ORAL MEDICINE

THIRD EDITION

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PREFACE TO THIRD EDITION

THE purpose of this edition remains the same as that of the previous two: to provide an up-to-date survey of the field of oral medicine as a help for undergraduates and as a guide for practitioners. The scope of the book has been somewhat expanded—some subjects have been introduced for the first time and other sections amplified.

Two issues have been decided as a matter of policy. The first is in relation to references. It is a frequently heard complaint of reviewers that books of this kind are incomplete without original reference lists. The author differs from this view. A number of fully referenced review texts are available for the research worker or advanced student; the great majority of the readership for which the present book is aimed do not have the time or facility to follow up original references. It is, indeed, the function of this book to present a review of such information in a readily available and self-contained format. The second is in regard to illustrations. It is generally accepted that black and white illustrations of oral mucosal lesions are, at best, only partially successful. It has, none the less, been decided to increase their number to some extent and it is hoped that the illustrations in the present book are helpful within their limitations. Clearly, the cost of illustrating a book of this kind in colour would increase its price in a quite undesirable way. A number of colour atlases of oral medicine have been produced (by the author and by others) which present far more accurate representations of oral lesions than is possible in monochrome reproduction.

The final sentence of the preface to the previous edition still applies: it is hoped that the present version of this book will accurately reflect current ideas and attitudes in a rapidly changing subject.

Liverpool W.R.T.
November 1988

ACKNOWLEDGEMENTS

JUST a little of the original material used in the *British Dental Journal* series may be recognized in the present edition; the Editor of the Journal has kindly agreed to its further use. Another undergraduate textbook produced by the author (*Oral Diagnosis*) has appeared in two English as well as in some foreign language editions. It has now been mutually agreed by the author and the publishers, Pergamon Press, that the need for this book has now passed. Pergamon have agreed that the material may be further used and, as a result, some of this may be found in the present publication in an updated form.

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1

Princip'

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 rate of turnover of the surface cells has not been determined in man, but in animals it is known that it is high, the surface cells being replaced every 2 or 3 hours. This is considerably faster than in skin and must play a part in the defence mechanism of the oral

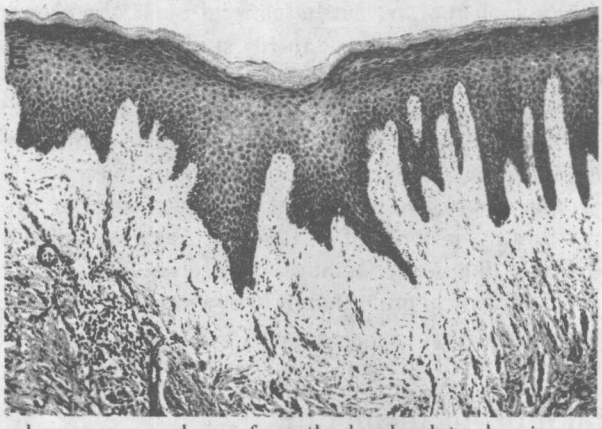


Fig. 1.1. Normal mucous membrane from the hard palate showing a surface layer of keratinized epithelium (E) lying over the corium (C).

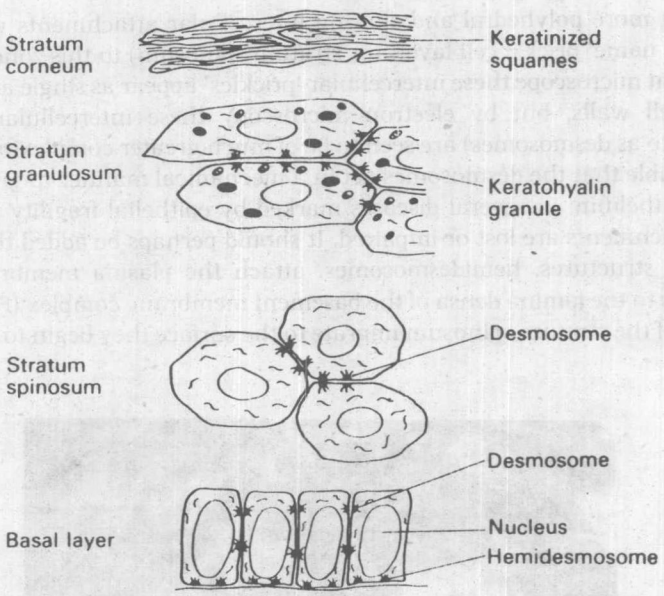


Fig. 1.2. Diagram of a keratinizing squamous epithelium. Compare with Figs. 1.1, 1.3, and 1.4.

cavity against infecting organisms which are denied a stable site in which to proliferate.

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 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. 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 desmosomes act in a mechanical manner to give strength to the 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 lamina densa of the basement membrane complex (Fig. 1.5). As the cells of the stratum spinosum migrate to the surface they begin to flatten and

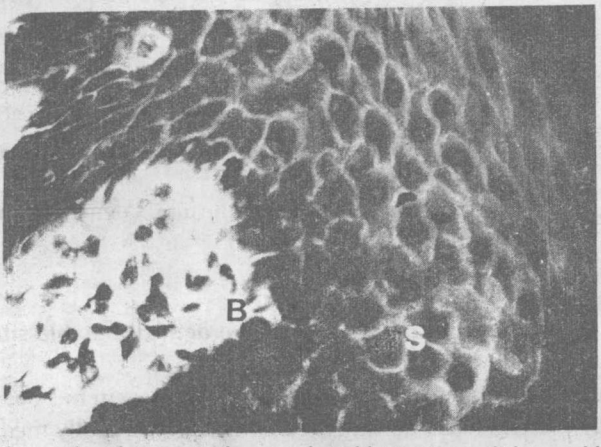
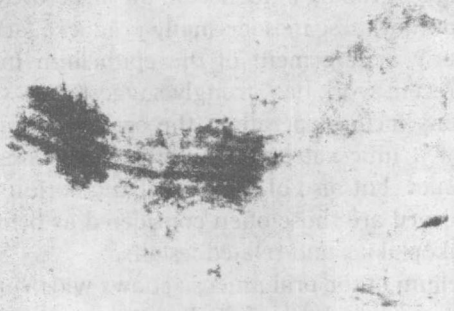


Fig. 1.3. Epithelium of oral mucosa showing basal layer (B) and the prickle cell layer (S) (the stratum spinosum).



g. 1.4. Electron micrograph of a desmosome—the intercellular connection in the basal id prickle cell layers of the epithelium.

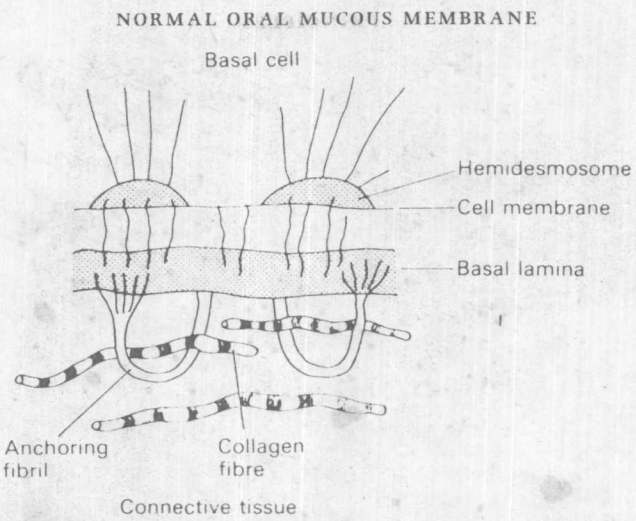


Fig. 1.5. Diagram of the basal complex of the oral epithelium. The connections between the basal cells and the underlying connective tissue are via the hemidesmosomes.

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 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 somewhat 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

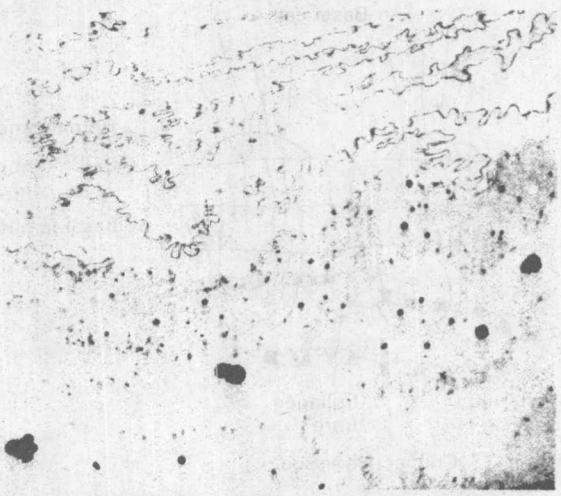


Fig. 1.6. Electron micrograph of granular cell layer of the oral epithelium (below) and the surface layer of keratin.

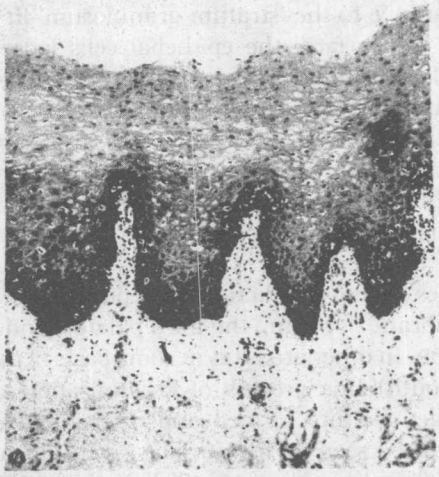


Fig. 1.7. Epithelium from the floor of the mouth showing parakeratosis. Nuclei are present in the surface layers.

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

Apart from the keratinocytes—the main cell component of the oral epithelium—there are other cells whose function and origin is still under intensive investigation. The two most important groups of cells of this kind are the melanocytes and the Langerhans cells. Both these types of cells appear in normally stained (H&E) sections of the oral epithelium as 'clear cells' in which the nucleus is surrounded by a clear zone of cytoplasm, but special stains (and electron microscopy) show considerable differences from the majority of the cells of the epithelium. These cells are dendritic, with cytoplasmic prolongations extending between the cells of the basal and suprabasal areas of the keratinocytes, but with no attachments to them. Other classes of dendritic cells have been demonstrated, with different characteristics, but the function of these is not yet known.

The melanocytes appear in, or very close to, the basal layer and on electron microscopy show granular structures (melanosomes) which are the precursors of melanin: the black pigment which modifies the colour of both skin and mucous membranes. The melanotic pigmentation of oral mucosa shows great racial variation, in parallel with that of the skin. However, this does not depend on variation of the numbers of melanocytes but on the number and activity of the melanosomes within them. The epithelia of all races contain approximately the same number of melanocytes; it is their activity which varies. It is known that hormonal influences are important in the stimulation of melanocyte activity, although the precise mechanisms remain obscure. In particular, the function of the so-called melanin-stimulating hormone (MSH) has, as yet, not been fully elucidated. In some circumstances the melanocytes may be stimulated to produce excess melanin by a wide range of non-hormonal stimulae. This will be discussed in later chapters.

The Langerhans cells were for long something of a mystery. There are a substantial number of these cells present near the basal complex of the oral epithelium, with dendritic processes extending between the keratinocytes and with recognizable ultrastructural features. In the previous edition of this book the Langerhans cells were described, in the light of the then available research

reports, as cells which in some way take part in the regulation of the keratinization process. This view has changed and it is now suggested that these cells have an immunological function, acting as peripheral scavenging cells of the immune system not unlike macrophages. It would seem that at least one function of these cells is to accept antigens and stimulate the activation of T lymphocytes against them. Recent work has suggested that there are variations from the normal both in the number and the immunological reactivity of the Langerhans cells in some lesions of the oral mucosa; for instance, in oral lichen planus and in candidal leukoplakia.

The role of iron metabolism in the maintenance of the structure of the oral mucosa has been the subject of much investigation. It is certainly the case that iron deficiency, even when relatively early in clinical terms, can result in generalized oral epithelial atrophy and loss of the papillary pattern of the lingual mucosa. It seems that other deficiencies which might affect iron metabolism and erythrocyte production, such as folate and B12 deficiencies, may also contribute to this destabilization of the oral epithelium. This will be discussed at greater length in Chapter 9.

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). The origin of the basal complex is not yet decided. Until recently, it was

thought to be of mesodermal origin, but current opinion is that the lamina densa and the lamina lucida are derived from the epithelium. 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. In particular, the advance of immunological techniques at the ultrastructural level is leading to detailed studies of the behaviour of the basal complex in disease processes. For instance, the existance of pemphigoid antigen sites has been described at which circulating antibodies, found in patients suffering from pemphigoid, may react. This results in weakening of the epithelial–connective tissue junction and the production of bullous lesions (see Chapter 8).

Although the oral mucous membrane has several functions, sensory and secretory among them, its main purpose is probably that of acting as a barrier. Recent work implies that there may be two sites at which this barrier function may occur. One of these is at the basal complex and the second is in the intercellular substances of the middle layers of the epithelium. At both these sites it appears that some molecules are selectively blocked from passing inwards into the tissues. 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.

In spite of this barrier function of the oral mucosa there is a degree of permeability which, apart from its theoretical and scientific interest, is also of clinical significance. During local therapy with mouth washes and similar preparations, drugs may be transported across the oral mucosa and may exert effects similar to those resulting from systemic therapy. This factor must evidently be considered if (for example) therapy with high concentration steroid mouthwashes is to be carried out. The permeability of the oral mucosa to drugs is most commonly utilized in the treatment of angina by glyceryl trinitrate and similar substances. In these circumstances the very rapid absorption of the drug is of obvious advantage. It is thought that, apart from the mechanism of simple diffusion, active transmission of some substances by cell-mediated mechanisms may occur. It has also been suggested that surface active agents such as are commonly used in toothpastes and mouthwashes may influence the permeability of the oral mucosa to other substances. There is currently a great deal of research activity in this field.

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 5) 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 3.

Age changes

It is generally accepted that changes occur in the oral mucosa of healthy individuals with increasing age. Reductions in overall epithelial thickness, flexibility of the collagen fibres, innervation, blood supply, and permeability of the mucosa have been described. It has generally been assumed that changes of this kind occur with comparative suddenness at a late age, but recent evidence implies that, at least in the case of the epithelium of the tongue, a continuous trend towards atrophy occurs throughout adult life. The clinical significance of this observation is that sudden changes in the structure of the oral mucosa (for example, depapillation of the tongue) should never be considered as being due to age alone without full investigation and the elimination of other factors: haematological, nutritional, and so on (see Chapter 5).

A further age change which may affect the function of the oral mucosa is in the salivary glands. It has been shown that gradually increasing degrees of atrophy and fibrosis affect the secretory units of both the submandibular and the labial salivary glands throughout life, even in the absence of disease processes which might be associated with such change (Chapter 5). As considered above, the resulting decrease in salivary flow from these glands may well affect the function of the mucosa as a whole. However, this is an area of current doubt since it has also been shown that, in general, parotid salivary flow remains