion of the other. On the other hand, FLOREY (1958) is of the opinion that conditions which produce hypertrophy in tissues composed of non-multiplying cells may produce hyperplasia in tissues composed of cells which have retained this capacity. Thus a tissue such as the oral mucosa which was classified by BIZZOZERO (1894) as a labile tissue is likely to produce a hyperplastic response, while a stable tissue such as kidney will produce a hypertrophic response. Generally speaking it may safely be said that the condition of hyperplasia, unlike that of hypertrophy, is often the result of irritation. Furthermore, the limits of hyperplasia are not as definite as those of hypertrophy and it gradually merges into the process of neoplasia (BOYD, 1961). For these reasons, the classification of hyperplastic and neoplastic lesions or the oral cavity becomes a matter of great difficulty (WOODBRIDGE, 1954).

4. Epulis.

This term is used in its clinico-topographical sense to denote a gingival outgrowth and was used by Galen in this sense (TIILILÄ, 1962). However BERNICK (1948) and AMIES (1951), while agreeing with this meaning, give credit to Virchow for coining the word. The name indicates neither the character nor the origin of the lesion and the significance of the clinical entity known as epulis probably lies in the fact that it covers a wide variety of conditions (HERTZ, 1956). In modern usage the word should therefore be accompanied by a histogenetic or cytogenetic identification, e.g., vascular epulis, giant cell epulis. In the present investigation the term has been avoided whenever possible.

5. Papilloma.

The papilloma is a benign epithelial tumour of surface-lining, non-secretory epithelium. The name papilloma is derived from the papillary or wart-like structure of the tumour growing outward from the surface (FLOREY, 1958). Histologically, the papilloma consists of epithelium which resembles, in an exaggerated form, the parent epithelium thrown into folds, with an internal core of normal connective tissue. Oral papillomas occur as single or multiple lesions and when a large area is covered by multiple lesions the condition is referred to as a papillomatosis (BERNIER, 1959). COOK (1951) and THOMA and GOLDMAN (1960) differentiate papilloma into the soft and hard varieties. The former type is usually a pedunculated, cauliflower-like mass of proliferated squamous epithelium and the central fibrous core is scant but projects in tree-like fashion. In some cases

the surface may show hyperkeratosis while there may be round cell infiltration if the tumour has been irritated. On the other hand, the hard papilloma occurs in areas affected by advanced leukoplakia and is usually made up of hyperplastic, keratinized, epithelial cells. The exact cause of true papilloma is unknown (TIECKE et. al. 1959). However, BERNIER (1959) is of the opinion that trauma is probably the greatest cause of these benign tumours.

FLOREY (1958) and THOMA and GOLDMAN(1960) have little doubt that true papilloma of the oral cavity, and particularly of the tongue, has a pronounced tendency to become malignant. This contention is doubted by GORLIN(1957) and the relationship between papilloma and carcinoma "is not completely clear" according to HALPERIN (1957). On the other hand TIECKE et. al. (1959) are of the opinion that oral papillomas are probably not premalignant with the possible exception of the multiple lesions of the palate. However, according to GORLIN(1957) and COLBY et. al. (1961) it is the rarer sessile, cauliflower type papilloma that clinically is difficult to distinguish from the papillomatous or exophytic carcinoma. TOTO (1957) and THOMA and GOLDMAN (1960) advise that lesions showing basal hyperplasia, anaplasia, and especially dyskeratosis, should be carefully watched since they are pre-cancerous. In any case it appears prudent to assume that lesions which appear clinically as papillomas should be considered as potentially malignant and therefore excised.

6. Fibroma.

If the modern system of tumour nomencalture is adhered to the fibroma must be defined as a benign tumour of connective tissue, or more strictly speaking, of fibrous tissue. However, FLOREY (1958) is of the opinion that fibroma shows few histological features that distinguish it from excessive fibrosis and the question is sometimes raised whether it is indeed a true neoplasm. As far as the oral cavity is concerned it has already been mentioned that this view is maintained in a great deal of the literature. Nevertheless, FLOREY, in describing fibroma, states that while it may show a diffuse picture in the early stages, the tumour later becomes encapsulated. This view is also taken by TIECKE (1957) and STONES (1962) and the former feels that in addition true fibroma occurs without an obvious cause. The oral fibroma is a painless tumour which has either a pedunculated or sessile base, and which may be soft or hard, depending on the histological structure. In the hard variety the tumour shows an abundance of thick interlacing bundles of collagen fibres and a scarcity of fibroblasts. The epithelium of this type may be hyperplastic with a well defined stratum corneum but in some cases it may appear thin and uniform (THOMA and GOLDMAN, 1960). In the soft variety the vascularity is more marked and the tumour is composed mainly of fibroblasts arranged in such a manner that a whorled appearance is produced. STONES (1962) notes that ossification, with the production of woven bone, is usually observed in soft fibromas and in addition oedematous or mucinous changes may occur in the tumour. The epithelium of the soft variety generally shows some hyperplasia together

with some spongiosis and loss of the stratum corneum. Inflammatory infiltrations are seen when there is surface ulceration or if there is irritation to the tumour during mastication. In both varieties the inflammatory cells tend to be present beneath the epithelium and only rarely are they found in the actual tumour (THOMA and GOLDMAN, 1960 and STONES, 1962). The accepted treatment is complete surgical removal. STONES states that malignancy has resulted from incomplete removal though this is rare.

In the present investigation only those fibrous lesions exhibiting the whorled cellular or interlacing appearance together with some attempt at capsule formation are classified as fibromas. Furthermore, whilst the presence or absence of an obvious cause was taken into account it is possible that the original cause of the lesion has subsequently been removed. Since this fact may not be known to the investigator or recognised by the patient, the absence of an initiating irritation at the time of examination is no proof that one did not originally exist.

In the oral mucosa the usual result of such irritation is a localized, but in some cases a diffuse, area of tissue hyperplasia. These conditions will be further discussed in the succeeding chapter.

CHAPTER IV

REACTIONS OF ORAL MUCOSA

While it is true that changes in the oral mucosa may be the result of changes in systemic conditions, most lesions of the soft tissues of the oral cavity are local in origin. Local diseases produce surface changes which almost always affect the epithelium first and then the underlying lamina propria and submucosa. On the other hand, systemic conditions affect the sub-epithelial structures primarily with the changes in the epithelium occurring as a secondary manifestation (THOMA and GOLDMAN, 1960).

The reactions of squamous epithelium to irritation are very limited and it is probably true that a prickle cell may either form keratin or continue to divide (RUSHTON and COOKE, 1959). Microscopically, the following conditions may be seen in a wide variety of diseases of epithelium and it is important to differentiate one from the other. It must be stressed that the conditions to be described are identified histologically rather than clinically.

1. Hyperkeratosis and Keratinization.

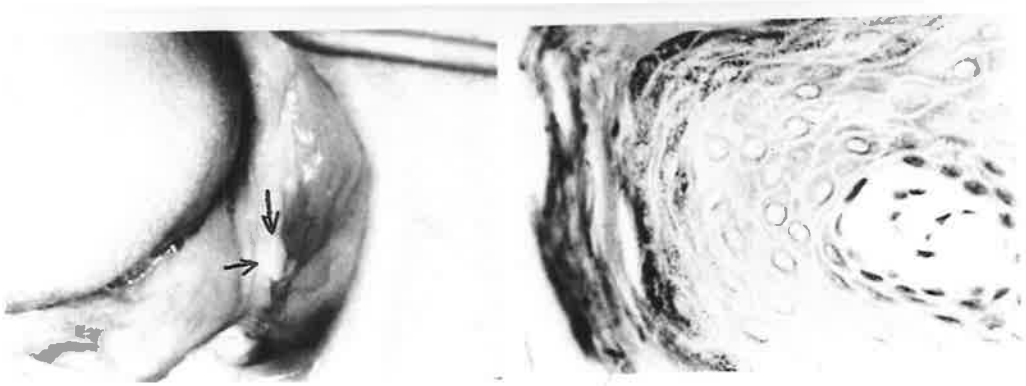
   Hyperkeratosis is an increase in the thickness of the keratin layer. This is caused either by failure of the cells of the stratum corneum to become desquamated or when they are produced so rapidly that as a result the hornified layer becomes greatly thickened. Keratin is a scleroprotein with a high content of the basic amino acids, arginine, lysine and histidine and the sulphur containing amino acid, cystine. The principal change occurring during cornification in the

normal human skin is the oxidation of -SH groups in the lower strata to form -SS groups in the stratum corneum (PEARSE, 1960).

In hyperkeratinized epithelium a stratum granulosum appears containing cells whose cytoplasm is laden with keratohyalin. PILLSBURY et.al. (1961) state that the process of keratin synthesis cannot be separated from the multiplication of epidermal cells. In addition, they emphasize that inflammatory conditions of the corium and epidermis invariably lead to a hyperkeratotic appearance of the stratum corneum. Since keratin production is almost completed in the basal layers of the epithelium, these authors conclude that the primary damage is not in the horny layer. Fig. 2.

In chronic irritations the first signs that the "biological potentialities" of the epithelial cells have become modified is that they form a harder, less desquamating, more completely keratinized, horny layer. This stage is generally reversible (ROTHMAN, 1954). It is stated by BERNIER (1942) and THOMA and GOLDMAN (1960) that hyperkeratosis is usually associated with a hyperplasia of one or more of the underlying layers of the epithelium.

Since the oral mucosa other than the masticatory mucosa is not normally keratinized the formation of an abnormal keratin layer may perhaps more properly be called a process of keratinization. SPOUGE and DIAMOND (1963) are of the opinion that this is a metaplastic process resulting from a mild degree of disorderly proliferation.



A. B.

Fig. 2 (Case 10)

A. Clinical appearance of lesion.

B. Microscopical appearance showing well defined stratum granulosum and hyperkeratosis. (H. and E. X 400)

2. Parakeratosis.

Whereas in the case of hyperkeratosis there is an increase in the thickness of the stratum corneum, in parakeratosis there is imperfect keratinization and the nuclei do not undergo lysis. The change is often associated with intercellular and intracellular oedema of the stratum spinosum.

3. Spongiosis.

This condition is a separation of the cells of the prickle layer caused by intercellular oedema. At the same time the intercellular bridges become more prominent. If the fluid accumulates in excess, then the intercellular bridges rupture and a vesicle is formed. The loss of intercellular bridges is called acantholysis. The condition of spongiosis appears to predispose to disturbances in cornification resulting in parakeratosis.

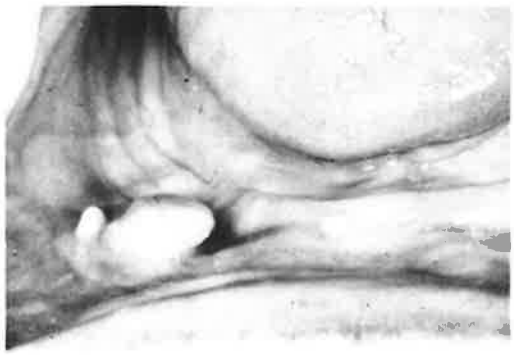
4. Intracellular oedema (hydropic degeneration).

The cells in this condition contain a vacuolated cytoplasm and a pyknotic nucleus.

5. Acanthosis.

This is a condition in which the cells of the stratum spinosum produce increased numbers of cells, this proliferation producing a broadening and lengthening of the epithelial ridges. The hyperplasia of the stratum spinosum is due to surface irritation or systemic causes and may be associated with other changes of the epithelium such as hyperkeratosis. However, acanthosis may exist without hyperkeratosis.

Fig. 3.



A.

B.

Fig. 3 (Case 43)

A. Clinical appearance of lesion.

B. Microscopical appearance illustrates the marked acanthosis of the epithelium. (H. and E. X 100)

6. Dyskeratosis.

This condition is a disturbance in the orderly maturation of the cells of the basal layer. It is characterized by abnormal or premature keratinization of the individual cells which are disorderly in their arrangement and have a strongly eosinophilic cytoplasm and a large nucleus. The nuclei are irregular, hyperchromatic, and may show an increased rate of mitosis (THOMA and GOLDMAN, 1960; BOYD, 1961).
ANDERSON (1957) and LEVER (1961) dintinguish two types of dyskeratosis.

(1) Benign dyskeratosis which occurs for example in Darier's disease and warty dyskeratosis or dyskeratoma. This type consists of "corps ronds" and "grains" in the stratum granulosum.

(2) Malignant dyskeratosis which shows anaplastic changes such as hyperchromatism, changes in polarity, increase in mitotic figures, enlargement of nuclei and nucleoli, and premature and atypical keratinization of individual cells. These changes signify potential or actual development of malignancy.

According to BOYD (1961) the changes in dyskeratosis may be summed up as an "atypicality" and a "jumbling" of the cells.

So far, only the reactions of squamous epithelium to irritation have been discussed. However, since inflammation has been defined by PEREZ-TAMAYO (1961) as the local reaction of vascular connective tissue to injury, a brief discussion of the reactions of the connective tissue to irritation must be included.

Tissue injury will almost invariably affect a section of connective tissue with or without involvement of epithelial elements. Repair generally follows inflammation and may be said to have begun with the mobilization of tissue cells which do not participate in phagocytosis but which are involved in the laying down of connective tissue. Since the fibroblasts are the chief cells of connective tissue, replacement is usually complete (BOYD, 1961; PEREZ-TAMAYO, 1961). On the other hand, in chronic inflammation the microscopic picture is generally a mixture of vascular and exudative changes and there is proliferation of fibroblasts with a resultant increase in connective tissue fibres. Furthermore, when in chronic inflammation the exciting agent is physical or chemical, the leucocytic reaction tends to be lessened and the proliferative phenomenon is more in evidence (WRIGHT, 1958). Constant irritation allows the cycle repair, destruction, repair to proceed and this state of affairs may create an unstable equilibrium (BOYD, 1961).

MOWLEM (1951) is of the opinion that repetitive insults may bring about stormy healing and these multiple episodes of fibroblastic proliferation due to repeated injuries may produce a "hypertrophic" scar. This excessive proliferation of connective tissue fails to be re-absorbed at the end of healing. The condition is more common in women (BOYD, 1961). On the other hand the work of GLÜCKSMAN (1951) suggests that scar "hypertrophy" is due in many instances to the proliferative response produced by various foreign body particles in sensitive persons.

The true fibroma of the oral cavity has already been described and is probably a rare entiry. However, the term is often used to describe localized proliferations of fibrous tissue which are hyperplastic scars or the result of long standing irritation (COLBY et. al. 1961). Other terms used to describe the latter condition have been "irritation" fibroma, "so-called" fibroma, epulis, fibrous epulis, fibrous hyperplasia, fibro-epithelial papilloma, fibro-epithelial polyp and fibro-epithelial lesion.

It becomes apparent therefore, that the most common soft tissue outgrowths of the oral mucosa are not neoplastic in origin but are localized inflammatory hyperplasias (THOMA and GOLDMAN, 1960). There appears to be a definite relationship between this hyperplasia and trauma (GORLIN, 1957). In very few of these lesions is the hyperplasia limited to connective tissue so that a variable inflammatory hyperplasia of the epithelium is almost always present. For these reasons then, it would seem logical to group these lesions together as fibro-epithelial hyperplasias. However, it may be of some advantage in the description of these lesions to label those having a pedunculated attachment as fibro-epithelial polyps (COOKE, 1952b). These terms are selected since they appear to aptly describe the conditions and also since they do not make the inference that the process is truly a neoplastic one.

As another subdivision of fibro-epithelial hyperplasias there is a lesion which because of its frequency, location, and obvious relationship to the wearing of dentures, may properly be called the "denture hyperplasia". If, in addition, the enlargement shows bifid folds or clefts of tissue, it is sometimes given the

name of epulis fissuratum (VAN HUYSEN and FLY, 1954; COLBY et. al. 1961). This group also includes the inflammatory papillary hyperplasia of the palatal mucosa that is frequently observed under ill-fitting dentures. THOMA and GOLDMAN (1960) point out that these hyperplasias are often blamed on poorly constructed dentures when in actual fact it is atrophy of the alveolar bone that has resulted in a badly fitting prosthesis.

Histologically, denture hyperplasias generally closely resemble the fibro-epithelial hyperplasias. The covering epithelium varies in thickness and is often acanthotic, but the hyperplasia of epithelium is usually not a prominent feature (BERNIER, 1959). However, the enlargement is mainly the result of fibrous tissue proliferation produced by inflammation. The connective tissue varies in quantity, vascularity, and degree of fibrosis, depending on the severity and duration of the irritation (VAN HUYSEN and FLY, 1954). These authors make the statement that there have been no cases reported in the literature showing malignant changes in denture hyperplasias and a similar view is expressed by BOYLE (1954) and SALMAN and LANGEL (1954). However, as far as the possibility of malignant changes in the papillary hyperplasias of the palate are concerned, opinions are varied. Thus SHARP et. al. (1956), HALPERIN (1957), THOMA and GOLDMAN (1960) and COLBY et. al. (1961) are of the opinion that malignant transformation is possible, while SHAFER et. al. (1958) feel that papillary hyperplasia of the palate is not a pre-neoplastic lesion.

In a general discussion on hyperplasias as pre-neoplastic states WILLIS (1960) comments that it appears that the abnormal stimuli which bring about a hyperplastic proliferation in some

tissues may eventually evoke progressive neoplasia as well. WILLIS also points out that the nature and causes of hyperplasia are of fundamental interest to the student of tumour causation. It must be remembered however that few hyperplasias end in tumour formation and that many tumours develop without any previous recognizable hyperplasia. WILLIS is of the opinion that the individual susceptibility of a particular tissue to tumour formation is of importance. In addition, it is probable that in susceptible tissues, mild physical or chemical stimuli of diverse kinds which are insufficient to effect permanent changes in normal tissues may be sufficient to evoke a hyperplasia and eventual neoplasia.

Treatment of these lesions is directed at removal of the irritant together with excision of the hyperplastic tissue. It is possible however that if the cause is eliminated in the early stages the proliferative response may disappear. COOPER (1964) reports twelve cases of denture hyperplasia in which regression took place without surgical intervention and concludes that these lesions have a tendency to disappear when the causative factor is eliminated. On the other hand PEREZ-TAMAYO (1961) points out that little is known regarding the re-absorption of the inter-cellular substances of connective tissue although it is certain that the fibres are metabolically relatively inert. In any case BERNIER (1959) is of the opinion that if dyskeratosis is present the lesion is irreversible and removal of the irritant is insufficient to cause regression.

CHAPTER V

MATERIALS AND METHODS

The 75 cases constituting the investigation were collected by the writer from 1962 to 1964. With the exception of 14 cases, all patients were examined and treated by the writer in the division of Oral Surgery of the Dental School, University of Adelaide, and the biopsies from the 75 cases were processed by the Department of Oral Pathology associated with this division.

The 14 lesions which were not excised by the writer were sent to the Oral Pathology department for examination by an oral surgeon and general medical and dental practitioners who kindly allowed the writer full access to the material. However, the case record sheet described later in this chapter was not always satisfactorily completed for these cases.

Of the 61 cases examined and treated by the writer, 6 were referred for diagnosis and treatment by general medical and dental practitioners. The remainder were either patients who had noticed the condition and sought treatment at the Dental Department, or patients in whom the condition was first noticed in other divisions of the Dental School or Dental Department of the Royal Adelaide Hospital.

For teaching material for its clinical students the Dental School obtains its patients from the Dental Department of the Royal Adelaide Hospital. These include pensioners, inmates of private and State institutions, consisting in general of persons of modest means. However, an emergency relief of pain service is provided for any member of the public without distinction.

On the other hand, the Department of Oral Surgery and Pathology of the Dental School, besides normal teaching commitments, provides a consultant service to the dental and medical professions of South Australia.

A history was obtained from each patient with regard to his health generally and more specifically, to the lesion. The patient's oral cavity was then thoroughly examined and the case history and examination were carefully recorded on the Case Record Sheet.

At the beginning of the investigation it was soon realised that while the orthodox dental treatment card could be used as a record sheet it would be inefficient and difficult to process the information obtained. It was therefore considered necessary to devote some time to designing the special Case Record Sheet which is shown in Appendix i. It will be seen from a study of this Sheet that the primary purpose of this system was to obtain a complete record of each case in a methodical, and at the same time, concise manner. No entry was recorded in the sections headed "Patient's Estimate of Duration of Lesion" and "Patient's Attitude to Lesion" when the patient did not discover the lesion. However, when the lesion was discovered by the patient the manner in which it was discovered was recorded. Where some form of irritation appeared to be closely associated with the lesion this was recorded as its possible cause.

Since no incisional biopsies were carried out, in all cases the completely excised surgical specimen was placed in 10 per cent buffered formalin at the time of operation. The formula of the solution used by the Oral Pathology Department is given in

Appendix ii. The period of fixation required in this solution is 24 hours or longer.

Following fixation a thorough macroscopic examination of each specimen was made in order to decide the most suitable position to trim it so that representative sections could be obtained. Thus if the specimen showed some ulceration, the plane of section was chosen to include this area. On the other hand, if the lesion was circular in chape and the mucosa showed no unusual landmarks the specimen was trimmed and sectioned as shown in Fig. 4.

The sections were routinely stained with Haematoxylin and Eosin. The method used by the Oral Pathology Department is given in Appendix iii. However, the Van Gieson connective tissue stain as described by JONES (1950), the Von Kossa stain for calcium (PEARSE, 1960), and the mucicarmine stain for mucin were used where it was thought necessary. In addition the peracetic-orcein-Halmi stain as described by FULLMER (1959) was used in the specimens which demonstrated peculiar eosinophilic bodies in the more superficial layers of the epithelium. Various stains were tried to demonstrate these bodies more clearly until it was finally decided that the peracetic-orcein-Halmi stain was the most suitable for this purpose. Appendix iv.

All sections were routinely reported upon by the Reader in Oral Pathology. Each section was also examined by the writer independently and then discussed and re-evaluated with the former and the results recorded. In addition, colour transparency photomicrographs were made of each section.

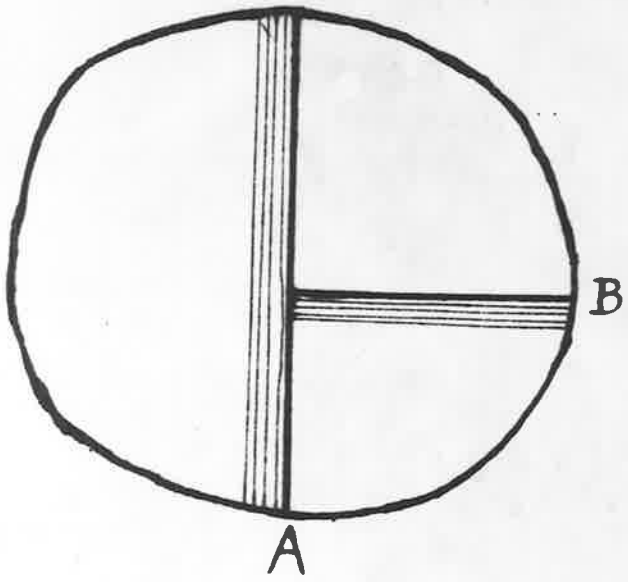


Fig. 4

Diagrammatical representation of trimming method for a circular specimen.
Line A represents the first trimming cut and line B the second trimming cut. The parallel lines indicate the sections obtained.

In the histological analysis, particular attention was focused on vascularity, presence of inflammatory elements, and the amount of fibrous and cellular hyperplasia in the connective tissue. The epithelium was examined for hyperplasia, presence of oedema, the degree of keratosis and parakeratosis, and the presence or absence of dyskeratosis. Cases showing the previously mentioned eosinophilic bodies were recorded as exhibiting dyskeratosis. The results were recorded in tabular form with the degree of each abnormality being recorded as ranging from plus (+) to four plus (++++).

CHAPTER VI

RESULTS

Of the 75 cases of soft tissue outgrowths, there were 55 cases in females and 20 in males. An analysis of the cases which were found in the females is given in Appendix v and an analysis of those found in the males in Appendix vi.

Age, Sex, and Site Distribution

The age distribution of the 55 female lesions in the series is shown in Table 1, and that of the 20 male lesions in Table 2. The age ranges are those used at the Dental School, University of Adelaide in other surveys and are as follows (BARRETT, 1953):

1. The period 0 - 5 years being that which includes only the deciduous dentition.
2. This group covers the period of the mixed dentition of from 6 - 12 years.
3. From 13 - 19 years may be called the period of adolescence, and in most cases is the period of completion of the permanent dentition.
4. The age group from 20 - 29 years is that of the young adult.
5. From 30 - 49 may be called the period of the mature adult.
6. The group beyond 50 years of age consists of the aged.

It can be seen from Table 1 that 46 of the 55 cases of soft tissue outgrowth occurring in females were classified histologically as fibro-epithelial hyperplasias. In the same group, 5 cases were fibrous hyperplasias, 3 cases were vascular outgrowths, and 1 case was a mucous extravasation cyst. Table 2 shows that in the male series of 20 lesions there were 15 cases

TABLE 1

AGE INCIDENCE OF LESIONS IN FEMALE SERIES

(55 occurrences)

Type of Lesion (on Histological Basis)	0 - 5	6 - 12	13 - 19	20 - 29	30 - 49	50 +	TOTAL
Fibro-epithelial hyperplasia	1	1	3	3	16	22	46
Fibrous hyperplasia	-	-	-	1	2	2	5
Vascular outgrowths	-	-	1	1	1	-	3
Mucous extravasation cyst	-	1	-	-	-	-	1
TOTAL	1	2	4	5	19	24	55

TABLE 2

AGE INCIDENCE IN MALE SERIES

(20 occurrences)

Type of Lesion (on Histological Basis)	0 - 5	6 - 12	13 - 19	20 - 29	30 - 49	50 +	TOTAL
Fibro-epithelial hyperplasia	-	1	3	1	3	7	15
Papilloma	-	1	-	-	1		2
Vascular outgrowth	-	1	-	-	-		1
Malignancy	-	-	-	-	-	2	2
TOTAL		3	3	1	4	9	20

of fibro-epithelial hyperplasia, 2 cases of papilloma, 1 vascular outgrowth, and 2 cases of malignancy. It is interesting to note that 83.5 per cent of the female cases and 75 per cent of the male cases were classified as fibro-epithelial hyperplasias. This distribution of type of lesion was found to be of statistical significance. It will also be noted that in this series the greatest number of fibro-epithelial hyperplasias occurred in the group above 30 years of age.

The distribution of site of the 46 occurrences in females of fibro-epithelial hyperplasia is shown in Table 3. A similar analysis of the 15 male occurrences is shown in Table 4. Analysis revealed that differences were not statistically significant.

Calcification

None of the male cases of soft tissue outgrowth in this series showed any form of calcification. On the other hand, 7 of the female cases showed some form of calcification and an analysis of these cases is shown in Table 5. While little significance can be attached to this fact, it can be seen that all lesions showing calcification could be labelled on a clinico-topographical basis as "epulides". Further, in this series, the maximum known duration of the cases showing bone formation was 2 years. However, in Case 54, which showed cartilage formation and which was removed from the incisive papilla, the patient's estimate of the duration of the lesion was 4 years.

It is interesting to note that with the exception of Case 54, all calcification took place in areas of ossification and did not appear to be dystrophic calcification.

TABLE 3

SITES OF 46 FEMALE CASES OF FIBRO-EPITHELIAL HYPERPLASIA

SITE	NUMBER
Lips	4
Buccal mucosa	3
Muco-buccal fold	16
Gingivae	10
Alveolar mucosa	8
Tongue	2
Floor of mouth	2
Palate	1
TOTAL	46

TABLE 4

SITES OF 15 MALE CASES OF FIBRO-EPITHELIAL HYPERPLASIA

SITE	NUMBER
Lips	2
Buccal mucosa	3
Muco-buccal fold	2
Gingivae	2
Alveolar mucosa	1
Tongue	1
Floor of mouth	-
Palate	4
TOTAL	15

Specimens showing atypical bone formation were also stained for calcium by the Von Kossa method and in all cases an intense dark stain in the areas of calcification could be seen.

Dyskeratosis

In 10 of the 46 female cases of fibro-epithelial hyperplasia there occurred unusual hyaline bodies in the more superficial layers of the epithelium. While no hyaline bodies were seen in any of the male cases, no statistical significance can be attached to this finding. The 10 lesions demonstrating these peculiar bodies are shown in Table 6.

It is interesting to note that in this series hyaline bodies occurred only in the fibro-epithelial hyperplasias. These bodies were generally circular in shape and ranged from 15 to 100 microns in diameter. Most of the bodies appeared to be surrounded by a clear vacuole and in 8 cases there was visible either adjacent or subjacent to them either spongiosis or hydropic degeneration of the epithelium. It is also noteworthy that while in 9 of these cases the bodies were definitely eosinophilic, the smaller bodies seen in Case 64 were slightly basophilic. In addition, Case 68, which occurred interproximally to the mandibular premolars, also showed extensive areas of bone in the connective tissue.

All cases showing hyaline bodies in the epithelium were further stained by the peracetic-orcein-Halmi method as described by FULLMER (1959). In all cases the bodies stained from a greenish orange to a dark orange colour (Appendix iv). Sections of normally keratinized oral mucosa were also treated by this method and it was noted that the stratum corneum of the normal specimen showed staining characteristics similar to those of the

TABLE 5

ANALYSIS OF 7 FEMALE CASES OF SOFT TISSUE OUTGROWTHS SHOWING THE PRESENCE OF BONE OR CARTILAGE

CASE NO.	AGE	TYPE OF LESION and hard tissue present	ESTIMATED DURATION	SITE OF LESION
26	32	F.E. hyperplasia (Bone)	Not known	Interprox. $\overline{45}$|
32	20	Vascular outgrowth (Bone)	4 - 5 months	Interprox. 32|
48	17	Vascular outgrowth (Bone)	2 years	Alveolar mucosa 54| region
53	4	F.E. hyperplasia (Bone)	2 - 3 months	Alveolar mucosa a| region
54	44	F.E. hyperplasia (Cartilage)	4 years	Incisive papilla
68	38	F.E. hyperplasia (Bone)	2 years	Interprox. $\overline{54}$| region
70	47	F.E. hyperplasia (Bone)	1 year	Gingiva $\overline{8}$| region

TABLE 6

ANALYSIS OF 10 FEMALE CASES OF FIBRO-EPITHELIAL HYPERPLASIA SHOWING HYALINE BODIES IN THE EPITHELIUM

CASE NO.	AGE	SITE OF LESION	OTHER CHANGES IN EPITHELIUM
11	83	Alveolar mucosa $\overline{4}$ region	-
21	45	Buccal mucosa $\overline{3}$ \ - / $\overline{3}$ region	Hydropic degeneration
31	51	M.-B. fold $\underline{3}$ | region	Ulceration and Hydropic degeneration
37	61	M.-B. fold $\overline{3}$ | - | $\overline{3}$ region	-
44	63	Interprox. $\overline{32}$ | region	Hydropic degeneration
57	65	M.-B. fold $\overline{8}$ | - $\overline{2}$ | region	Ulceration and Hydropic degeneration
58	21	M.-B. fold $\underline{8}$ | - $\underline{2}$ | region	Ulceration and Hydropic degeneration
63	34	Alveolar mucosa $\overline{3}$ | region	Hydropic degeneration
64	71	M.-B. fold $\overline{4}$ | - $\overline{3}$ | region	Hydropic degeneration
68	38	Interprox. $\overline{54}$ | region	Hydropic degeneration

hyaline bodies. Whilst there is no conclusive evidence to show that these bodies consist of keratin, it is highly suggestive that they represent some form of dyskeratosis.

Including the 10 cases showing hyaline body formation, there were 17 cases in the series exhibiting some form of dyskeratosis.

Other lesions

In the female lesions of the series there were 3 cases of vascular outgrowths (Cases 32, 48, and 55) and in all of them the pre-operative diagnosis was essentially correct. All these lesions occurred either on the gingiva or on the alveolar mucosa and could therefore be described as "epulides". Two of these were associated with pregnancy. However, in Case 48 the proper diagnosis was probably granuloma pyogenicum. In this case excision of the lesion had been carried out one year previously when a similar histo-pathological diagnosis had been made.

Case 69 in a 9 year old female was diagnosed clinically as a fibro-epithelial polyp. Histological examination, including mucicarmine stain, showed that the lesion was in fact a mucous extravasation cyst.

No case of true fibroma or papilloma was found in the females of the series. However, in the males, while no true fibromas were seen, there were two cases of papilloma (Cases 36 and 41). Clinical diagnosis was correct in one of these cases.

Only one case of vascular outgrowth was found in the males (Case 34). The clinical diagnosis not confirmed histologically, was a giant cell tumour. The lesion occurred palatal to the maxillary incisors and the area was being heavily traumatised by the lower anterior teeth.

Malignant Lesions

Both cases of malignancy occurred in male patients. In Case 40 the lesion occurred interproximally between maxillary left lateral incisor and canine in a 51 year old male. The lesion was round in shape, approximately 1 cm. in diameter and the mucosa was slightly lighter in colour than normal with some ulceration. The lesion was of fairly hard consistency and the attachment was sessile in nature. A clinical diagnosis of fibro-epithelial hyperplasia was, on this evidence, justifiable. (Fig. 22, p. 82.)

The patient was referred by his general dental practitioner for investigation and treatment of the lesion. As far as he was aware, it had only been present for some weeks, and it was confirmed by his dentist that at the time of routine dental examination one year previously the lesion was not present. Previous medical history showed that the patient had been treated for chronic alcoholism and cirrhosis of the liver.

Following excision and preparation of the specimen, histological examination showed that the body of the specimen was composed of cords and sheets of epithelial cells with little surrounding stroma. The epithelial cells were immature having a high nucleus-cytoplasmic ratio, hyperchromatic nuclei, numbers of unusual mitotic divisions, and evidence of invasion into small vessel walls. The stratified squamous epithelium covering the specimen was ulcerated and in some areas appeared to be in continuity with the underlying sheets of immature cells. A diagnosis of anaplastic carcinoma was established but it was not possible to determine whether the tumour was of primary or metastatic origin.

The patient was referred to the Professorial Surgical Unit of the Royal Adelaide Hospital for further investigation and management. He was discharged from this Unit some three weeks later, it having been established that there was a disseminated tumour present. However, no primary source had been found. During this period a biopsy of a lymph gland in the left groin disclosed a similar histology to that of the gingival lesion.

Paracentesis abdominis was performed but further ascites accumulated and the patient was re-admitted to hospital when a further 6 litres of fluid were drained. His condition quickly deteriorated and death followed, some three months after discovery of the gingival lesion. The autopsy report showed the cause of death as liver failure, and hepatoma with gross dissemination.

The second malignancy occurred in a 53 year old male (Case 66). This lesion was found on the cheek opposite the maxillary right first molar and seemed to be intimately associated with the jagged edges of this tooth. The general medical history was non-contributory. On examination, the lesion was round in form, approximately 1 cm. in diameter, slightly whiter than normal, and of firm consistency. The surface was smooth and not ulcerated, and the attachment was sessile in nature. According to the patient, the lesion had been present for some 5 years and he was totally unconcerned. A tentative diagnosis of fibro-epithelial hyperplasia was made pre-operatively. (Fig. 23, p. 83.)

The pathological report reads as follows:

"The tissue of origin is difficult to determine but the tumour appears to be of mesodermal origin.

The cell nuclei are large with finely reticular chromatin and one distinct nucleolus, and the cytoplasm is scanty. There is considerable variation in nuclear size and some mitoses are present.

Van Gieson stain shows isolated bands of collagen fibres but these are not plentiful and some areas are completely devoid of them. A capsule is present in some areas but in most it is absent. Thin-walled blood vessels are present. Mucicarmine indicates the absence of mucin. The appearance is suggestive of a sarcoma. The degree of malignancy is difficult to determine.

The oral lesion should be carefully investigated at regular intervals, as removal may have been incomplete. This is important in view of the malignancy of the lesion."

The patient was referred to the Cancer Clinic of the Royal Adelaide Hospital who referred him to Radiotherapy. Since only a few months have elapsed since the lesion was first observed no prognosis can be given at this stage.

The relationship between chronic trauma or other possible causes of the lesions in the 55 female occurrences is shown in Table 7. A similar analysis of the 20 male occurrences is shown in Table 8.

TABLE 7

RELATIONSHIP OF CHRONIC TRAUMA OR OTHER CAUSES TO TYPE OF LESION IN 55 FEMALE OCCURRENCES

TYPE OF LESION	DEFINITE RELATIONSHIP	PROBABLE RELATIONSHIP	NO RELATIONSHIP ESTABLISHED	TOTAL
Fibro-epithelial hyperplasia	30	3	13	46
Fibrous hyperplasia	3	1	1	5
Vascular outgrowths	2 (pregnancy)	-	1	3
Mucous extravasation cyst	-	1	-	1
TOTAL	35	5	15	55

TABLE 8

RELATIONSHIP OF CHRONIC TRAUMA OR OTHER CAUSES TO TYPE OF LESION IN 20 MALE OCCURRENCES

TYPE OF LESION	DEFINITE RELATIONSHIP	PROBABLE RELATIONSHIP	NO RELATIONSHIP ESTABLISHED	TOTAL
Fibro-epithelial hyperplasia	7	2	6	15
Papilloma	-	1	1	2
Vascular outgrowth	-	1	-	1
Malignancy	-	1	1 (metastasis from liver)	2
TOTAL	7	5	8	20

Estimated duration of lesions

Table 9 relates the type of lesion, as determined histologically, to the patient's estimate of its duration as recorded in the 55 occurrences in females. Table 10 illustrates this relationship in the 20 male occurrences. From these two tables it will be seen that in 18 cases the duration of the lesion was unknown. In 10 female and 5 male cases the lesions were not discovered by the patient and in the remaining cases no result was recorded. The manner in which the lesion was discovered by the patient is also of interest. Thus a prominent finding in all the vascular outgrowths was bleeding either spontaneous or with slight trauma. With regard to the lesions which showed malignancy, in Case 40 discovery was made because of some pain and discomfort, while in Case 66 although the patient had been aware of the lesion for some years, he could not recall how he had discovered it. In the 2 cases of papilloma, 1 was not discovered by the patient and no entry was made in this section for the other.

With regard to the fibrous and fibro-epithelial hyperplasias, 31 were discovered because of pain or discomfort and 21 were discovered by other means. These included accidental discovery during the patient's own visual inspection, or by a parent or other relative.

In view of the general dissemination of information regarding cancer to the lay public, it is interesting to observe the attitude of the patients in this series to the lesion when they themselves had discovered it.

TABLE 9

PATIENTS ESTIMATE OF DURATION OF LESION, RELATED TO TYPE OF LESION, IN 55 FEMALE OCCURRENCES

TYPE OF LESION	< 6 months	6 months-1 yr.	1-2 yrs.	> 2 yrs.	Unknown	TOTAL
Fibro-epithelial hyperplasia	6	7	6	17	10	46
Fibrous hyperplasia	-	-	-	4	1	5
Vascular outgrowths	2	-	1	-	-	3
Mucous extravasation cyst	1	-	-	-	-	1
TOTAL	9	7	7	21	11	55

TABLE 10

PATIENTS ESTIMATE OF DURATION OF LESION, RELATED TO TYPE OF LESION, IN 20 MALE OCCURRENCES

TYPE OF LESION	< 6 months	6 months-1 yr.	1-2 yrs.	> 2 yrs.	Unknown	TOTAL
Fibro-epithelial hyperplasia	4	-	2	3	6	15
Papilloma	1	-	-	-	1	2
Vascular outgrowths	1	-	-	-	-	1
Malignancy	1	-	-	1	-	2
TOTAL	7	-	2	4	7	20

The lesion had been discovered by the patient in 60 of the 75 cases under investigation. Of these, 16 stated that they were worried about the lesion but the impression gained by the writer was that most individuals in this group were actually deeply concerned. However, it seems strange that both patients with malignancy were in the group of 44 patients who showed no concern.

CHAPTER VII

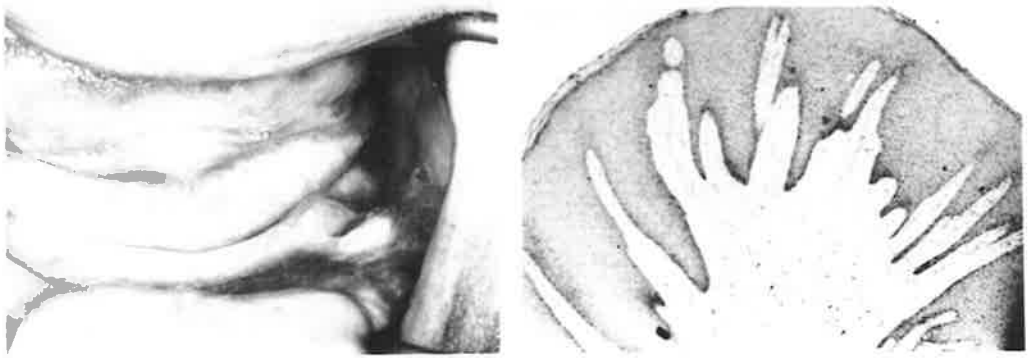
DISCUSSION

In this series, the female cases outnumbered the male cases by almost three to one. Since no random sampling was carried out, no statistical significance can be attached to this finding. However, some statistical significance can be attached to the finding that in excess of 75 percent of the lesions in each of the sexes were fibro-epithelial hyperplasias. In addition, it is important to note that a majority of the fibro-epithelial and fibrous hyperplasias could be related to some form of chronic irritation. (Figs. 5, 6, 7, 8)

1. FIBRO-EPITHELIAL AND FIBROUS HYPERPLASIAS

A study of Tables 1 and 2 shows that most of the fibro-epithelial and fibrous hyperplasias occurred in persons above 30 years of age. While this age incidence is not statistically significant, it is perhaps reasonable to assume that in the older individual there is more likelihood of chronic irritation having acted over long periods.

A study of Appendices v and vi shows that while the fibrous hyperplasias exhibited little vascularity and inflammation, in the fibro-epithelial hyperplasias these processes were usually present to some degree and in many cases frank ulceration was evident. Furthermore, the connective tissue of the fibrous hyperplasias showed minimal cellularity while in the fibro-epithelial hyperplasias connective tissue cells and fibres were present in varying proportions. In general, the lesions which were soft clinically showed a relatively greater proportion of the cellular elements.

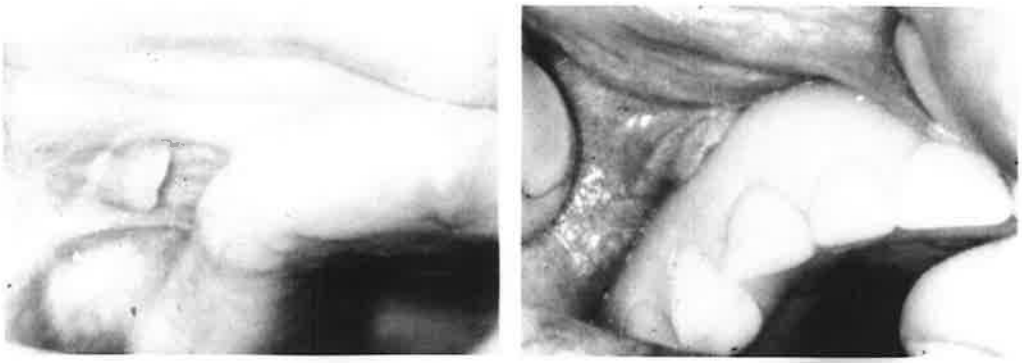


A. B.

Fig. 5 (Case 11) Fibro-epithelial hyperplasia

A. Clinical appearance of lesion.

B. Microscopical appearance illustrates acanthosis of the epithelium and hyperplasia of the connective tissue. The epithelium also shows some parakeratosis. (H. and E. X 100)



A. B.

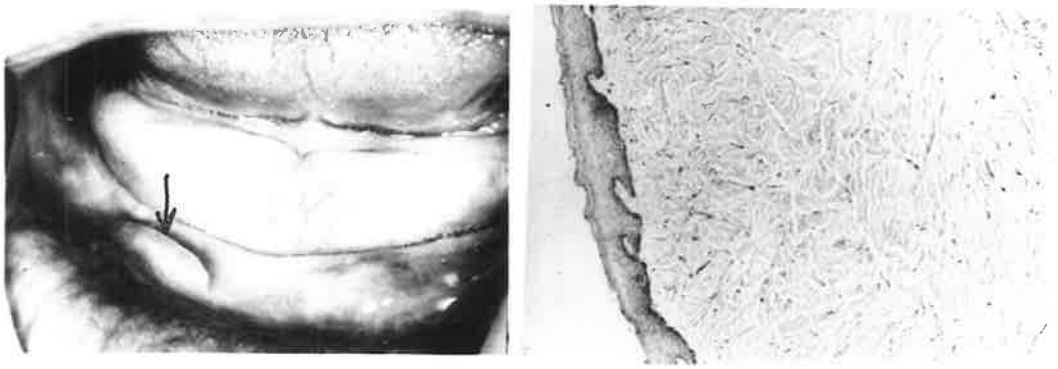
C.

Fig. 6 (Case 35) Fibro-epithelial hyperplasia

A. Clinical appearance of lesion.

B. Relationship of lesion to complete upper denture.

C. Microscopical appearance. In this field the hyperplasia is more marked in the connective tissue which is also fairly vascular. (H. and E. X 100)

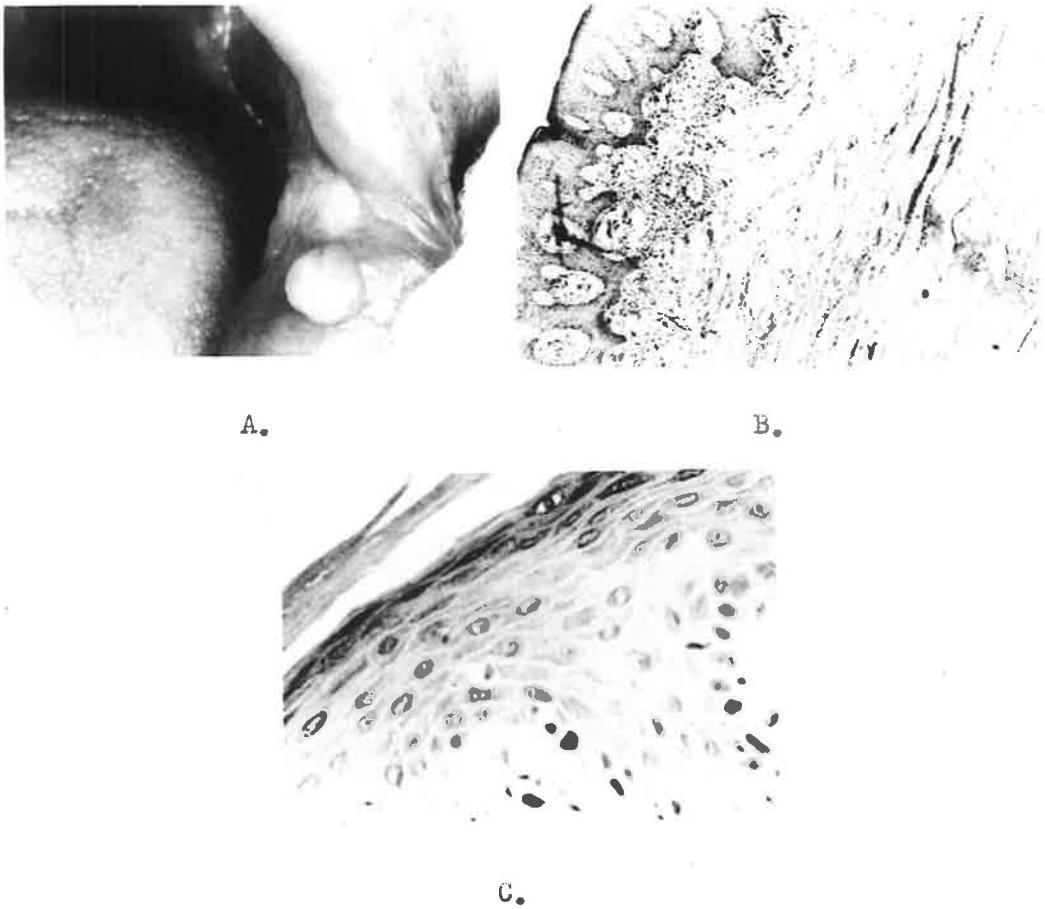


A. B.

Fig. 7 (Case 24) Fibrous hyperplasia

A. Clinical appearance of lesion.

B. Microscopical appearance showing relatively thin epithelium but marked hyperplasia of connective tissue which is mainly fibrous in character. (H. and E. X 100)



A. B.

C.

Fig. 8 (Case 1) Fibro-epithelial hyperplasia

A. Clinical appearance of lesion.

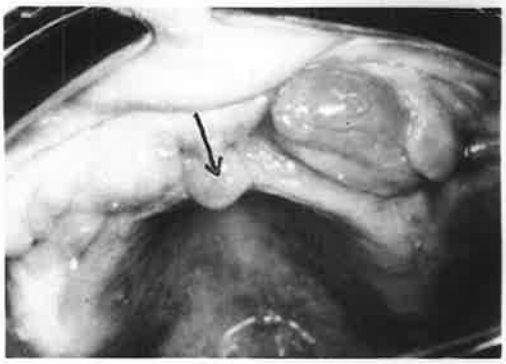
B. Microscopical appearance showing acanthosis of the epithelium and hyperplasia of the connective tissue. A well defined sub-epithelial layer of inflammatory elements is also visible. (H. and E. X 100)

C. Higher magnification showing well defined stratum granulosum and some keratinization more superficially. (H. and E. X 400)

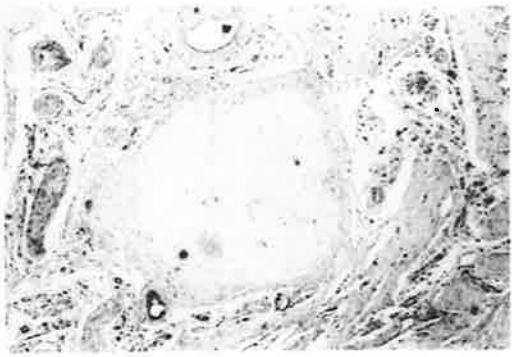
Analysis of Tables 3 and 4 with regard to site of each lesion, revealed that no statistical significance could be attached to the observed differences. However, it will be seen that in areas in which denture irritation is commonly observed, that is, alveolar mucosa, muco-buccal fold, and the buccal mucosa, the fibro- epithelial hyperplasias occurred relatively more frequently in the females. COOPER (1964) has made a similar finding in his series of denture hyperplasias although he makes no explanation for this finding. However, the impression gained by the writer was that this is perhaps due to the higher incidence of denture wearers in the females of this series, but mainly because of the greater willingness of the female to tolerate denture discomfort in the interests of appearance.

A. Lesions showing Calcification

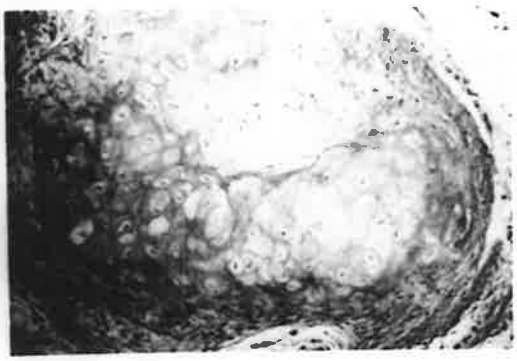
Little statistical significance can be attached to the fact that while cartilage or bone was found in 7 of the female lesions, none occurred in the males of this series. In all of the female cases which showed such calcification, the lesions could be broadly described as epulides. In the cases which contained bone, the maximum known duration according to the patient was 2 years. Case 54 contained cartilage and was removed from the region of the incisive papilla after a known duration of 4 years. (Fig. 9) However, SICHER (1962) has shown that irregular islands of hyaline cartilage, which are vestigial extensions of the paraseptal cartilages, may surround the palatine ducts. Furthermore, in some cases the cartilage may be found in the anterior part of the papilla where it shows no apparent relationship to the nasopalatine ducts. It is likely therefore that the cartilage found in Case 54 did not arise from the lesion.



A.



B.



C.

Fig. 9 (Case 54) Fibro-epithelial hyperplasia

A. Clinical appearance of lesions.

B. Microscopical appearance of section from central lesion in A showing central island of cartilage. (H. and E. X 100)

C. Higher magnification of cartilaginous tissue. (Van Gieson X 400)

Of the remaining 6 lesions in this group, 4 were classified as fibro-epithelial hyperplasias and 2 as vascular outgrowths -- one of the latter (Case 32) being associated with pregnancy.

COOKE (1952b) shows that the incidence of the fibrous type of epulis in females is four times as common as in males. According to COOKE, about 20 per cent of these epulides show some degree of bone formation and he concludes that they are hyperplasias resulting from chronic irritation. Furthermore, the varied histological picture seen in these lesions represents different stages in the natural history of the lesion. In the cases showing bone formation in this series only in Cases 32 and 53 could some form of irritation be related to the lesion.

With the exception of the vascular outgrowths, all cases in this series containing bone showed some epithelial hyperplasia as well as connective tissue hyperplasia although the latter was more marked. This is probably the reason why most authors in the past have referred to these lesions as fibrous epulides. STONES (1962) states that the lesion which arises from the oral mucosa as a result of chronic trauma presents a similar histological appearance of fibro-epithelial hyperplasia although as the lesion grows older more fibrous tissue is laid down. Furthermore, STONES expresses the opinion that in any of these if the source of irritation is removed the histological picture becomes one of irregular collagen fibres and little vascularity. The view that many of the epulides may show epithelial hyperplasia is also expressed by BERNIER and ASH (1948), COOKE (1952b), TOTO (1957), ORBAN and WENTZ (1960) and ASH (1961). In addition all these authors are agreed that bone formation is more likely in lesions arising from the gingival region than in

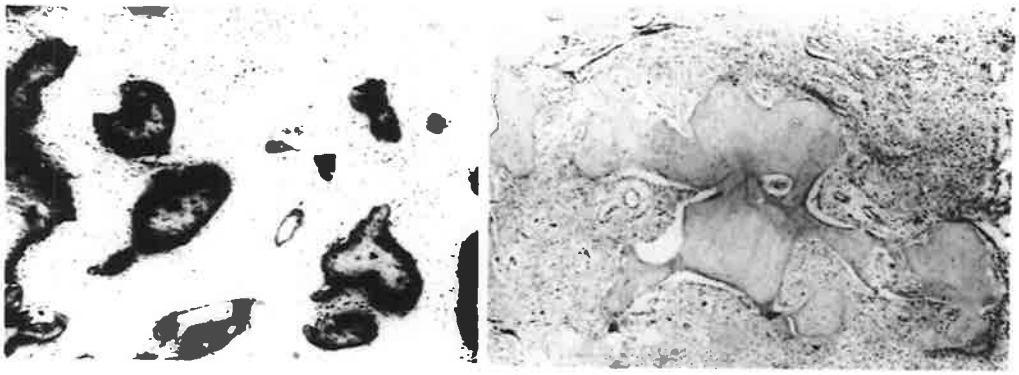
similar reactions to irritation occurring in other areas of the oral mucosa. In COOKE's series of cases bone was not found in the older more fibrous lesions but mainly in those which were less than one year old. The opinion expressed by COOKE is that in the firm avascular lesion there is no further stimulus to differentiation of the undifferentiated mesenchymal cells and that as a result, no bone is formed. (Fig. 10)

Although the maximum known duration of the fibro-epithelial lesions showing bone formation in this series was 2 years, the mean duration was 13 months. In these cases, the connective tissue surrounding the areas of bone formation was of the cellular variety which lends support to the opinions expressed by COOKE.

B. Formation of hyaline bodies in the epithelium and dyskeratosis

It has already been mentioned that no statistical significance can be attached to the finding that while 10 of the 46 female cases of fibro-epithelial hyperplasia displayed peculiar eosinophilic bodies in the superficial layers of the epidermis, none of these were seen in any of the male cases. (Figs. 11, 12, 13, 14, 15)

ZISKIN and NESSE (1946), in discussing pregnancy gingivitis, describe an unusual case of degeneration characterized by the formation of hyaline bodies in the epithelium near the surface. Illustrations of these bodies show that they are similar to those found in the present series. In discussing the epithelial changes in epulis gravidarum (pregnancy tumour) TIILILÄ (1962) comments that the epithelium is almost invariably hyperplastic and hydropic degeneration is frequently seen. With regard to the hyaline bodies she writes as follows:-

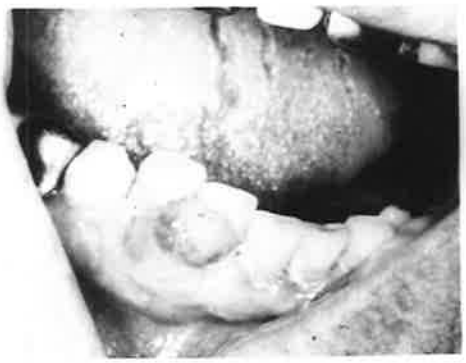


A. B.

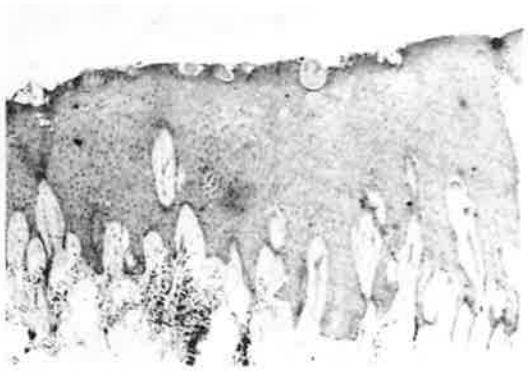
Fig. 10

A. (Case 68) Fibro-epithelial hyperplasia. Microscopical appearance illustrating irregular islands of atypical bone surrounded by a cellular connective tissue. (Von Kossa X 100)

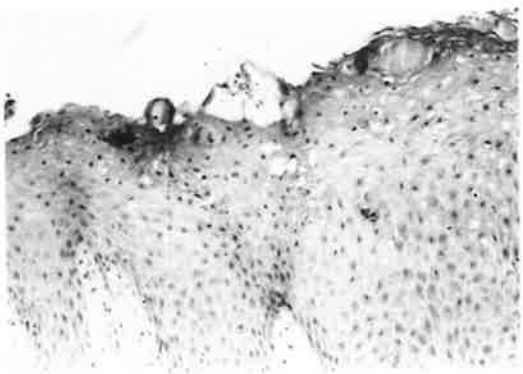
B. (Case 26) Fibro-epithelial hyperplasia. Atypical bone containing osteocytes and surrounded by cellular connective tissue. (H. and E. X 100)



A.



B.



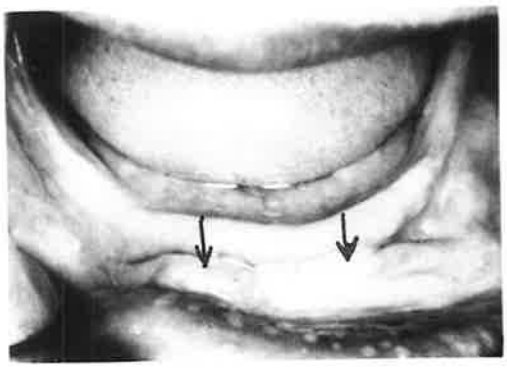
C.

Fig. 11 (Case 44) Fibro-epithelial hyperplasia

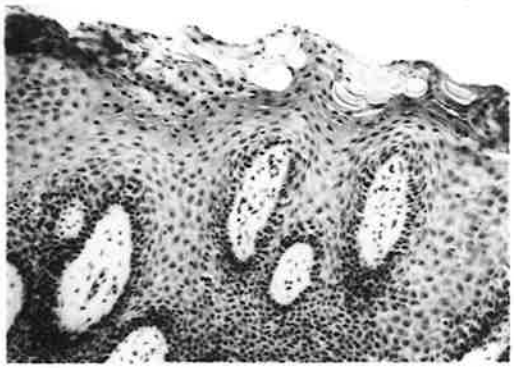
A. Clinical appearance of lesion.

B. Microscopical appearance. There is marked acanthosis and numerous hyaline bodies are visible in the superficial layer of the epithelium. In the superficial layers of the connective tissue there is visible a collection of inflammatory cells. (H. and E. X 100)

C. Higher magnification (X 400) of hyaline bodies. The field includes the left hand margin of that seen in B.



A.



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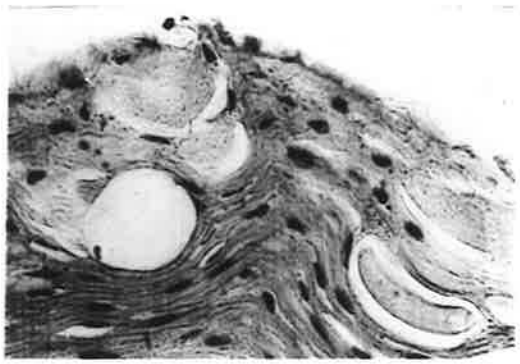


C.

Fig. 12 (Case 21) Fibro-epithelial hyperplasia

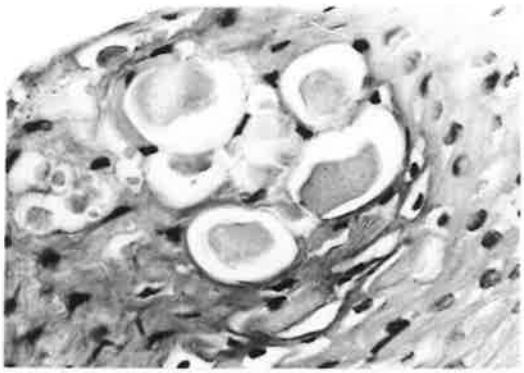
A. Clinical appearance of lesion.

B. Epithelium shows large hyaline bodies in the superficial layers. (H. and E. X 100)

C. Higher magnification of hyaline bodies. In this case the bodies appear to have a granular structure. (H. and E. X 400)

A.

B.



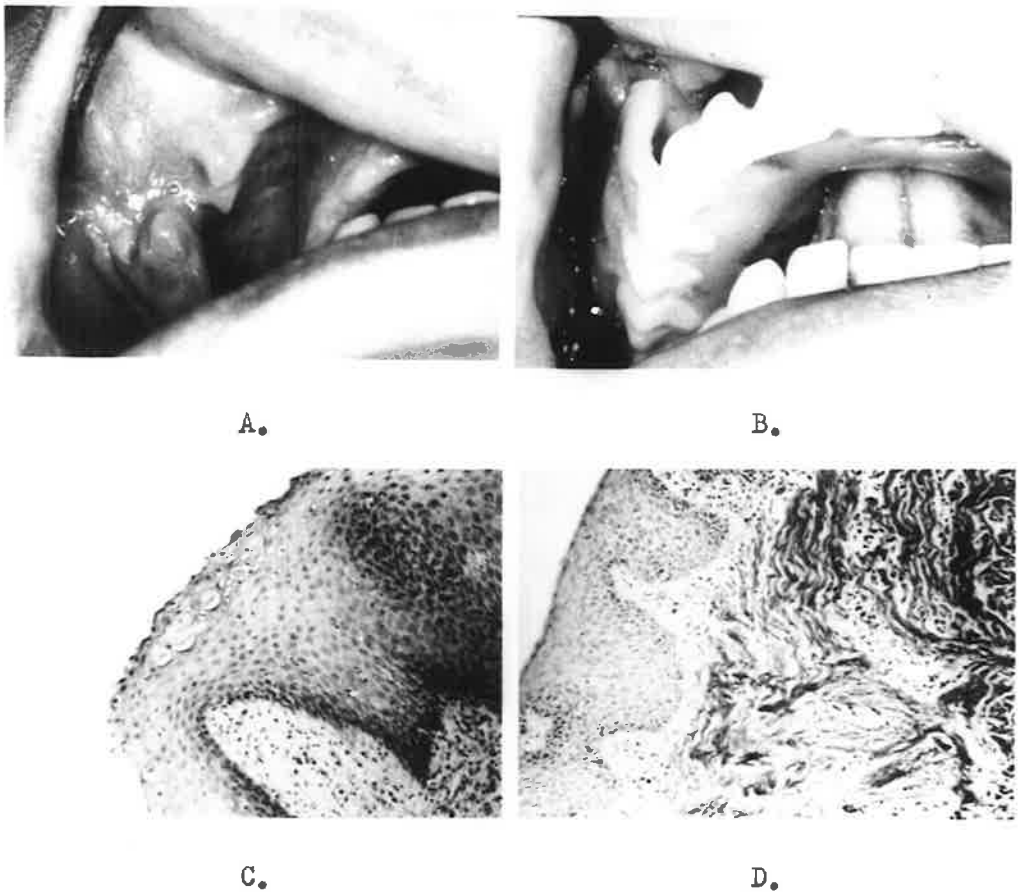
C.

Fig. 13 (Case 31) Fibro-epithelial hyperplasia

A. Clinical appearance of lesion.

B. Epithelium showing acanthosis, some hydropic degeneration, and the presence of hyaline bodies. (H. and E. X 100)

C. Higher magnification of hyaline bodies. Bodies of different sizes are visible. (H. and E. X 400)



A. B.

C. D.

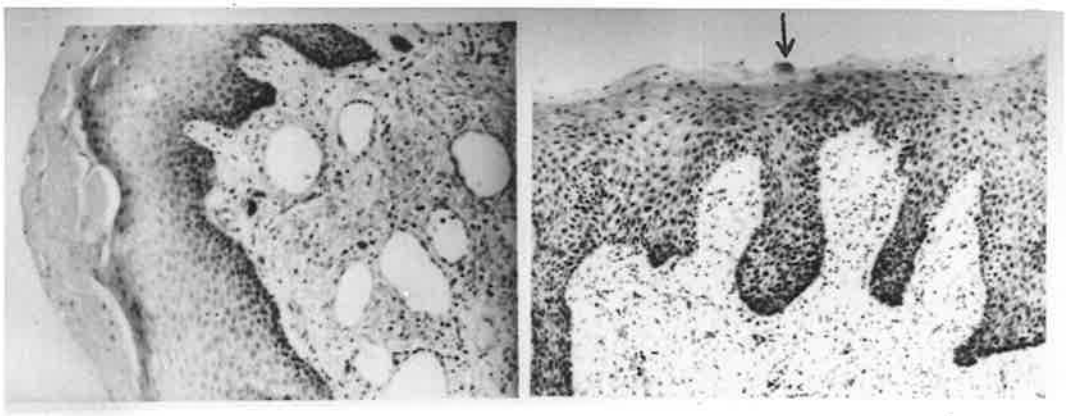
Fig. 14 (Case 58) Fibro-epithelial hyperplasia

A. Clinical appearance of lesion.

B. Relationship of complete upper denture to lesion. In this view the denture is not completely in position.

C. Small hyaline bodies associated with hydropic degeneration and acanthosis of the epithelium. (H. and E. X 100)

D. In this field there is marked fibrous hyperplasia and little epithelial hyperplasia. (Van Gieson X 100)



A. B.

Fig. 15

A. (Case 57) Relatively large hyaline bodies. (H. and E. X 100)

B. (Case 64) Single small faintly basophilic body in the most superficial layer of the epithelium. (H. and E. X 100)

"Dyskeratosis, associated with the development of hyaloid bodies in the superficial layer of the epithelium, appears more rarely. The hyaloid bodies may be the size of cells or larger cyst-like formations which - like keratin - stain intensely red by the azan method. There are cases in which some of these formations stain red, and some blue. The latter probably contain keratohyaline."

According to LEVER (1961), in Darier's disease, the corps ronds occur in the upper stratum malpighi, particularly in the granular layer. They possess large, round, homogenous, basophilic nuclei and a homogenous (hyalinized) deeply eosinophilic cytoplasm, and are much larger than normal squamous cells. Corps ronds develop because of premature partial keratinization of the squamous cell, and the process is called benign dyskeratosis. It is interesting to note that the aetiology of this disease has been attributed to vitamin A deficiency (ANDERSON, 1957). Furthermore, LEVER (1961) states that the oral mucosa is involved commonly, but in this region, while dyskeratosis is seen there is no hyperkeratosis.

Hyaline bodies in the epithelium of dental cysts have been described by RUSHTON (1955). These appear to be of two basic types described as linear and circular or polycylic in shape. Histochemical study of these bodies carried out by WERTHEIMER, FULLMER and HANSEN (1962) was suggestive of keratin in some respects. However, in outline and microscopic structure these bodies bear little resemblance to those described as occurring in the superficial layers of the epithelium of the fibro-epithelial lesions in the series under investigation. Furthermore, it was not intended to investigate histochemically the structure of the

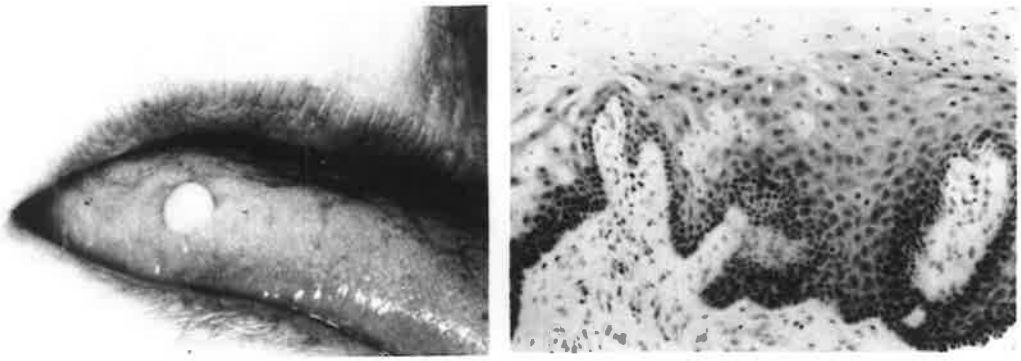
hyaline bodies found in the course of this investigation.

The peracetic-orcein-Halmi stain was selected since it appeared to best demonstrate the hyaline bodies which stained from a greenish orange to a dark orange colour. Appendix iv. In addition the stratum corneum of normally keratinized oral mucosa exhibited similar staining characteristics. It is highly suggestive, therefore, that these bodies represent some form of dyskeratosis. In addition, since there were no other associated anaplastic changes and the sub-jacent epithelium was normal except for hyropic degeneration in some cases, it was felt that they represent a benign dyskeratosis resembling that seen in Darier's disease.

The importance of the malignant type of dyskeratosis has already been stressed. In this series, two cases of possible dyskeratosis were seen in males and five in females - all arising in fibro-epithelial hyperplasias. (Fig. 16) In view of the fact that dyskeratosis is regarded as signifying irreversibility of the lesion, (BERNIER, 1959) it is important that the irritative cause be removed and the lesion excised.

C. Relationship to chronic irritation

Some form of chronic irritation could be associated with approximately 70 per cent of the fibro-epithelial and fibrous hyperplasias which occurred in this series. However, it may be impossible to find a definite cause-effect relationship in all cases of these lesions since the absence of an obvious cause at the time of examination is no proof that one did not exist at some previous date.



A. B.

Fig. 16 (Case 30) Fibro-epithelial hyperplasia

A. Clinical appearance of lesion.

B. Well marked dyskeratosis of the epithelium. (H. and E. X 100)

In most cases, where a source of irritation could be related to the lesion this was found to be some form of dental irritation such as artificial dentures, jagged edges of natural teeth, or lip biting habits. However, in Cases 25 and 27 the lesions were situated on the buccal mucosa of the cheek opposite a missing molar tooth and the patient was aware of a strong cheek sucking habit. This was felt to be the possible aetiologic factor. GORLIN (1957), states that the fibro-epithelial lesion or irritation fibroma may be observed opposite a natural diastema or one produced by tooth extraction. It is GORLIN's contention that the lesion may be generated by the heaping-up of normal mucosa due to the unconscious habit of applying negative pressure to this interdental space.

D. Duration of lesion

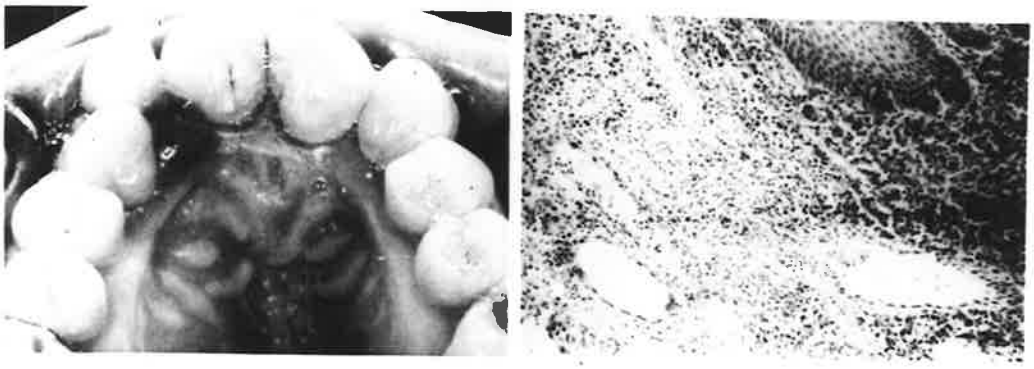
With regard to duration it is apparent that if the lesion was not first discovered by the patient, it became almost impossible to estimate its duration with any degree of accuracy. In many cases however, the patient could definitely remember a date on which a medical or dental practitioner had examined the oral cavity and had made no comment regarding any abnormal outgrowth. While it is possible that a lesion was present at this time, for the purpose of this investigation such information was recorded to show the lesion as arising subsequent to this date. In addition, the recorded duration of the lesion was no doubt greatly influenced by the patient's attitude to it. For example, if the lesion was discovered by the patient in the more remote past and he was totally unconcerned, the chances of his seeking advice were relatively poor.

2. VASCULAR LESIONS

The four vascular lesions which occurred in the series could all be classified as epulides; three of them occurring in females and one in a male. It is noteworthy that in view of the probable relationship between giant cell tumour, pregnancy tumour, vascular epulis and granuloma pyogenicum, the pre-operative diagnosis was essentially correct (ANDERSON, 1939; EULER, 1953). Two of the lesions in females were associated with pregnancy and one of these (Case 55, Fig. 17), had been excised one month previously but had recurred. In the other case, deposits of calculus were closely related to the lesion. However, in Cases 32 and 48 no form of chronic irritation could be associated with the lesion. On the other hand, with the male lesion (Case 34, Fig. 18) there seemed little doubt that it was related to the deep overbite which was causing the soft tissues palatal to the maxillary incisors to be heavily traumatised by the mandibular anterior teeth.

All of the lesions were detected by the patient and a common finding was bleeding, either spontaneous or with slight trauma. In three cases the patient's estimate of the duration of the lesion was less than six months. In Case 48 the lesion had been excised one year previously but had recurred. (Fig. 19)

According to ZISKIN and NESSE (1946) gingival growths associated with pregnancy may be related to disturbances in hormonal balance that occur during this period. TIILILÄ (1962) considers that inflammation due to trauma is the primary cause but under the influence of pregnancy the inflammatory response becomes intensified. It may be however, that hormonal imbalance has a direct action upon the endothelial cells which operates even in the absence of local infection. Trauma accentuates and complicates the change.

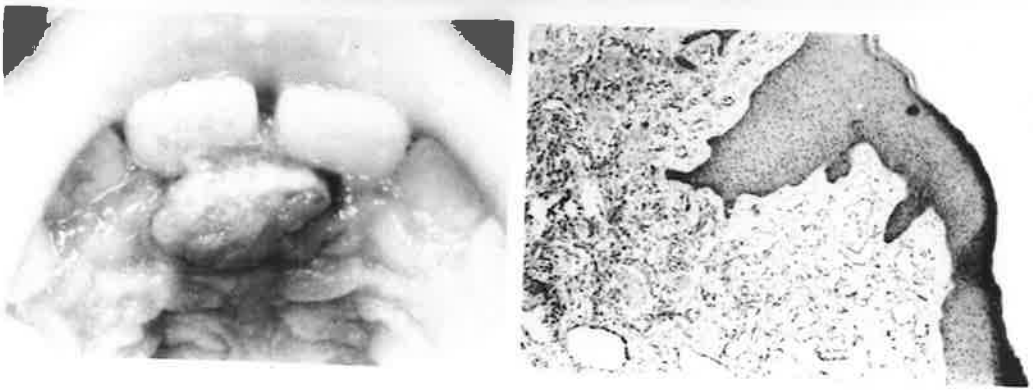


A. B.

Fig. 17 (Case 55) Vascular lesion

A. Clinical appearance showing palatal extension of lesion.

B. Microscopical appearance showing large, thin-walled blood vessels and the presence of inflammatory exudate. (H. and E. X 100)

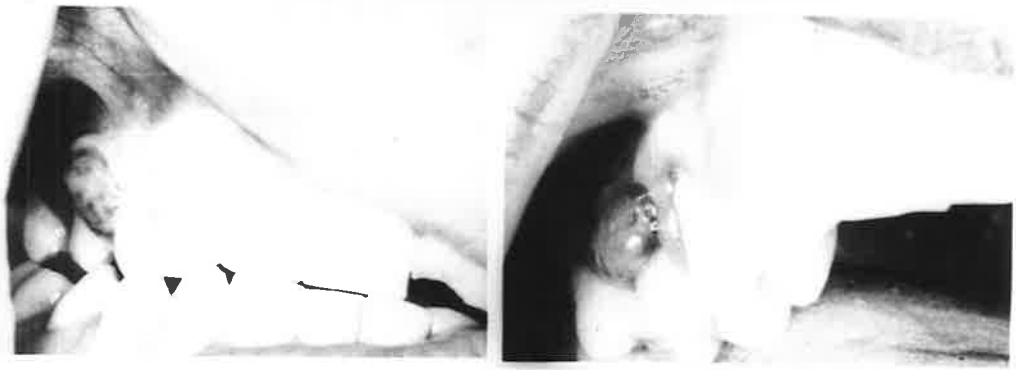


A. B.

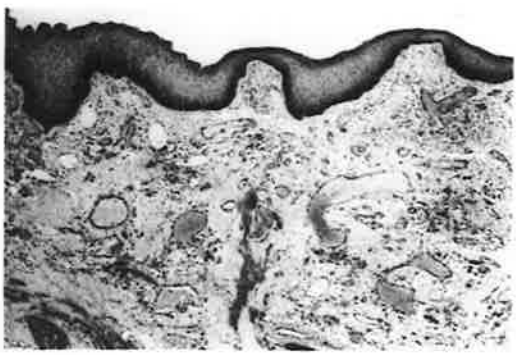
Fig. 18 (Case 34) Vascular lesion

A. Clinical appearance of lesion.

B. Microscopical appearance. Some parakeratosis and acanthosis of the epithelium are evident. In addition, numerous thin-walled blood vessels can be seen in the connective tissue. (H. and E. X 100)



A. B.



C.

Fig. 19 (Case 48) Granuloma pyogenicum

A. Clinical appearance on 18.6.62.

B. Clinical appearance on 14.6.63.

C. Microscopical appearance of B. The epithelium in this section is relatively thin. There are numerous thin-walled blood spaces in the connective tissue. (H. and E. X 100)

3. MUCOUS EXTRAVASATION CYST (Case 69)

This lesion occurred in a nine year old female and, according to the patient's mother who discovered it, had been present for three months. In addition, there was a definite history of lip-biting of the region of the right lower lip, where the lesion was situated.

Clinically, the lesion was round in shape, some 7 mms. in diameter, and the mucosa was slightly lighter than normal in colour. The surface was smooth, and the lesion moderately soft in consistency, with an attachment which was pedunculated in nature. (Fig. 20) Pre-operative diagnosis was fibro-epithelial polyp.

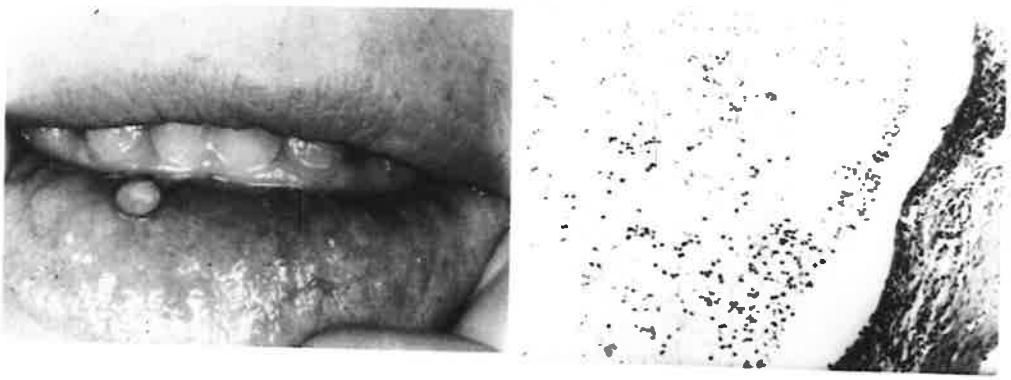
The pathologist's report in part was as follows:-

"Central cavity showing mucous is surrounded by connective tissue and lined in places with a thin layer of epithelial cells. This is a mucous extravasation cyst."

GORLIN, (1957), and THOMA and GOLDMAN (1960) give as the pathogenesis of this condition, occlusion of the outlet of the secretory duct of a mucous gland. This occlusion may be caused by biting or other injury to the area as was apparently the case with the lesion found in this series.

4. BENIGN NEOPLASMS

There were only two cases of true benign neoplasms in the series under investigation and both were papillomas found in male patients. In one of these (Case 36) the lesion occurred on the tongue of a 45 year old male and was not noticed by the patient. In this case, there appeared to be some relationship to a tongue-biting habit. The patient was a syphilitic



A. B.

Fig. 20 (Case 69) Mucous extravasation cyst

A. Clinical appearance of lesion.

B. Microscopical appearance showing thin walled lining and contents of cystic cavity. (Mucicarmine X 100)

(Wasserman ++++) and when seen was aphasic.

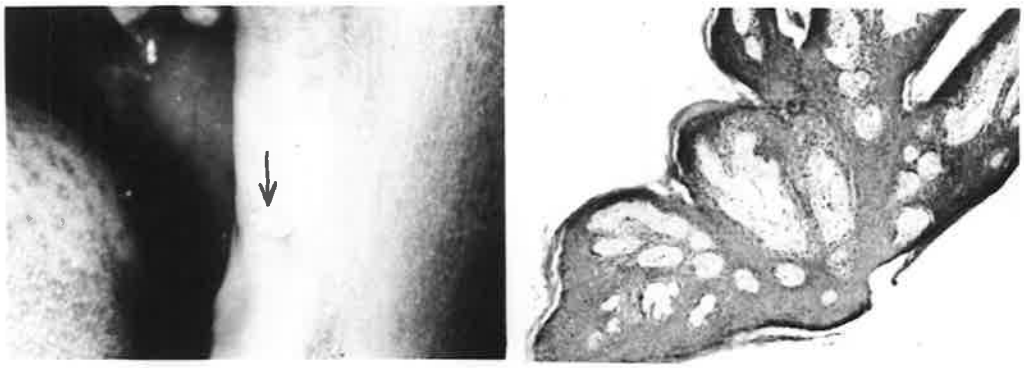
In Case 41, the lesion occurred on the lip of a 6 year old male there being no visible form of chronic irritation associated with the lesion which had been noticed by a parent some three weeks previously. (Fig. 21) At the time of examination the patient had numerous warts on his fingers. In this case, as in Case 36, the pre-operative diagnosis was essentially correct.

THOMA and GOLDMAN (1960) and STONES (1962) state that many papillomas may be related to chronic irritation and this seems a possibility in Case 36. TIECKE (1957) suggests trauma, infection, metabolic disturbances, and viruses, as possible aetiological factors. In Case 41 of this series the microscopic picture was similar to that seen in verruca vulgaris as described by LEVER (1961). This, combined with the clinical finding of crops of warty outgrowths on the hand, suggests a papillomatous lesion of viral origin.

5. MALIGNANT NEOPLASMS

The case histories of both the malignant tumours in this series have already been described. However, because of their importance in the field of clinical Oral Pathology, there are some points that bear re-emphasis.

(1) In both cases the lesion was diagnosed clinically as a fibro-epithelial hyperplasia. Although, the possibility of malignancy should always enter into the differential diagnosis of some oral lesions, there was little to suggest, excepting the short duration of the lesion in Case 40, a possible malignancy. It is important



A. B.

Fig. 21 (Case 41) Papilloma

A. Clinical appearance of lesion.

B. Microscopical appearance. There is keratinization of the epithelium and scarcity of connective tissue. In addition the branching pattern of the lesion is evident. (H. and E. X 100)

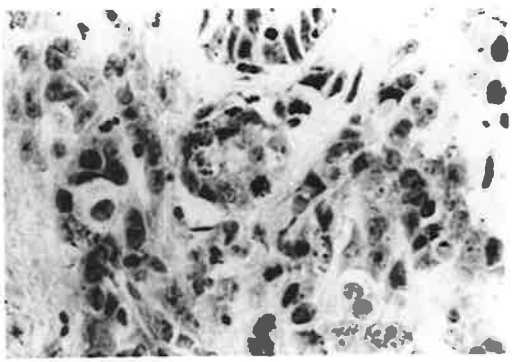
therefore to investigate all soft tissue outgrowths of the oral cavity, and as part of the investigation a thorough histological examination of each lesion should be carried out.

(2) Although Case 40 was of metastatic origin from the liver, and Case 66 was primary in origin, the clinical picture was similar in both cases. Histologically however, the difference was marked. (Figs. 22, 23)

(3) In Case 66 the lesion had been noticed by the patient 5 years previously and clinically appeared to be associated with chronic irritation.
It has already been stated that there is little experimental evidence to relate chronic mechanical irritation to the onset of malignancy (PEREZ-TAMAYO, 1961), but, in view of the previously noted statements of WILLIS (1960) regarding the relationship between hyperplasia and neoplasia, the possibility of such a relationship cannot be ignored. Case 66 of the present series tends to support this view.

A.

B.



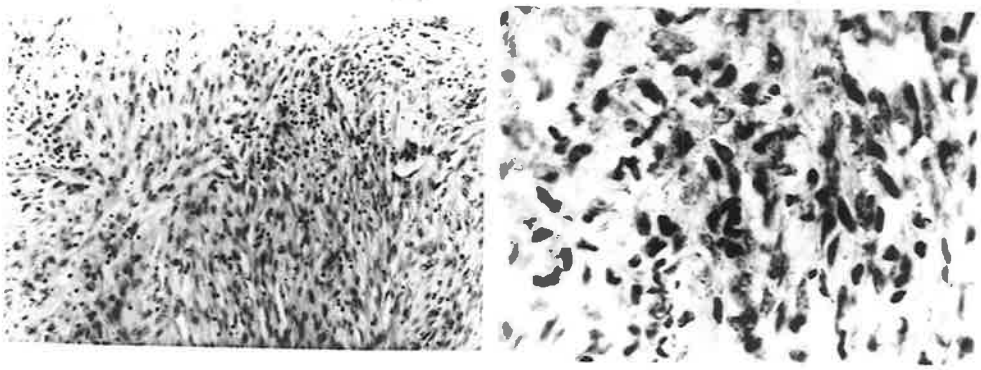
C.

Fig. 22 (Case 40) Hepatoma

A. Clinical appearance of lesion.

B. Microscopical appearance of comparatively normal epithelium with large numbers of tumour cells in the superficial layers of the dermis. (H. and E. X 100)

C. Higher magnification of tumour cells. Several bizarre mitotic figures can be seen and in addition there is hyperchromatism and pleomorphism of other cells in the field. (H. and E. X 400)



A. B.

Fig. 23 (Case 66) Fibrosarcoma

A. Microscopical appearance showing extreme cellularity and pleomorphism of the lesion. (H. and E. X 100)

B. Higher magnification showing pleomorphism, hyperchromatism, and increase of nuclear-cytoplasmic ratio of cells. (H. and E. X 400)

CHAPTER VIII

SUMMARY AND CONCLUSIONS

An investigation on tumours and tumour-like lesions of the soft tissues of the oral cavity has been carried out and is based on a series of 75 cases. Of this number, 61 were obtained from patients presenting for treatment to the Dental Department of the Royal Adelaide Hospital. The remaining 14 cases were referred for histological examination to the Oral Pathology Department of the Dental School by medical and dental practitioners.

Such an investigation was considered necessary because of the confusion that exists in the literature regarding tumours and tumour-like conditions of the oral cavity. Since a great deal of the confusion appears to arise from loose terminology, an attempt has been made to standardize this during the investigation.

The present investigation was primarily concerned with benign tumours and tumour-like conditions of the oral cavity. For the reasons stated below it was found impossible however, to avoid some discussion on malignant conditions:-

1. Malignant tumours may clinically resemble benign conditions.

2. Malignant changes may develop in pre-existing benign conditions.

3. Although of relatively lower incidence, malignant tumours are of grave importance to the welfare of the patient.

Clinical findings, as comprehensive as possible, of each case, together with a histological report have been carefully recorded and the results analysed.

From the series consisting of 75 cases of tumour and tumour-like conditions of the soft tissues of the oral cavity the following conclusions have been reached.

1. The conditions were found more frequently in the females. This may be due to the higher incidence, or less reticence on the part of the females to seek advice, or a combination of both.

2. The majority of lesions in both sexes were in the nature of fibro-epithelial hyperplasias. A smaller precentage showed almost a pure fibrous hyperplasia and these tended to be of longer duration. Irrespective of duration, most cases of fibro-epithelial and fibrous hyperplasia appeared to be related to some form of chronic irritation.

3. In seven cases in females some form of calcification occurred in lesions which could be described on a clinico-topographical basis as epulides. However, with regard to the lesion in which cartilage was found, it is unlikely that the calcification was pathological. In 4 of the remaining cases the epulides were of the fibro-epithelial type and in 2 cases they were of the vascular type.

4. The four cases of vascular outgrowths were also epulides. Two of these were associated with pregnancy.
It is therefore important that the term epulis, if used, be qualified to indicate the histological structure of a lesion in order to ensure proper treatment of the lesion.

5. There were only 2 cases of true benign soft tissue neoplasms in the series and these were both papillomas. No true fibromas were seen and it can be said that this tumour rarely occurs in the oral cavity.

6. In most cases clinical diagnosis of the vascular outgrowths and the papillomas was confirmed histologically.

7. A benign type of dyskeratosis characterized by the formation of hyaline bodies in the more superficial layers of the epithelium was seen in 10 of the female cases of fibro-epithelial hyperplasia. Perhaps of greater significance was the finding that 7 other cases of fibro-epithelial hyperplasia exhibited some degree of the malignant type of dyskeratosis.

8. Clinically, the 2 malignant tumours could not be differentiated from the benign fibro-epithelial hyperplasias. Furthermore, in one of the malignant tumours it is possible that chronic irritation from the teeth was an aetiological factor.

9. The importance of thorough investigation, including histological examination, of all oral soft tissue outgrowths has been emphasized.

10. The role of preventive dentistry in the maintenance of a healthy oral cavity must be extended to include the prevention of any form of chronic irritation and a high degree of vigilance as far as oral neoplasia is concerned.

APPENDIX I

ORAL SOFT TISSUE OUTGROWTHS -- RECORD SHEET

Serial No. . . . . . **Hospital No.** . . . . . .

Name . . . . . Marital Status . . . . . .

Age . . . . . Sex . . . . . .

Occupation . . . . . Photograph . . . . . .

General Health

(a) Past medical history

(b) Present medical history

Dental Health

(a) Chart

(b) Edentulous - denture type and age . . . . . .

Possible cause and its history

Patient's estimate of duration of lesion . . . . . .

How discovered by patient

(a) pain . . . . . (b) discomfort . . . . . (c) others . . .

Patient's attitude to lesion

(a) unconcerned . . . . . (b) worried . . . . . .

APPENDIX I (cont.)

Clinical Examination of Lesion

(a) Position:

	Maxillary	Mandibular
lips	.....	.....
buccal mucosa	.....	.....
cheek	.....	.....
muco-buccal fold	.....	.....
gingivae	.....	.....
alveolar mucosa	.....	.....

tongue - dorsum ....., sides ....., inferior surface .....
floor of mouth .....
palate .....

(b) Shape :

rounded ....., elongated .....

(c) Size (mms.):

.....

(d) Color (compared to normal mucosa)

whiter ....., normal ....., darker .....

(e) Surface appearance:

smooth ....., corrugated ....., papillary .....,
keratinized ....., ulcerated .....

(f) Consisteney:

hard ....., firm ....., rubbery ....., soft .....,
friable .....

(g) Attachment:

pedunculated ....., sessile .....

Bone Involvement

Provisional Diagnosis

(a) Fibro-epithelial lesion
(b) Denture hyperplasia
(c) Papilloma
(d) Fibroma
(e) Vascular lesions
(f) Others

Histopathology

(including treatment of specimen)

APPENDIX II

FIXING SOLUTION USED BY ORAL PATHOLOGY DEPARTMENT, UNIVERSITY OF ADELAIDE.

FORMOL SALINE

Formaldehyde (40 per cent)	100 ml.
Sodium chloride	9 gm.
Tap water	900 ml.

The solution is buffered with magnesium carbonate to excess.

The period of fixation required in this solution is 24 hours or longer.

APPENDIX III

HAEMATOXYLIN AND EOSIN STAINING METHOD AS USED BY THE ORAL PATHOLOGY DEPARTMENT, UNIVERSITY OF ADELAIDE.

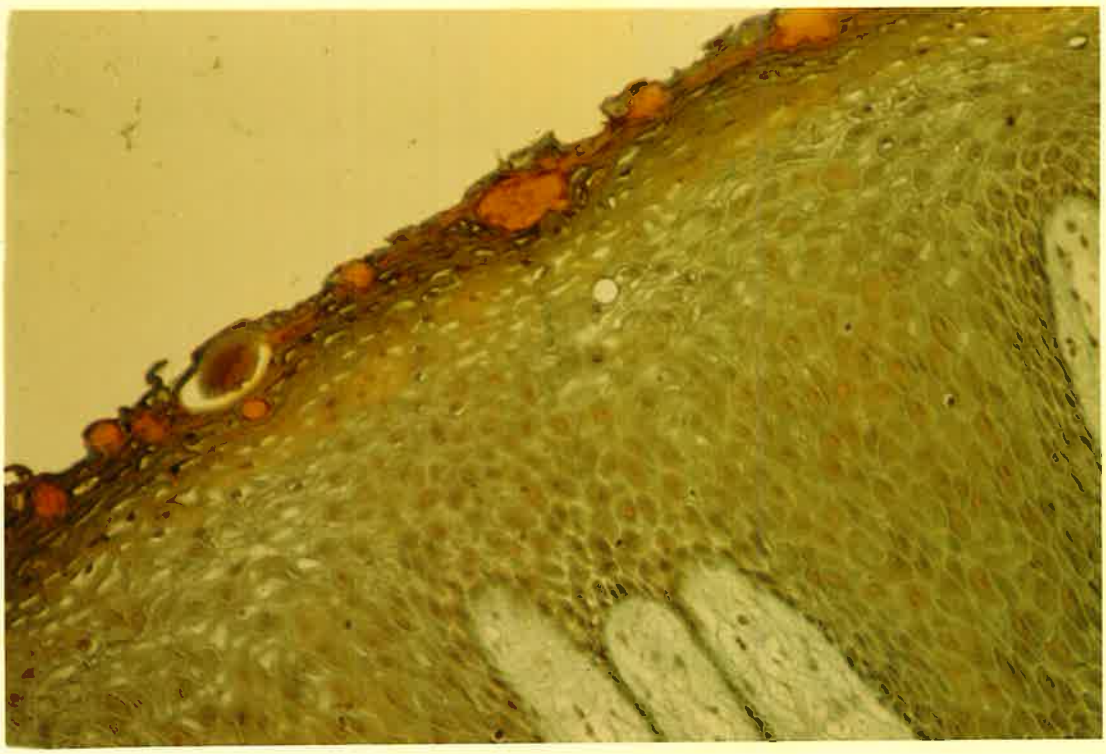
The section is de-paraffinised in xylol and then passed through absolute alcchol, 90 per cent alcohol, to 70 per cent alcohol, and water in succession. It is then stained for 15 minutes in well ripened Ehrlick's haematoxylin following which it is "blued" for 20 minutes in warm tap water. Differentiation in acid alcohol (1 per cent hydrochloric acid in 70 per cent alcohol) is then carried out and the section is then "re-blued" in warm tap water for 20 minutes. It is then placed in 1 per cent aqueous eosin for one minute after which it is differentiated in warm tap water - the time taken for the latter step is determined by periodic microscopical examination. The section is then blotted, passed directly through two changes of absolute alcohol, thence to xylol and finally mounted in Xam (neutral canada balsam).

APPENDIX IV

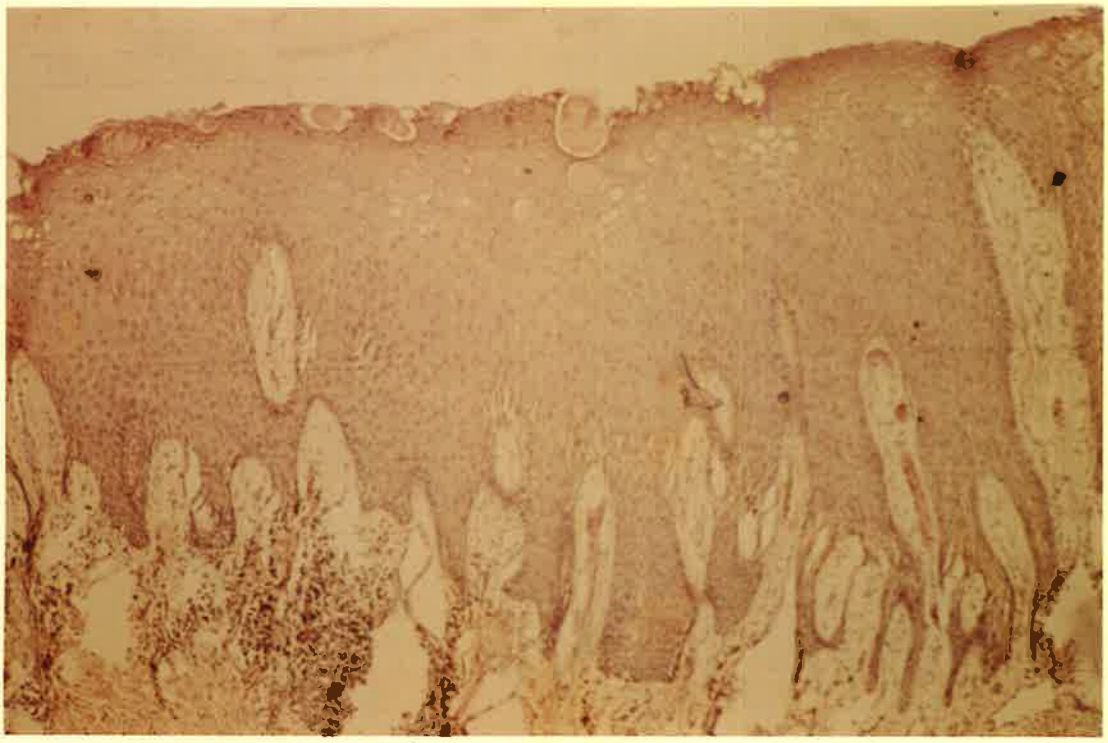
Case 44 - Fibro-epithelial hyperplasia showing hyaline bodies in the epithelium.

A. Peracetic-orcein-Halmi stain X 400. The definite orange colour of the hyaline bodies is well illustrated.

B. Haematoxylin and eosin stain X 100. In both sections some hydropic degeneration of the epithelium beneath the bodies is also visible.



A.



B.

APPENDIX V

55 Female Occurrences of Oral Soft-tissue Outgrowths

CASE NUMBER	AGE	POSSIBLE AETIOLOGY	LOCATION	CLINICAL DIAGNOSIS	HISTOLOGICAL DIAGNOSIS	PEDUNCULATED (P) OR SESSILE (S)	CONSISTENCY	CONNECTIVE TISSUE			EPITHELIUM			OTHER HISTOLOGICAL FINDINGS
								VASCULARITY	INFLAMMATION	HYPERPLASIA OF C.T.	HYPERPLASIA	KERATOSIS (K) PARAKERATOSIS (P.K.)	DYSKERATOSIS	
2	69	Ill-fitting dentures	M.-B. fold $\overline{2}$|	Denture hyperplasia	F.E. hyperplasia	S	F	++	++	++	++	PK++	±	Ulceration
3	41	" "	Ridge $\overline{3}$| - |$\overline{3}$	" "	" "	S	R	N	++	++	++	PK++	+	"
4	36	?	Tip of tongue	Papilloma	" "	S	F	N	+	+	++	PK+	-	
7	50	Ill-fitting dentures	Alv. mucosa |$\overline{1}$ - $\overline{3}$	Denture hyperplasia	" "	S	S	+	+++	++	+	-	-	Ulceration
8	12	Adj. to tooth root	Ging. |$\overline{45}$ region	F.E. polyp	F.E. polyp	P	F	N	++	+	++	PK+	-	Some ulceration
9	64	Ill-fitting dentures	M.-B. fold $\overline{3}$| region	Denture hyperplasia	F.E. hyperplasia	S	R	+	+++	++	+	K+, PK+	-	Ulceration
11	83	" "	Alv. mucosa |$\overline{4}$ region	" "	" "	S	F	N	±	++	++	PK+	+	Hyaline bodies
12	48	" "	M.-B. fold $\overline{3}$| - |$\overline{3}$	" "	Fibrous hyperplasia	S	F	N	+	++	-	-	-	Atrophic epithelium
13	29	" "	M.-B. fold $\overline{3}$| - |$\overline{3}$	" "	" "	S	S	N	++	+	N	PK+	-	
18	15	Carious tooth	Interproximal $\overline{1}$|$\overline{1}$	F.E. polyp	F.E. polyp	P	S	++	+++	++	++	PK+	-	Ulceration
19	33	?	Interproximal $\overline{1}$|$\overline{1}$	" "	" "	P	R	+	+	++	+++	K++	-	Ulceration
20	53	? Carious tooth	Cheek $\overline{7}$| region	" "	" "	P	F	N	++	+	++	K+	-	Ulceration, hydropic epith.
21	45	Ill-fitting denture	Buccal mucosa $\overline{3}$| - |$\overline{3}$	Denture hyperplasia	F.E. hyperplasia	S	S	N	++	++	++	PK+	+	Ulceration, hyaline bodies
23	48	?	Left lower lip	F.E. hyperplasia	" "	S	S	N	+	+	±	PK+	-	
24	66	Ill-fitting denture	M.-B. fold $\overline{3}$| region	Denture hyperplasia	Fibrous hyperplasia	S	R	N	+	++	N	PK+	-	Ulceration
25	47	? Suction	Cheek $\overline{7}$| region	F.E. hyperplasia	" "	S	R	N	-	++	N	PK±	-	
26	32	?	Interproximal $\overline{54}$|	" "	F.E. hyperplasia	S	F	+	++	++	++	PK+	-	Atypical bone, ulceration
28	57	Lip biting	Mid line upper lip	F.E. polyp	F.E. polyp	P	S	++	-	+	±	PK+	-	
29	77	?	Retromolar right side	" "	" "	P	S	++	+	++	++	PK++	+	
30	69	Tongue biting	Tongue, right side	" "	" "	P	F	++	-	++	++	PK+	±	
31	51	Ill-fitting dentures	M.-B. fold $\overline{3}$| region	Denture hyperplasia	F.E. hyperplasia	P	R	+	+++	+	++	K+, PK+	+	Ulceration, hyaline bodies, hydropic epithelium

55 Female Occurrences of Oral Soft-tissue Outgrowths

32	20	Pregnancy, calculus 3|	Interproximal 32|	Pregnancy tumour	Vascular outgrowth	P	S	+++	++	+	-	-	-	Ulceration, bone formation
33	29	Ill-fitting dentures	M.-B. fold |8 region	Denture hyperplasia	F.E. hyperplasia	S	R	+	++	++	++	-	-	
35	68	" "	M.-B. fold 3| region	F.E. polyp	F.E. polyp	P	S	+++	++	++	++	PK++	-	Ulceration
37	61	" "	M.-B. fold 3| - |3 region	Denture hyperplasia	F.E. hyperplasia	S	S	N	+	++	++	PK+	+	Hyaline bodies
38	40	" "	M.-B. fold 4| - |4 region	" "	" "	S	R	+	++	++	+	PK+	-	
39	55	" "	M.-B. fold 2| - |2 region	" "	" "	S	F	N	+	++	+	PK+	-	
43	66	" "	M.-B. fold 5| region	F.E. polyp	F.E. polyp	P	S	N	+	++	++	PK+	-	
44	63	Carious cavity	Interproximal 32| region	" "	" "	P	F	++	++	++	++	K++	+	Hyaline bodies, hydropic epithelium
45	35	?	Ridge |8 region	F.E. hyperplasia	F.E. hyperplasia	S	F	-	-	++	±	K++	+	
46	76	Ill-fitting dentures	M.-B. fold 1| - |1 region	" "	" "	S	F	N	-	+++	+	PK+	-	
48	17	? Excised 1 year ago	Alv. mucosa 54| region	Gran. pyogenicum	Vascular outgrowth	S	S	++++	++	-	-	PK+	-	Ulceration, bone formation
49	29	?	Interproximal 21| region	Fibroma	F.E. hyperplasia	S	F	N	+	++	++	K++	-	
50	43	?	Md. lower left lip	F.E. polyp	F.E. polyp	P	R	±	+	+	+	K+, PK+	-	
51	42	Broken-down |5	Left cheek	F.E. hyperplasia	F.E. hyperplasia	S	S	+	-	++	++	K++	-	Spongiosis of epithelium
52	51	?	On lingual frenum	F.E. polyp	F.E. polyp	P	S	+++	+	++	+	K+, PK+	-	
53	4	Trauma "months" ago	Alv. mucosa 8| region	F.E. hyperplasia	F.E. hyperplasia	S	R	±	+	++	++	PK+	-	Bone formation
54	44	Ill-fitting dentures	Incisive canal region	Denture hyperplasia	" "	S	R	++	++	++	++	PK+	-	Cartilage formation
55	34	? Pregnancy	Gingiva, palatal |2	Pregnancy tumour	Vascular outgrowth	S	S	++++	+++	+	++	PK+	-	Ulceration
57	65	Ill-fitting dentures	M.-B. fold 8 - 2| region	Denture hyperplasia	F.E. hyperplasia	S	R	±	++	++	++	K+	+	Ulceration, hyaline bodies, hydrophic epithelium
58	21	" "	M.-B. fold 8 - 2| region	" "	" "	S	R	++	+++	++	++	PK+	+	Ulceration, hyaline bodies, hydrophic epithelium
59	48	" "	M.-B. fold 3 - 1| region	" "	" "	S	R	±	+	++	++	K+, PK+	-	
60	63	" "	M.-B. fold |1 - 8 region	" "	" "	S	R	+	+++	++	+++	PK+	-	Ulceration
61	63	" "	M.-B. fold 3 - 1| region	" "	" "	S	R	+	+++	++	+++	PK+	-	Ulceration
62	41	? Lip biting	Lower left lip	F.E. polyp	F.E. polyp	P	S	±	-	++	++	-	-	
63	34	? Trauma 18 months ago	Alv. mucosa 3| region	Fibroma	" "	P	F	+	++	+	++	HK++, PK++	+	Hyaline bodies, hydropic epithelium
64	71	Ill-fitting dentures	M.-B. fold 43| region	Denture hyperplasia	F.E. hyperplasia	S	R	++	±	++	++	HK+	+	Hyaline bodies, hydropic epithelium
67	16	?	Interproximal 76| region	F.E. polyp	F.E. polyp	P	S	±	±	++	++	PK+	-	
68	38	?	Interproximal 34| region	F.E. hyperplasia	F.E. hyperplasia	S	F	+	++	++	++	PK++	+	Hyaline bodies, bone formation, hydropic epith.

55 Female Occurrences of Oral Soft-tissue Outgrowths

69	9	? Lip biting	Lower left lip	F.E. polyp	Retention cyst	F	S	++	++	±	±	FK+	-	
70	47	?	Gingiva $\overline{8}$| region	" "	F.E. polyp	F	F	+	++	++	++	FK++	-	Ulceration, bone formation
72	55	Ill-fitting dentures	Alv. mucosa $\overline{6-2}$| region	Denture hyperplasia	F.E. hyperplasia	S	S	±	-	++	++	FK++	-	
73	13	?	Interproximal $\overline{32}$| region	F.E. hyperplasia	" "	S	R	+	+++	++	++	FK+	-	Ulceration
74	71	Ill-fitting dentures	Floor of mouth	Denture hyperplasia	" "	S	R	+	±	++	++	FK+	-	
75	72	?	Hard palate	Fibroma	Fibrous hyperplasia	S	F	-	-	++	-	HK+	-	

F.E. - Fibro-epithelial, M.-B. - Muco-buccal, F - firm, S - soft, R - rubbery, H - hard, N - normal.

APPENDIX VI

20 Male Occurrences of Oral Soft-tissue Outgrowths

CASE NUMBER	AGE	POSSIBLE AETIOLOGY	LOCATION	CLINICAL DIAGNOSIS	HISTOLOGICAL DIAGNOSIS	PEDUNCULATED(P) OR SESSILE(S)	CONSISTENCY	CONNECTIVE TISSUE: VASCULARITY	CONNECTIVE TISSUE: INFLAMMATION	CONNECTIVE TISSUE: HYPERPLASIA OF C.T.	EPITHELIUM: HYPERPLASIA	EPITHELIUM: KERATOSIS (K) PARAKERATOSIS (P.K.)	EPITHELIUM: DYSKERATOSIS	OTHER HISTOLOGICAL FINDINGS
1	73	Sharp ⌈4	Left cheek	F.E. polyp	F.E. polyp	P	F	+	+	++	++	K+, PK+	-	
5	85	?	Alv. mucosa 2 region	Fibroma	F.E. hyperplasia	S	F	±	-	++	+	PK+	-	
6	42	Ill-fitting dentures	M.-B. fold 8⌋ region	F.E. hyperplasia	" "	S	S	N	++	+	++	PK+	+	
10	43	Adjacent to root tips	Ridge ⌈5 region	Papilloma	" "	S	F	±	±	++	++	K+++	-	
15	80	Ill-fitting dentures	Palate (mid-ant.)	F.E. polyp	F.E. polyp	P	F	N	+	++	+	K++	-	
16	25	?	Interproximal ⌈12	F.E. hyperplasia	F.E. hyperplasia	S	H	N	+	++	++	K++	-	
17	73	?	Left cheek	" "	" "	S	R	+++	++	++	+++	PK++	-	Hydropic epithelium
22	47	Missing ⌈7	Tip of tongue	" "	" "	S	R	±	-	+	+	PK+	-	
27	17	? Suction	Right cheek	F.E. polyp	F.E. polyp	P	H	±	++	++	++	PK+	-	Ulceration
34	12	? Trauma (occlusal)	Palatal to 1|1	Giant cell tumour	Vascular outgrowth	P	S	++++	++	++	++	PK++	-	Ulceration
36	45	Trauma from teeth	Tongue, right side	F.E. polyp	Papilloma	P	F	+	-	±	++++	PK+	-	
40	51	?	Interproximal ⌊23	F.E. hyperplasia	Hepatoma	S	H							Malignant
41	6	?	Md. left lip	Papilloma	Papilloma	P	F	-	-	±	++++	PK++	-	
42	68	Ill-fitting dentures	M.-B. fold 3|3	Denture hyperplasia	F.E. hyperplasia	S	R	±	-	++	+	PK++	-	
47	14	?	Lip 1|1	F.E. polyp	F.E. polyp	P	F	+	+	++	++++	PK++	-	
56	60	?	Soft palate	Papilloma	F.E. hyperplasia	S	F	++	++	++	++	K+, PK++	-	Ulceration, hydropic epith.
65	13	?	Ant. palate	F.E. polyp	F.E. polyp	P	F	±	±	++	++	Pa++	-	
66	53	? Trauma from tooth	Cheek opposite 6⌋	F.E. hyperplasia	Fibrosarcoma	S	F	+++						Malignant
71	57	? Denture	Incisive foramen	F.E. polyp	F.E. polyp	P	H	++	++	++	+	K+	-	Ulceration
76	10	Trauma from tooth	Lip opposite 2⌋	F.E. hyperplasia	F.E. hyperplasia	S	R	+	-	++	++	PK++	+	

F.E. - Fibro-epithelial, M.-B. - Muco-buccal, F - firm, S - soft, R - rubbery, H - hard, N - normal.

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