Oral medicine

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Preface

The origin of this book was a series of articles written for the *British Dental Journal* on the subject of 'Oral Medicine for the Dental Practitioner'. The purpose of these articles was defined by their title – in 1974 very little had been written to help the dental practitioner in assessing the importance of soft tissue lesions of the oral cavity or to advise on their treatment. This first version was deliberately designed to consider only these soft tissue lesions of the oral cavity – other topics (such as facial pain) which might also be considered to lie within the field of oral medicine were omitted. To the author's gratification (and surprise) the articles and the booklet later made up from their very slightly modified versions have been used as undergraduate and postgraduate teaching material on quite a wide scale. This fact clearly reflects the need for such information presented in a practical guise.

When it became necessary to consider a second edition it was clear that the scope of the material should be widened to include other conditions such as neurological disturbances and diseases of bone which had not been considered in any detail in the original version. The present book, therefore, deals with the subjects most often encountered in the oral medicine clinic. It is evident that there is no clearly defined margin between the subjects of oral medicine and oral surgery. However, there is a very prolific literature concerned with those conditions generally considered to be within the province of oral surgery and it is unnecessary to deal with these in a book devoted to the subject of oral medicine.

In the rewriting much of the original material has been modified and greatly expanded. Very few of the facts presented in the original articles have proved to be erroneous but attitudes have changed and research and clinical experience have modified some of the ideas put forward. It is hoped that the present book will accurately reflect current ideas and attitudes in this rapidly changing subject.

Liverpool WRT
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Principles and therapy

Oral medicine is generally understood as being the study and non-surgical treatment of the diseases affecting the oral tissues – especially the oral mucous membrane, but also other associated tissues and structures such as the salivary glands, bone, and the facial tissues. The boundaries of oral medicine are poorly defined – for instance the investigation of facial pain and other neurological disturbances may be considered to be in the field of either oral medicine or of oral surgery. However, in the present book the discussion will be restricted to soft tissue lesions in and about the mouth and to the effect of systemic disease on the oral tissues and related structures. It is the responsibility of the general practitioner to treat some of these conditions; others are often better treated in specialist clinics, but the general dental practitioner to a very great extent bears the responsibility for the recognition of oral disease at an early stage.

Perhaps the most important role of those working in the field of oral medicine is in the recognition of changes in the oral cavity resulting from generalized disease processes, many oral lesions which in the past were considered to be of entirely local origin are now known to be associated with systemic abnormalities. The most potent factor in the recent expansion of the scope of oral medicine has been the change of emphasis from the purely descriptive to the investigative. The modern concept of the subject implies a recognition of basic aetiological factors, of the histopathological changes occurring in the involved tissues, and of the significance of such matters as the general medical status of patients. As recently as 1955 Cooke pointed out in his study of leukoplakias and related lesions that previous workers had virtually ignored the significance of histopathology in their assessment, thus making it impossible to apply any but purely descriptive criteria to the conditions involved. The development of the discipline of oral medicine has depended largely on the adoption of an analytical approach based on the application of fundamental principles such as those mentioned above. It follows that the practice of oral medicine as a specialty depends largely on the availability of diagnostic facilities, often greater than those available to the general dental or medical practitioner, or even to some practitioners working in a hospital environment.

NORMAL ORAL MUCOUS MEMBRANE

In its basic structure the oral mucous membrane resembles other lining mucous membranes, for example those of the vagina or the oesophagus, although within the mouth there is a wider range of epithelial structures than that seen in these

other sites. These variations depend largely on differences in the degree of keratinization shown by the mucosae in different areas of the mouth. However, some of the reactions of the oral mucous membrane resemble those of the skin – this presumably is because of its position in the transition area between the gastro-intestinal tract and the skin. As a result of this, diseases both of mucous membranes and of the skin may produce lesions in the mouth. However, the oral mucosa characteristically behaves as a mucous membrane, its behaviour in disease processes perhaps most closely resembles that of the vaginal mucosa.

The oral mucous membrane consists both anatomically and functionally of two layers, one (the corium or lamina propria) essentially of mesodermal origin and one epithelial (Fig. 1.1). When considering variations of structure the behaviour of the corium must be taken into account even though the major changes may appear to be within the epithelial layer. In normal mucous membrane the integrity of the epithelium is maintained by the division of cells at, or near, the basal layer. As each cell divides one resulting cell remains effectively *in situ*, whilst one migrates towards the surface undergoing various structural modifications until it reaches the surface (Fig.1.2). These modifications, which are dependent on the process of keratinization, vary according to the precise site of the mucosa involved and result in the production of a surface layer of cells which are either fully, partially, or non-keratinized and which are shed into the oral cavity at a rate dependent on the rate of mitosis at the basal layer. For each dividing cell one cell is lost from the surface and, thus, the integrity and dimensions of the epithelial layer are maintained.

The similar structuring of the epithelial layer of the skin has been shown to be maintained by a series of regulating mechanisms, chemically mediated, some of which are intrinsic to the epithelium and some concerned with mesodermal–epithelial relationships. Recent work has demonstrated the existence of 'chalones', chemical regulators of mitotic division which are produced within the epithelium and can be chemically separated. Other chemical mediators have been

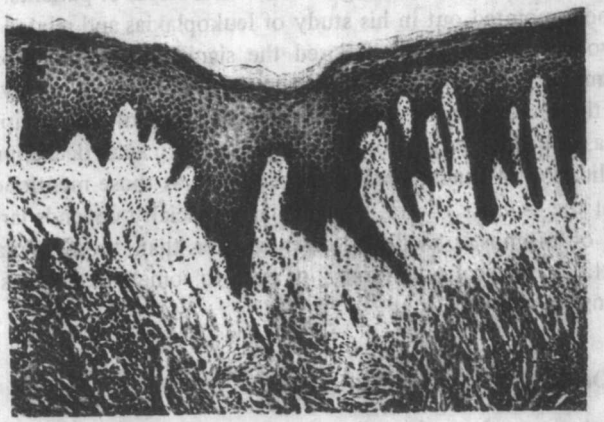

Fig. 1.1. Normal mucous membrane from the hard palate showing a surface layer of keratinized epithelium (E) lying over the corium (C).

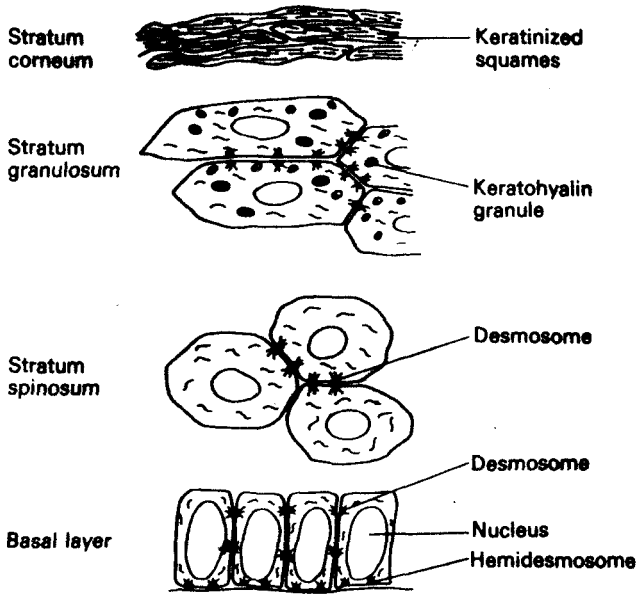

Fig. 1.2. Diagram of a keratinizing squamous epithelium. Compare with Figs. 1.1, 1.3, and 1.4.

described which are produced within the mesodermal tissues and which exert a strong controlling influence on the structure of the overlying epithelium; it would seem that these mesodermally produced factors are active in maintaining the orderly arrangement of the epithelium from the basal layer to the surface. Apart from such biochemical regulating mechanisms there is at least a suggestion of a cell-mediated regulatory system in the presence of the dendritic Langerhans cells of the epithelial layer. These cells are of unknown origin (although they are probably mesodermal) and it is thought that they take part in the regulation of the keratinization process. All recent work has strongly suggested that a similar series of complex and interacting factors operate in the oral mucosa, emphasizing the fact that any study of a mucosal lesion must include consideration not only of the epithelial tissues but also of the underlying corium. This is so even when the lesions concerned are those often considered as being entirely epithelial as, for instance, leukoplakias and related lesions.

The epithelium of the oral mucosa shows wide variations in the extent of the keratinization process. In the fully keratinized situation the rather cubical cells formed by mitosis at or near the basal layer migrate towards the surface, becoming more polyhedral and sharing intercellular attachments which have given the name 'prickle cell layer' (or stratum spinosum) to this zone (Fig. 1.3). In the light microscope these intercellular 'prickles' appear as single attachments of the cell walls but, by electron microscopy, these intercellular junctions (referred to as desmosomes) are seen to be of much greater complexity (Fig. 1.4). It is probable that the desomosomes act in a mechanical manner to give strength to the

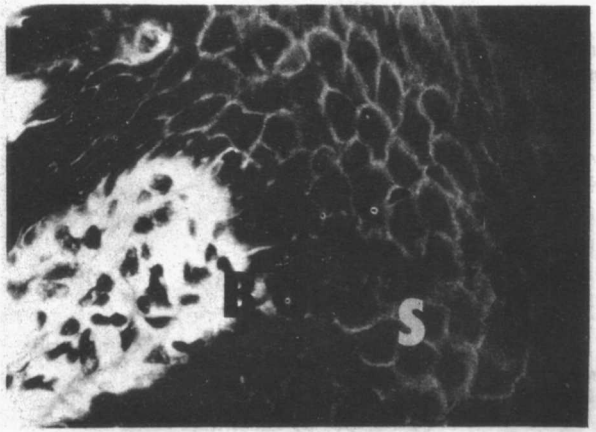

Fig. 1.3. Epithelium of oral mucosa showing basal layer (B) and the prickle cell layer (S) (the stratum spinosum).

epithelium; in several diseases marked by epithelial fragility the desmosome attachments are lost or impaired. It should perhaps be added that similar, one-sided structures, hemidesmosomes, attach the plasma membrane of the basal cells to the basal lamina of the basement membrane complex (Fig. 1.5). As the cells of the stratum spinosum migrate to the surface they begin to flatten and granular structures (keratohyalin granules) appear within them. The origin and function of these granules are as yet undetermined but it is known that they are closely involved with the process of keratinization. These granules give the characteristic appearance to the 'stratum granulosum' in keratinized epithelia. Finally, at or near the surface, the epithelial cells loose their detailed inner structure, the nuclei degenerate, the keratohyalin granules fragment and disappear and the insoluble protein complexes mentioned above fill the cell – now fully keratinized (Fig. 1.6). At this stage the desmosomes have effectively degenerated also and the flattened cells ('squames') are eventually lost into the

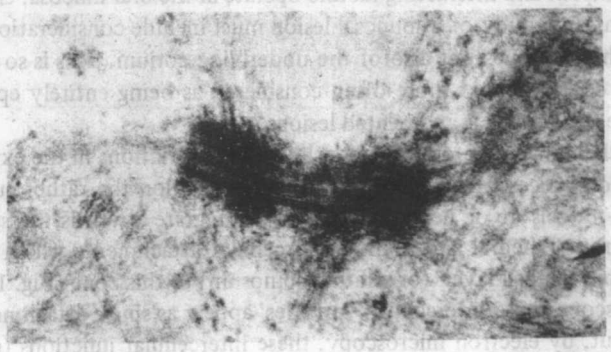

Fig. 1.4. Electron micrograph of a desmosome – the intercellular connection in the basal and prickle cell layers of the epithelium.

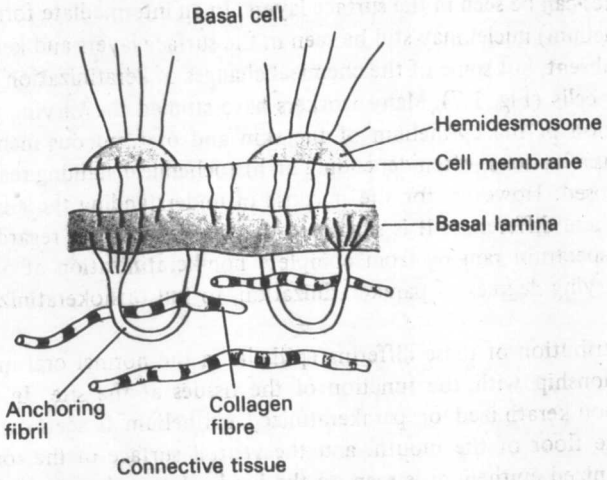

Fig. 1.5. Diagram of the basal complex of the oral epithelium. The connections between the basal cells and the underlying connective tissue are via the hemidesmosomes.

oral cavity. As has been pointed out, each keratinized cell lost in this way must be matched by a dividing cell in the proliferating compartment of the epithelium in order for stability to be maintained.

This process applies only to fully keratinized epithelium – as seen for instance in the mucous membrane overlying the hard palate – and is usually referred to as orthokeratinization. In other areas (as in some parts of the buccal mucosa and the floor of the mouth) this process of keratinization does not take place, keratohyalin granules are not formed and nuclei and organelles (although some-

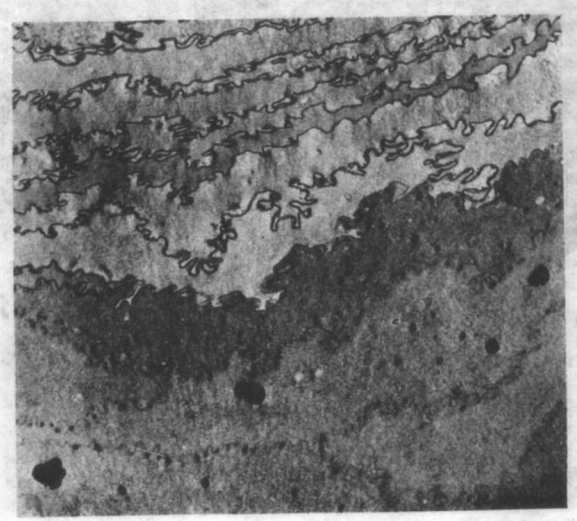

Fig. 1.6. Electron micrograph of granular cell layer of the oral epithelium (below) and the surface layer of keratin.

what effete) can be seen in the surface layers. In an intermediate form (parakeratotic epithelium) nuclei may still be seen in the surface layers and keratohyalin is sparse or absent, but some of the chemical changes of keratinization occur in the superficial cells (Fig. 1.7). Many workers have studied the varying processes of keratinization of the epithelium of the skin and oral mucous membranes and varying classifications, often depending on histochemical staining reactions, have been proposed. However, for the purpose of understanding the clinical significance of these differences it is suggested that they should be regarded as being part of a spectrum ranging from complete non-keratinization at one extreme, through varying degrees of parakeratinization, to full orthokeratinization at the other.

The distribution of these differing epithelia in the normal oral mucosa has a close relationship with the function of the tissues at the site. In the normal situation non-keratinized or parakeratinized epithelium is seen on the buccal mucosa, the floor of the mouth, and the ventral surface of the tongue whilst orthokeratinized epithelium is seen on the hard palate and parts of the gingivae. The dorsal surface of the tongue is also orthokeratinized but differs from the other oral mucosal surfaces in that there are a number of specialized structures present – predominantly the papillae. These latter (particularly the filliform

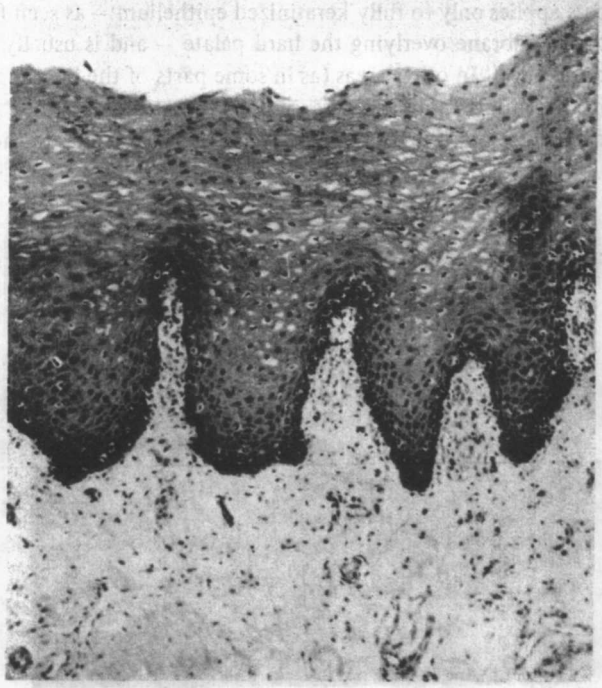

Fig. 1.7. Epithelium from the floor of the mouth showing parakeratosis. Nuclei are present in the surface layers.

papillae) are of considerable clinical significance in that their atrophy is often an early sign of mucosal abnormality.

Lying deep to the corium of the oral mucous membrane is the submucosal layer – separated from the corium by a gradual zone of transition rather than by a clear boundary. The submucosal tissue components are widely variable: blood vessels, fat, and fibrous tissue being present in differing proportions according to the precise site. In the corium and submucosa lie the minor glands and sebaceous glands of the oral cavity; again these are widely variable in distribution, the mucous glands being most frequent in the mucosa of the lips and posterior palate whilst the sebaceous glands are mostly concentrated in the buccal mucosa. Within the corium and submucous tissues are scattered cells of the leukocyte series in varying proportions and concentrations. During disease processes these may alter radically, both in number and in type, depending on the basic nature of the pathological process involved. There is, in fact, evidence that in certain diseases of mucosa and skin in which the apparent abnormalities are epithelial such alterations in the subepithelial leukocyte population may represent the initial pathological change – lichen planus is a good example of this.

Lying between the epithelium and corium of the oral mucous membrane is a dividing structure, the basement membrane. When viewed in the light microscope this appears as a relatively substantial layer, but the electron microscope has shown that this appearance is deceptive. The 'basement membrane' of the light microscopist is, in fact, a zone of biochemical activity as can be demonstrated by a number of special stains. On ultrastructural study it is seen that the components of the basal zone are much finer than suggested by light microscopy and that, rather than a single membrane, at least two zones are visible (the zona lucida and the lamina densa). In this area fibres attach the lamina densa to the underlying tissue and, probably, to the hemidesmosomes of the basal cells of the epithelium (Fig. 1.5). As yet, the behaviour of the basal complex in varying pathological states is not fully assessed but there is no doubt that many oral mucosal changes are associated with abnormalities in this area.

Although the oral mucous membrane has several functions, sensory and secretory among them, its main purpose is probably that of acting as a barrier. In considering this protective function it is also necessary to discuss other factors, in particular the role of saliva. The oral mucosa is constantly bathed by saliva which not only maintains the physiological environment necessary for the maintenance of epithelial integrity but also includes a number of protective, antibacterial components. A number of these have been described, but perhaps the most important are the secretory immunoglobulins, predominantly of the IgA class, which are found in saliva and which attach to sites on the epithelial surface (see Chapter 2). It seems possible also that salivary mucosubstances form a physical coating which remains intact over the oral epithelium in the healthy individual and which may also exert a protective action.

Although the full significance of the role of saliva in maintaining the health of the oral mucosa is, as yet, not fully understood there can be no doubt that a

free salivary flow is an essential part of the oral environment. If the flow is diminished, either by degenerative changes in the salivary glands or by the action of drugs, soreness and atrophic changes in some areas of the oral mucosa rapidly follow. The tongue is perhaps most markedly affected in this way. In some conditions (for example Sjögren's syndrome – Chapter 4) it is difficult to distinguish between primary mucosal changes and those secondary to diminished salivary flow, but on a clinical basis it is reasonable to accept that atrophic changes in the oral epithelium are regularly associated with dryness of the mouth.

A further component to be considered as part of the normal healthy oral environment is the microbial flora of the mouth. A wide range of organisms may be present in the oral cavity, living in a commensal relationship with the host. When this relationship is upset by a change in the local or generalized conditions then the commensal organisms may become pathogenic. A number of the more common oral infective conditions represent such a variation in the host resistance to organisms normally present in a commensal state. Acute ulcerative gingivitis is an example of this, although the precise change in the host leading to clinical infection is not easy to identify. It need hardly be said that some other infections of the oral cavity (for instance, syphilis) result from straightforward primary inoculation by external pathogenic organisms to which the patient has little or no resistance. A more complete discussion of the aetiological factors in some common oral infections is given in Chapter 2.

ABNORMAL ORAL MUCOUS MEMBRANE

Many oral lesions represent the end result of breakdown or abnormality of the normal structuring of the epithelium. Variation in the rate of keratin formation, disproportion between the different layers of the cells, breakdown of the normal intercellular bonds of the prickle cells, splitting of the epithelium from the connective tissue and many other similar abnormalities may occur in different diseases. For instance, in a number of mucosal abnormalities hyperkeratosis occurs (Fig. 1.8). This may arise as a result of abnormal irritation of the mucosa or apparently spontaneously in some conditions. In other lesions, atrophy of the epithelium may occur. This represents a thinning of the normal epithelial layer, perhaps to only a few layers of cells, often accompanied by incomplete keratinization. Such epithelium is easily lost following a minor degree of trauma and so atrophic lesions of the mucosa readily become ulcerated (Fig. 1.9). Many of the so-called erosive lesions are of this type. It should be remembered that ulceration is in itself a quite unspecific process and implies only the loss of epithelium from the mucosal surface followed by inflammatory changes in exposed connective tissue. Bullae or blisters of the mucosa may occur in one of two ways – either by degeneration of the cells and of the intercellular links in the prickle cell layer of the epithelium (Fig. 1.10) or by separation of the whole of the epithelium from the underlying corium (Fig. 1.11). In the former case, the bulla is entirely within the epithelium and may include within its contents

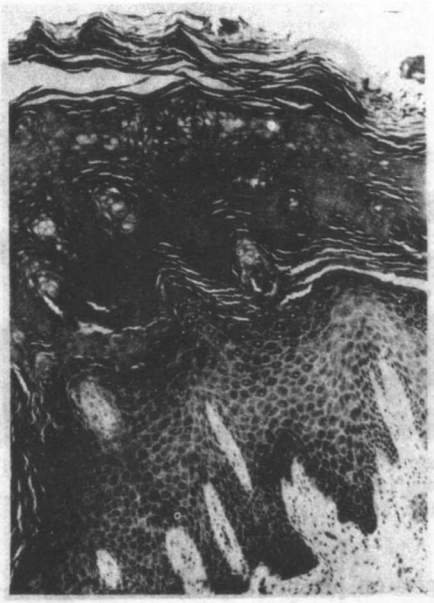

Fig.1.8. Hyperkeratosis – the production of an excessively thick layer of orthokeratin.

the rather rounded cells which result from the degeneration of the prickles. These cells may be examined in a diagnostic smear and the process (known as acantholysis) recognized (Fig. 1.12). On the other hand, the bullae formed by the lifting off of the epithelium from the corium will contain only inflammatory cells and no acantholytic epithelial cells. This difference is important in the differential diagnosis of bullous lesions in the mouth. It must be reiterated that changes seen in the oral epithelium are not confined to the epithelium alone. Frequently there are also changes in the supporting tissues and, in some cases, the visible epithelial changes may be secondary to changes in the underlying corium which affect the nutrition and metabolism of

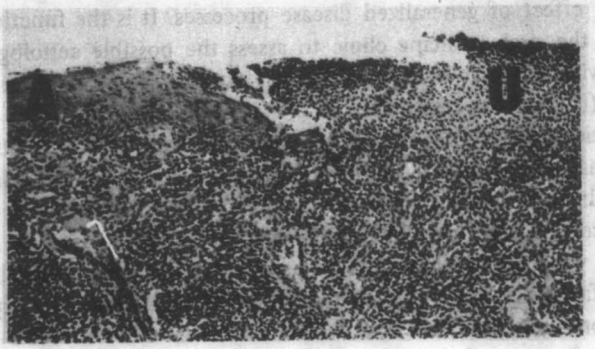

Fig. 1.9. Atrophic epithelium (A) which has been lost over part of the area with resulting ulcer formation (U).

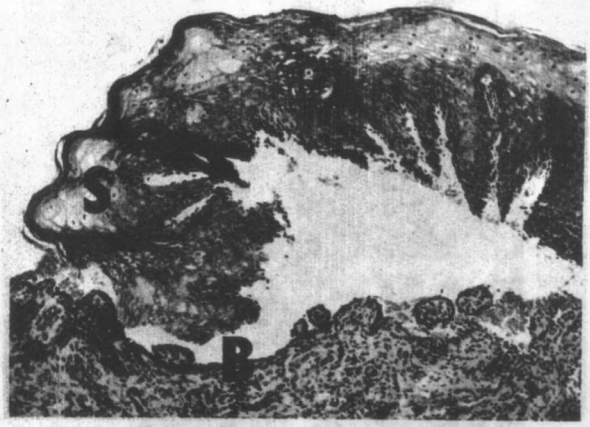

Fig. 1.10. A bulla (or blister) formed as a result of loss of intercellular cohesion. The bulk of the epithelium (S) has separated off to form a bulla, leaving the basal cells (B) to form the base of the lesion. This is an intra-epithelial bulla.

the epithelium. The greatest practical significance of this fact is, perhaps, the necessity when taking a biopsy of lesions of the oral mucosa, to include a representative thickness of corium in the tissue removed for microscopic examination. In many cases a biopsy consisting largely of epithelium alone is virtually useless for diagnosis.

The integrity of the oral mucosa is maintained by a complex of interacting factors superimposed on the localized stabilizing mechanism discussed above. The general hormonal status of the patient and a number of nutritional and metabolic factors are involved in maintaining the cell metabolism and the ordered structure of the mucous membranes. If any single factor is disturbed then sequential changes occur and clinically significant abnormalities of the oral mucosa may follow. It is often difficult to decide which of the various possible factors are involved in initiating these changes – these may evidently occur either as a primary manifestation of localized mucosal abnormality or as a secondary effect of generalized disease processes. It is the function of those working in the oral medicine clinic to assess the possible aetiological factors associated with mucosal lesions of this kind and to ensure appropriate investigations and (if needs be) treatment.

The reactions of the oral mucosa are not exclusively those of a mucous membrane; as has been pointed out, a number of diseases of the skin also find expression in oral lesions. This is not entirely surprising on anatomical grounds since the larger part of the oral mucosa is derived from an embryonic invagination which carries inwards some of the precursor epithelial cells from which both facial skin and oral mucosa are developed. As might be expected, the lesions of oral mucosa and skin which occur in these mucosal–cutaneous diseases are often superficially different although the basic histological changes seen in the tissues are similar. Such differences are seen in the primary lesions

Fig. 1.11. A bulla formed by the separation of the entire epithelium, including the basal cells (E) from the underlying corium. The bulla fluid contains inflammatory cells and red blood cells (I). This is a subepithelial bulla.

and, presumably depend on the differences between the structure of the mouth and of the skin. Quite often secondary changes also occur in oral lesions. The continually wet environment of the mouth, in combination with repeated mild trauma of the tissues by teeth and foodstuffs and the presence of a wide range of microbial flora further modifies the nature of the lesions produced in a number of diseases; for instance, should the epithelium be thinned by atrophy or weakened by the formation of blisters, it is likely to be lost and the initial lesion be replaced by an ulcer. For reasons such as these oral lesions, particularly at an advanced stage, may show less characteristic features than, for instance, the equivalent skin lesions of the same disease. Clinical diagnosis in such circumstances may be quite difficult since only areas of ulceration of a relatively non-specific nature may be present rather than fully developed specific lesions. For the diagnosis of an oral mucosal disease by histological criteria, it is often necessary to await the appearance of new lesions and to examine these at an early stage before the secondary changes occur.

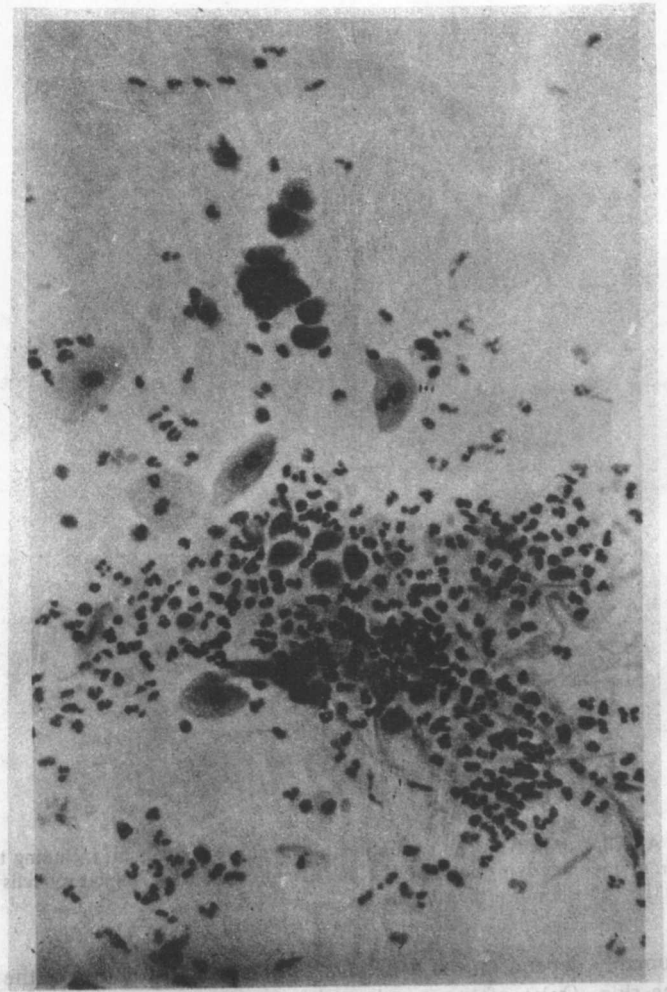

Fig. 1.12. A smear made from the bulla fluid in a case of pemphigus. Although many inflammatory cells are present the rounded acantholytic epithelial cells of pemphigus can be seen.

Histological changes

It may be helpful to recall some of the terms used to describe changes seen on histological study of the oral mucosa. These include:

Hyperkeratosis – an increase in the thickness of the keratin layer of the epithelium, or the presence of such a layer in a site where none would normally be expected (Fig. 1.8). Hyperorthokeratosis is the term used to specify a thickened, completely keratinized layer whilst in hyperparakeratosis there is incomplete keratinization with nuclei remaining in the surface cells.

Acanthosis – an increase in thickness of the prickle cell layer of the epithelium. This may or may not be accompanied by hyperkeratosis.