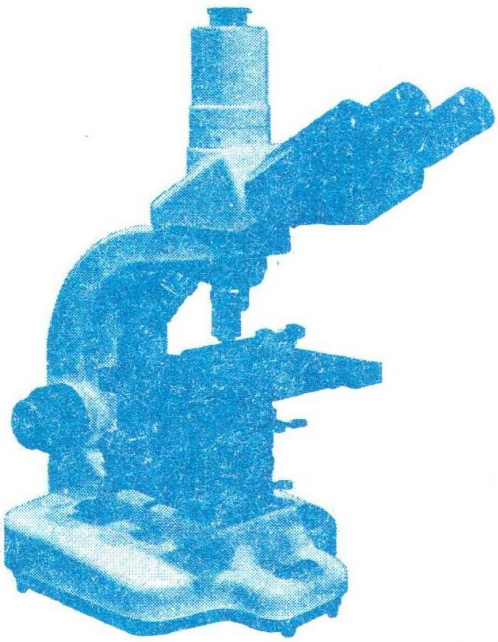
Ministry of Public Health of Ukraine
Central Methodical Department of Higher Medical Education
Higher State Educational Establishment of Ukraine
"Ukrainian Medical Stomatological Academy"

O. V. HANCHO

# ORAL CAVITY FLORA

Manual



О. В. ГАНЧО

# МІКРОФЛОРА РОТОВОЇ ПОРОЖНИНИ

Навчальний посібник

POLTAVA 2010

**Ministry of Public Health of Ukraine**
**Central Methodical Department of Higher Medical Education**
Higher State Educational Establishment of Ukraine
"Ukrainian Medical Stomatological Academy"

**Hancho O.V.**

# Oral Cavity Flora

**Manual for dental faculty students of higher medical educational establishment of III-IV levels of accreditation**

**Ганчо О.В.**

# Мікрофлора ротової порожнини

**Навчальний посібник для студентів стоматологічних факультетів вищих медичних навчальних закладів III-IV рівнів акредитації**

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The aim of this manual is to provide an accurate comprehensive and up to date coverage of Microbiology, Virology and Immunology of human oral cavity. It includes a review of the oral flora composition, methods of the microflora study and oral infection diagnostics. Special attention has been directed to the aetiology of caries and parodontitis. Wide-spread bacterial, fungal and viral infections of the oral mucosa have been described in the 4-7 parts of the manual.

The book is principally intended for dental students, but practicing dentists will find it useful.

I would like to thank professor`s assistance of the foreign languages department Znamenskaya I.V. for her advises in English text editorship.

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# Preface

Study of the oral flora is complicated by the large number of species, their fastidious nutritional requirements and slow growth together with the complexities of species identification.

Despite these distinctions the mouth is similar to other body regions which having a resident normal flora with a characteristic composition, including large number of anaerobes. The oral flora exists, normally, in a harmonious relationship with the host. This relationship can be disturbed by any changes to the habitat which affect the stability of the microflora, for example xerostomia or the use of broad-spectrum antibiotics. Some bacteria, including many oral microorganisms, can exploit these lapses and behave as opportunistic pathogens. Changes in the balance between the host and the microbial flora may lead to mucosal infections and increase the prevalence of both dental caries and periodontal disease. The latter pose large, essentially preventable, public health problems in both industrialized and non-industrialized nations, costing many millions of dollars per year for treating.

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# A list of abbreviations

AUG - acute ulcerative gingivitis

BANA - benzoyl-DL-arginine-naphthylamide

CDC - Centers for Disease Control

CMC - chronic mucocutaneous candidosis

EBV – Epstein-Barr virus

ELISA - enzyme linked immunosorbent assay

GCF - gingival crevicular fluid

IPS - intra-cellular polysaccharides

HAART - highly active anti-retroviral therapy

HHV-8 - human herpes virus 8

HPV - human papilloma virus

HSV - herpes simplex virus

NNRTI - non-nucleoside reverse transcriptase inhibitor

NRTIs - nucleoside reverse transcriptase inhibitors

PCR - polymerase chain reaction

PMC - pseudomembranous candidosis

VZV - varicella zoster virus

# Preface

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Despite these distinctions the mouth is similar to other body sites in having a resident normal flora with a characteristic composition, including large numbers of anaerobes. The oral flora exists, normally, in a harmonious relationship with the host. This relationship can be disturbed by any changes to the habitat which affect the stability of the microflora, for example xerostomia or the use of broad-spectrum antibiotics. Some bacteria, including many oral microorganisms, can exploit these lapses and behave as opportunistic pathogens. Changes in the balance between the host and the microbial flora may lead to mucosal infections and increase the prevalence of both dental caries and periodontal disease. The latter pose large, essentially preventable, public health problems in both industrialized and non-indusrrialized nations, costing many millions of dollars per year to treat.

# Part 1

# Oral cavity flora

## 1.1. Study of the oral microflora

In order to understand the aetiology of many oral and dental diseases and to interpret the results of microbiological analyses of clinical specimens, knowledge of the microorganisms which comprise the resident flora within different ecological niches of the oral cavity is important. However, there are technical problems at all stages of analysing the oral microflora, which potentially compromise the accuracy of studies. The various methods and associated problems involved in specimen collection and processing are shown in Fig. 1. The initial sample collection is often the most important step in a microbiological investigation and will significantly influence the results obtained.

Historically, culture of microorganisms has been the mainstay of microbiological diagnosis, but the methods are labour-intensive and slow. In addition, some microorganisms cannot be grown in artificial media. Some of the newer non-cultural methods, such as antigen detection or the detection of microbial genome, are very rapid and in the long term are likely to supplant many of the currently employed cultural techniques.

| **Stage of study** | **Examples** | **Comments** | **Problems** |
|---|---|---|---|
| **Sample collection** | Aspirate from dental abscess.<br>Paper point sample from periodontal pocket. Oral rinse to | Each method will depend on the habitat sampled and the organism sought | Sampling methods should be standardized, reproducible and prevent |

| | | | |
|---|---|---|---|
| | assess.<br>Candida carriage | | contamination of the specimen |
| **Transport to laboratory** | Use appropriate transport media, for example fastidious anaerobe broth for anaerobes. | The shorter the transport time the better | A crucial stage since bacteria will not survive under adverse conditions |
| **View sample** | Dark field microscopy | Allows visualization of organisms that are difficult to grow, such as spirochetes | Difficult to obtain detailed specific information about the microorganisms involved |
| | Gram stain | Provides 'rough guide' to microorganisms in sample | Identification |
| | Specific fluorescence | May permit identification | |
| **Treat sample** | Disaggregate sample if necessary by adding small glass granules and shaking vigorously | An essential step to separate individual bacteria in specimens such as plaque | Difficult to disperse all the micro-organisms stuck together in plaque. Delicate organisms may rupture and die |
| **Culture sample** | Semi-selective agars used e.g. Sabouraud's agar for *Candida spp.*, Mitis Salivarius Bacitracin (MSB) | The method of culture will depend to a large extent on the organisms sought | Many organisms require special growth factors and atmospheric conditions |

| | | | |
|---|---|---|---|
| | agar for mutans streptococci Anaerobic culture method for grows of anaerobes | | Slow growing species overgrown by rapidly proliferating species |
| **Identification of organism** | Enzyme profiles, sugar fermentation patterns, cellular lipids, antigen-antibody profiles, DNA probes and PCR | Some are rapid and commercially available, such as API 32 Strep kit for identification of streptococci | Can be very time consuming and expensive if large numbers of different species are investigated |

**Fig.1 Analysis of the oral microflora**

Microscopy is an important element of diagnostic microbiology. Light microscopy is employed for visualizing bacteria, fungi and parasites while electron microscopy is necessary for the detection of viruses.

The commonest form of light microscopy is called bright field microscopy and may be used to examine either wet preparations or stained preparations. The former allow demonstration of microorganisms in fluid specimens such as urine or feces and are also used to detect fungi in skin. The motility of microbes, for example *Vibrios* species, can also be detected.

In dark ground microscopy, the microorganisms appear brightly lit against a dark background. The method is useful for visualizing very thin cells such as spirochaetes, since the reflection of the light makes them appear larger. Motility can also be seen. Dark ground microscopy is used in the rapid diagnosis of syphilis *(Treponema pallidum)* and has also been employed by dental researchers to examine for spirochaetes in specimens collected from periodontal pockets.

More frequently, the microbiologist produces stained preparations of dried material that has been fixed to the microscope slide and which is examined at a

magnification of 1 000 through an oil immersion lens. The most important staining technique in bacteriology is the Gram stain, which allows the division of bacteria into two broad groups. Gram-positive bacteria stain purple and Gram-negative bacteria stain pink. Some bacteria do not take up the Gram stain and require special staining techniques. For example, mycobacteria have a waxy cell wall and are stained with the Ziehl-Neelsen stain, in which the red dye fuchsin is forced into the cells by heating and the cells subsequently withstand decolorization with acid. Other staining techniques may be employed to demonstrate particular features of cells such as spores.

Finally, fluorescence microscopy is a valuable tool. Specific antibodies tagged with fluorescent dyes are now used widely in microbiology, for example in antigen detection tests. Specimens are examined through a microscope fitted with an ultraviolet light source.

Electron microscopy allows rapid detection of virus particles through direct examination of specimens. It is especially useful for viruses that are non-cultivable. Electron-dense stains such as osmium tetroxide are applied to the specimen to improve contrast. Electron microscopy alone is often insufficient to allow accurate identification of a virus, but both the sensitivity and specificity can be increased by reacting the specimen with specific antiviral antibody, resulting in clumping of the virus particles.

Detection of microbial antigens with serological tests are more rapid than cultural tests although they often lack sensitivity. There are two main types of assay. First, some antigens (for example *Streptococcus pneumonias* capsule) can be detected by their interaction with specific commercially available antibodies. The specificity of this form of test has been increased greatly by the availability of monoclonal antibodies. The antibodies are often coated onto latex particles or red blood cells and used in agglutination assays. Alternatively, the antibodies may be labelled with a radioisotope, an enzyme or a fluorescent marker to permit detection of the antigens to which they have bound.

The second type of assay detects microbial toxins. These include both exotoxins (for example *Clostridium difficile* cytotoxin) and endotoxin (detected by the limulus

lysate assay). Toxins may be detected either by their antigenic properties or by demonstrating their action in appropriate bioassays.

A gene probe is a nucleic acid molecule which, when in a single stranded state and appropriately labelled, can be used to detect a complementary sequence of DNA by hybridization. The label may be either a radioactive isotope, or an enzyme which produces a colour change in a substrate when it is included in the reaction mixture.

If probes are produced for virulence factors such as toxins, organisms carrying these genes can be detected in specimens without the need for culture. Such technology is especially useful for organisms that are slow or difficult to grow in the laboratory and increasing numbers of gene probes are likely to be developed. However, detection of small numbers of organisms can be a limiting factor. This problem can be overcome through gene amplification by the polymerase chain reaction (PCR) in which a specific DNA sequence can be amplified to produce millions of copies within a few hours. Confirmation of the identity of the product is by subsequent gene probing or sequencing. Whilst PCR is still largely a research tool, it is already employed as the 'gold standard' method in virology laboratories for confirmation of infection with hepatitis C virus.

### 1.2. Diagnosis of oral infections

The accurate diagnosis of oral infections posses several difficulties for clinical microbiologists. Many oral infections are endogenous (caused by members of the normal oral flora). The size and complexity of the oral flora means that this can complicate interpretation of results, especially if specimens have been collected incorrectly and are contaminated with organisms from the normal flora. In addition, many of the bacteria involved in purulent oral infections are strict anaerobes with fastidious growth requirements, often requiring prolonged incubation times for colonies to develop. It is essential that there is good understanding and communication between the dentist treating the patient and the rnicrobiologist handling the specimen, if the outcome is to be successful.

Specimens submitted to an oral microbiology laboratory can be divided broadly into three categories. First, there are those collected from purulent infections, for example a dental abscess. Second, specimens relating to oral mucosal infections such as candidosis or herpetic stomatitis are often examined. Finally, specimens may be collected to help in the management of periodontal disease and dental caries. These will be dealt with in turn.

### 1.2.1. Diagnosis of purulent infections

If possible, clinicians should submit an aspirate of pus, rather than a swab. This prevents contamination of the specimen and maintains viability of anaerobic organisms. The needle should be removed with appropriate precautions and the hub of the syringe protected with a small plastic cover.

Once the specimen has been received by the laboratory and booked in, a direct Gram film is prepared. If large numbers of leucocytes are seen, this confirms that an infection is present. The morphology of any bacteria visualized may also give early information on the types of organism present.

The specimen is next inoculated onto blood agar plates for aerobic and anaerobic incubation, and into a bottle of sterile broth. Additional nutrients, such as vitamin K and haemin, are required in media for the growth of anaerobes. A metronidazole disc is usually placed on the anaerobic plate to help in the detection of anaerobic bacteria. Primary antibiotic sensitivity plates are also set up with the neat specimen, to allow an early indication of which antimicrobial agents the clinician should choose for treatment.

All cultures are examined after incubation for 48 hours. Purity plates are prepared of representative colony types for identification and antibiotic sensitivity testing.

### 1.2.2. Diagnosis of oral mucosal infections

**Fungal infections.** Yeasts can be cultured readily from the oral cavity. Specimens may be collected from specific sites on the oral mucosa by swabbing. Alternatively, the presence of yeasts can be determined by collecting an oral rinse, in which patients swill their mouths with sterile saline and expectorate it. The rinse can then be inoculated

onto media selective for yeasts (Sabouraud`s agar). An advantage of the oral rinse is that that it can also be inoculated onto media for isolation of other potential pathogens, for example *Staphylococcus aureus* and coliforms. It also provides a semi-quantitative result.

Sabouraud's agar is the most widely used isolation medium for yeasts, but most species have the same colonial morphology when grown on this medium. This is unfortunate, because although *Candida albicans* is the commonest yeast isolated from the mouth, other species are also frequently present and patients often carry more than one species simultaneously. It is important, therefore, to use an additional agar on which different species produce different types of colony, for example CHROMagar® .

Following incubation, yeast colonies are picked off the primary-plates. All are subjected to a germ tube test, which identifies potential isolates *of Candida albicans* from other *Candida*. spp., Germ tube negative yeasts are identified on the basis of further tests, for example sugar assimilation or sugar fermentation tests. Commercial kits are also available for yeast identification.

Antifungal sensitivity tests can be use. The reproducibility of these tests has been difficult to standardize, and some of the laboratory methods required are technically demanding. However, surveillance of antifungal resistance, particularly to the azoles, is becoming increasingly important.

**Viral infections.** Herpes simplex virus is the commonest cause of viral infection of the oral mucosa. This virus can be cultured readily in tissue culture cells from a viral swab of lesional tissue and a result may be available within 48 hours. However, with the advent of specific antiviral drugs, a more rapid result is desirable and this may be achievable through the use of rapid antigen detection tests such as immunofluorescence. Serological techniques are of little use in the clinical setting, because they are too slow for diagnosis of primary infections and there are no serological markers of reactivation disease.

Diagnosis of shingles is usually made clinically, but may be confirmed by laboratory tests. Antigen detection and serology are the most valuable methods.

### 1.2.3. Diagnosis of caries and periodontal disease

Bacteria are very important factors in the aetiology of both caries and periodontal disease, but the role of a microbiology laboratory in the management of these infections is limited.

In the case of dental caries, salivary counts of lactobacilli (on Rogosa agar) and *Streptococcus mutans* group organisms (on MSB agar) can be undertaken. Such counts, however, are poor predictors of future caries activity if taken in isolation. More recently there has been renewed interest in caries activity tests based not only on bacterial counts, but also taking into account factors such as dietary analysis and salivary buffering capacity. Lactobacillus counts are a useful marker of patient compliance to a low carbohydrate diet.

The microbiology of periodontal disease is extremely complex. The examination of a deep gingival smear to demonstrate the fusospirochaetal complex is a useful aid to the diagnosis of acute necrotising ulcerative gingivitis. However, for other forms of periodontal disease there is still no consensus on which organisms are the key pathogens. Plaque can be screened for putative periodontal pathogens, including *Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus* and *Actinobacillus actinomycetemcomitans,* using methods such as anaerobic culture, antigen detection tests and gene probes. However, for the present, treatment of periodontal diseases is based largely on non-specific plaque control measures, with the use of antimicrobial agents in certain circumstances.

## 1.3. Composition of the oral microflora

Most bacteria found in the oral cavity can be classified as Gram-positive (Fig. 2) or Gram-negative (Fig. 3). Streptococci comprise a major part of the oral flora and play an important role in dental caries, purulent oral infections and infective endocarditis. Modern taxonomic methods have permitted their division into several major groups, as summarized in Fig. 4.

| Genus | Morphology | Atmospheric requirement | Comments and example |
|---|---|---|---|
| Streptococcus spp. | Cocci | Facultative anaerobe | These form largest proportion of the oral flora. They comprise almost 50% of the total cultivable flora from saliva and the tongue but only 30% of the total flora from the gingival crevice and supra gingival plaque. **Example:** S.oralis |
| | | Obligate anaerobe | Anaerobic streptococci are present in the mouth and commonly isolated from purulent infections |
| Staphylococcus spp. | Cocci | Facultative anaerobe | Coagulase negative staphylococci, for example S.epidermidis, are part of the normal flora. S.aureus is not considered part of the oral flora, but frequently isolated from children, the elderly and those with systemic disease |
| Actinomyces spp. | Bacilli | Facultative anaerobe | From a major proportion of bacteria found in dental plaque, especially at approximal sites. Numbers increase in gingivitis and in root surface caries **Example:** A.naeslundii |
| Lactobacillus spp. | Bacilli | Facultative anaerobe | Form a small percentage of the normal flora. Numbers increase in gingivitis and in root surface caries Example: L.acidophilus |
| Eubacterium spp. | Bacilli | Obligate anaerobes | Found at periodontitis sites and in dental abscesses. **Example:** E.brachy |

**Fig. 2. Gram-positive bacteria in the mouth**

Some species of spirochaetes, protozoa and mycoplasma are also members of the normal oral flora but are very difficult to cultivate. Spirochaetes are best demonstrated by the technique of dark field microscopy. Other bacteria such as the coliform *Escherichia coli* are present only transiently in the healthy oral cavity but may become established in the elderly or immunocompromised. *Candida albicans* is rhe most common fungal isolate and an average carriage rate of 40% has been observed in asymptomatic adults. Candidal counts increase in the immunocompromised, denture wearers and following some types of antibiotic treatment. Certain viruses, for example Epstein-Barr virus and human herpes virus type 6, are also shed frequently in saliva of healthy individuals.

The oral microflora, in common with many other ecosystems, contains a large proportion (approximately 50%) of currently uncultivable bacteria. Therefore our present knowledge of oral microbiology and oral diseases is only partially complete. More recently, molecular biology techniques have identified some of these uncultivable microorganisms. However, to understand their role in oral health and disease will require new methods to facilitate their isolation, culture and study.

| **Genus** | **Shape** | **Atmospheric requirement** | **Comments and example** |
|---|---|---|---|
| Neisseria spp. | Cocci | Aerobic | Early colonizers of teeth. Isolated in low numbers from most sites in the oral cavity. **Example:** N.subflava |
| Veillonela spp. | Cocci | Obligate anaerobe | Isolated from most surfaces in the oral cavity. High numbers on tongue and in dental plaque. **Example:** V.parvula |
| Haemophilus spp. | Bacilli | Facultative anaerobe | Commonly present in saliva, dental plaque and on epithelial surfaces. **Example:** H.aphrophilus |

| | | | |
|---|---|---|---|
| Eikenella spp. | Bacilli | Facultative anaerobe | Found mainly in sub gingival plaque. Increased numbers in gingivitis. **Example:** E.corrodens |
| Capnocytophaga spp. | Bacilli | Capnophilic | Often isolated in periodontal disease. **Example:** C.gingivalis |
| Actinobacillus spp. | Bacilli | Capnophilic | Found in periodontal pockets and implicated in juvenile periodontitis. **Example:** A.actinomycetemcomitans |
| Porphyromonas spp. | Bacilli | Obligate anaerobe | Found mainly in sub gingival plaque. Implicated in the etiology of adult periodontitis. **Example:** P.gingivalis |
| Prevotella spp. | Bacilli | Obligate anaerobe | Found mainly in sub gingival plaque. Implicated in the etiology of adult periodontitis. **Example:** P.intermedia |
| Fusobacterium spp. | Bacilli | Obligate anaerobe | Found mainly in sub gingival plaque. Implicated in the etiology of adult periodontitis. **Example:** F.nucleatum |
| Spirochetes | Spiral | Obligate anaerobe | Found mainly in periodontal pockets. Very difficult to culture or stain. Best visualized by dark field microscopy. **Example:** Treponema denticola |

**Fig.3. Gram-negative bacteria in the mouth**

### 1.4. Acquisition of the oral microflora

The oral cavity of the foetus is sterile and although during bitch the neonate comes into contact with the microflora of the mother's vagina, these organisms do not usually become established. The mouth is a highly selective environment for bacteria and only a few species are able to colonize the mouth of the new-born. From the first feeding, microorganisms

are transferred from the surrounding environment such as maternal saliva or the skin flora of the mother and nursing staff.

By 24 hours after birth the first (pioneer) species have become established. Streptococci, particularly *S. salivarius,* which bind to epithelial cells are usually the first to colonize. The early colonizers develop into a pioneer microbial community and begin co modify their environment by producing extracellular products, which enhance conditions for growth of other species. For example, *S. salivarius* produces extracellular polymers from sucrose to which other bacteria, for example *Actinomyces* spp., can attach. This process of microbial succession and increasing diversity will result in the eventual formation of a climax community.

By one year of age, when teeth have erupted, the predominant species isolated are *Streptococcus* spp., *Neisseria* spp., *Veilonella* spp. and *Staphylococcus* spp. Less frequently isolated species include *Lactobacillus, Actinomyces*, *Prevotella* and *Fusobacterium.*

Tooth surfaces and gingival tissues provide new habitats for colonization, with resultant formation of dental plaque. Other shifts in the microbial flora take place during the lifetime of an individual; for example only 18% of 5 year olds have spirochaetes and black pigmenting anaerobes, compared with 90% of 13-16 year olds. The flora of adults remains relatively stable but denture wearers have an increased carriage rate *of Candida albicans.* From approximately 70 years of age there is an increased proportion of *Lactobacillus* and *Staphylococcus* species in saliva of non denture wearers, whilst after 80 years of age the number of yeasts increases.

| **Streptococcal group** | **Appearance on blood agar** | **Species found in humans** | **Comments** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Mutans** | Alpha-hemolytic | S.mutans | Most common species isolated and implicated in human caries. Colonizes teeth, especially in fissures. |
| | | S.sobrinus | Less commonly isolated. |
| | | S.cricetus | Rarely isolated. |
| **Salivarius** | Alpha-hemolytic | S.salivarius | Prefers keratinized surfaces. Commonly isolated from most areas but especially the tongue. |
| | | S.vestibularis | Commonly isolated from vestibular mucosa. |
| **Oralis** | Alpha-hemolytic | S.oralis | An early colonized of smooth surfaces. Produces IgA protease and glucans (polymers of glucose) |
| | | S.sanguis | Colonized teeth and produces IgA protease. |
| | | S.mitis | May occur in plaque but has a predilection for non-keratinized surfaces in the mouth. |
| | | S.gordonii<br>S.parasanguis | Found in dental plaque.<br>All members of the 'oralis group' may act as opportunistic pathogens and are frequently isolated from cases of infective endocarditis. |
| **Anginosus** | Most are beta-hemolytic | S.anginosus<br>S.intermedius<br>S.constellatus | Are isolated readily from dental plaque. A common and important cause of purulent disease, e.g. dental and brain abscesses. |

**Fig.4. Classification of oral streptococci**

### 1.5. Dental plaque formation

Adherence to a surface in the mouth is essential for survival of oral bacteria. In the case of supragingival plaque formation, organisms do not colonize clean enamel but interact with a layer of material on the tooth surface called the pellicle. The pellicle comprises mucins, salivary glycoproteins, minerals and immunoglobulins. Pellicle formation occurs in seconds on cleaned enamel and reaches a maximum thickness in 90—120 minutes.

#### 1.5.1. Bacterial attachment

The attachment of bacteria to surfaces is a complex process and can be divided into four main stages as follows:

**Stage 1: Transport.** Bacteria must first approach the surface to which they will later bind. They can do this in several ways including liquid flow, diffusion through Brownian motion, or bacterial movement (chemotactic activity).

**Stage II: Initial adhesion.** Two types of forces are involved at this stage. At distances of 10-100 nm, weak forces such as Van der Waal's and electrostatic forces come into effect. These forces are highly dynamic and are influenced by the ion content of surrounding saliva. As a result they are readily reversible.

As the bacterium approaches closer (2 nm), strong forces, such as hydrogen bonding between hydroxyl groups in the pellicle and phosphate groups in the bacterial cell wall, come into play.

**Stage III: Attachment.** Following initial adhesion, a more permanent attachment can occur by covalent, ionic or electrostatic bonding. These bonds form between specific receptors on the host surface, termed ligands, and components on the bacterium called adhesins. The latter ate often situated on bacterial appendages such as fimbriae. Oral bacterial attachment, and therefore plaque formation, is affected by a number of host and microbial factors and by saliva.

**Stage IV: Colonization** and biofilm formation once bound to a surface, the bacterium can divide and remain attached. Extracellular products are formed and daughter cells repeat the process so that microcolonies develop. Salivary glycoproteins

and dietary sugars such as glucose and sucrose can be metabolized leading to the formation of bacterial cell wall, intra-cellular polysaccharides (IPS), and soluble and insoluble extracellular polysaccharides. The IPS serve as a nutrient store for the organism and are degraded to release energy and organic acids.

Gradually the microcolonies coalesce, producing a more complex three-dimensional arrangement. This is clue to coaggregation between similar species (intrageneric) e.g. among streptococci, and aggregation between different bacterial species (intergenetic) e.g. between *S. sanguis* and *A. naeslundii* or between *Streptococcus* spp. and *Porphyromonas* spp. The resultant biofilm is called dental plaque which is a general term for the complex microbial community found on the tooth surface, embedded in a matrix of polymers of bacterial and salivary origin. Plaque maturation is characterized by increasing quantity and diversity of micro-organisms on the tooth surface. After 7 days streptococci ate still the main organisms present, but after 14 days there is a shift to anaerobic rods and filaments, with streptococci comprising only 15% of the cultivable flora.

The situation on oral mucosal cells is slightly different because of a modified pellicle that covers their surface. The number of bacteria initially adhering to mucosal cells is small and regular desquamation ensures a light microbial load.

There is increasing interest in the complex ecosystem of dental plaque, since this can be used to study the biofilm phenomenon. A biofilm can be defined as a microbially derived sessile community characterized by cells that are attached to a substratum or interface or to each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription.

Biofilms are a major problem in many systems, for example contamination of dental unit water lines and infections associated with indwelling prosthetic devices such as hip joints. There is a growing body of evidence to support the fact that microbes behave differently when attached within a biofilm (sessile) as opposed to cells floating in a liquid (planktonic phase). These phenotypic changes may be expressed in a number of different ways. Certain genes may be switched on to alter

the composition of the biofilm, for example production of more extracellular polysaccharide. One of the more important clinical effects of biofilms is their inherent resistance to physical or chemical removal. Thus, some microorganisms can survive in biofilms at concentrations of antibiotics or disinfectants 1000 times greater than those required to kill their planktonic counterparts. The resistance may be due to binding of the active ingredient to extracellular components of the biofilm or to the reduced growth rate of bacteria. This phenomenon may be important in the generation of antibiotic resistant microorganisms.

An equilibrium exists between the forces of retention and removal. Rough surfaces allow more plaque to adhere because of the increased surface area and protection from the forces of removal. In addition, surfaces with a low surface free energy (water-repel ling) such as Teflon® bind fewer micro-organisms than those with a high surface free energy (water-attracting) such as enamel. Therefore in order to minimize plaque accumulation, intra-oral devices should be designed with a smooth surface and possess a low surface free energy.

### 1.5.2. Calculus

Dental plaque can become calcined; saliva is super-saturated with calcium and phosphate ions which may be deposited within the deeper layers of plaque. These ions accumulate within the plaque matrix together with organic debris from dead micro-organisms, while plaque phosphatases and proteases degrade some of the calcification inhibitors in saliva (statherin and prolinerich proteins). These processes lead to the formation of insoluble calcium phosphate crystals, which coalesce to form calculus. Many anticalculus toothpastes contain pyrophosphate compounds designed to adsorb excess calcium thus reducing intra-plaque mineral deposition. Mature calculus consists of about 80% (dry weight) mineralized material (mostly hydroxyl-apatite) and 20% organic compounds, although the actual composition will vary with the individual, age, site of the deposit and the location of the tooth.

The bacterial flora associated with calculus is relatively nonspecific and reflects the bacterial composition of the dental plaque with which it was associated. Thus, early supragingival calculus (2 days) contains primarily Gram-positive cocci whilst older and subgingival calculus will contain more Gram-negative rods. Calculus has a roughened surface and is porous, allowing bacteria and bacterial products such as toxins to be absorbed, thus providing an ideal reservoir for substances potentially harmful to the host. Calculus must therefore be removed from tooth surfaces to halt tissue damage and to promote healing from periodontal disease.

### 1.6. Factors affecting the growth of oral microorganisms

As described early, maintenance of the microbial community requires a degree of symbiosis between the microorganisms and the host. This will reflect a balance between factors that encourage growth and those that tend to inhibit growth. The oral flora, specifically, is influenced by a wide range of factors which may be associated with the diet, saliva, gingival crevicular fluid, microbial products and host factors (Fig.5).

#### 1.6.1. Diet

The chemical composition of foods ingested will affect the availability of nutrients, since large molecular weight dietary polysaccharides must first be broken down by salivary enzymes before they can be utilized. The presence of fermentable carbohydrates such as sucrose, maltose, lactose and glucose will lead to increased plaque formation and the accumulation of microbial products such as organic acids and dextrans. Thus, frequent eating of sucrose is associated with high caries activity. The physical consistency of large molecules such as starches and proteins restricts availability to bacteria, since they may be removed from the mouth before they have been degraded. However, some foods are retained between the teeth or stick to fissures more easily and the longer that bacteria have nutrients available, the more they can metabolise, grow and release by-products such as lactic acid.

| Factor | Comments and examples |
|---|---|
| Diet | Chemical composition, physical consistency and frequency of intake |
| Saliva | Flow rate, pH balance and antimicrobial factors, e. g. lysozyme |
| Gingival crevicular fluid | Contains many antimicrobial components, e.g. IgG |
| Microbial interactions | Some are beneficial, others harmful |
| Gaseous environment | Relative oxygen concentrations help to determine species distribution |
| Host factors | Systemic disease, antibiotic use and oral hygienic measures |

**Fig.5. Important influences on the composition of the oral microflora**

### 1.6.2. Saliva

One of the essential properties of saliva is its action as an efficient buffer that regulates the pH of most surfaces. The mean pH of unstimulated saliva is 6.75-7.25. Many of the predominant bacterial components of healthy plaque can tolerate brief exposure to low pH but are killed or inhibited by prolonged exposure. A regular decrease in pH by frequent sugar intakes will lead to the proliferation of *S. mutans* and *Lactobacillus* species and an increase in dental caries. Changes in the flow rate will affect the concentrations of the ions bicarbonate, urea, ammonium, calcium and phosphate, which are of great importance to the balance of mineralization and demineralization.

Saliva contains many important growth factors, such as glycoproteins, proteins and minerals that may be utilized in bacterial adherence and metabolism. However, the microbial flora has to act synergistically to bring about the complete degradation of these compounds. Within the microbial community there are a multitude of possible interactions between the products produced by different species,

some beneficial (Fig.6) and some harmful. Extracellular endoproducts produced by one species may be essential for the growth of another species; for example isobutyrate, a cell wall fatty acid produced by *Fusobacteria* may be used by *Treponema mlcrodentium.*

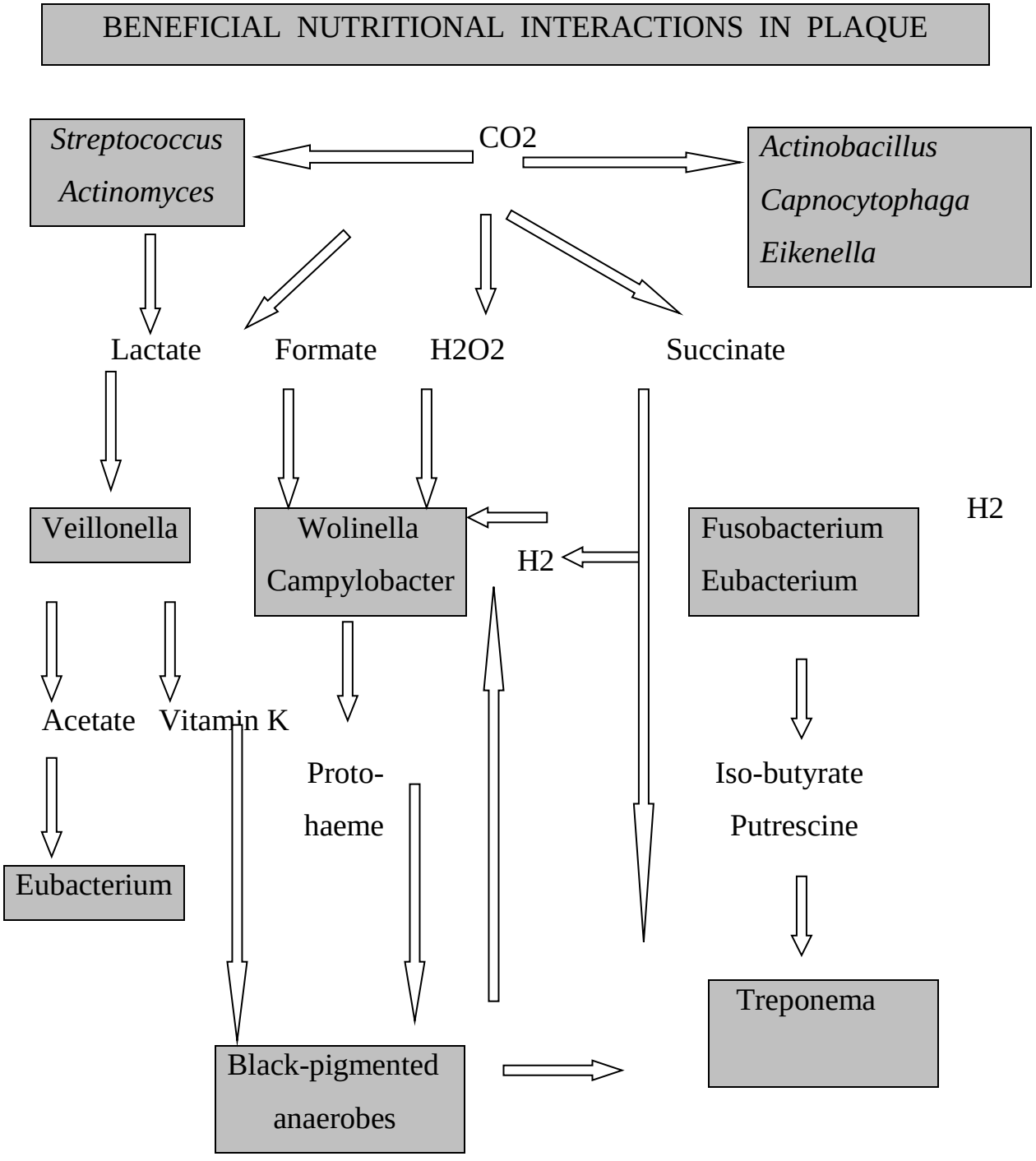


**Fig.6. Some nutritional interaction between plaque bacteria**

**(Redrawn from Marsh and Martin, 1992)**

Similarly, *Veillonella parvula* can produce vitamin K3 which, in turn, is essential for the growth of *Porphyromonas* spp.. Conversely, metabolic products such as hydro-

gen petoxide produced by the *Streptococcus orale* group or butyrate produced by *Porphyromonas gingivalis* may inhibit other bacteria.

Saliva also contains numerous antimicrobial factors such as the salivary peroxidase systems, myeloperoxidase (peroxidases inhibit bacterial cell metabolism), lysozyme (lyses some bacterial cell walls), lactoferrin (binds iron which bacteria need for growth), histidine-rich peptides (inhibit *Candida albicans)* and immunoglobulins.

### 1.6.3. Gingival crevicular fluid (GCF)

This is a scrum transudate which contains proteins such, as albumin and immunoglobulins as well as amino acids, minerals, vitamins and glucose. GCF has protective functions for the host by virtue of its flushing effect and high numbers of viable polymorphs, antibodies and complement proteins.

### 1.6.4. The gaseous environment

Most oral micro-organisms are facultative anaerobes, although if oxygen is present, aerobic respiration is preferred. However, some organisms are obligate anaerobes and are killed by oxygen.

The relative amounts of oxygen will help to determine the distribution of certain species within the oral cavity. Normal air contains 20% $O_2$**,** the anterior surface of the tongue 16%, the posterior surface of the tongue 12% and the buccal folds 0.3%. This will be reflected in the number of anaerobic bacteria recovered from these sires. Sometimes the conditions available for the growth of bacteria are expressed as the oxidation-reduction level and are usually described as the redox potential (Eh), which is recorded in mV. A low Eh (negative value) is a highly reduced environment and favours the growth of anaerobes. Oxygen accepts electrons and raises the redox potential. Thus, a clean enamel surface has a redox potential of + 200mV whilst after 7 days of plaque accumulation the Eh has fallen to -141 mV.

Early colonisers of plaque utilise $O_2$ and produce $CO_2$**,** thus allowing bacteria that are capnophilic ($CO_2$ requiring), for example anginosus group streptococci, to become established. Late colonizers of plaque will produce $H_2$ and other reducing agents, such as sulphur-containing compounds, which will gradually lower the Eh,

allowing mote anaerobic bacteria, such as *Prevotella* spp., to colonize. Thus, periodontal pockets are more reduced (-48 mV) than healthy gingival crevices (+ 73 mV).

### 1.6.5. The host

In addition to host factors such as diet and salivary flow others, for example the presence of systemic disease, broad spectrum antibiotic usage, or chemotherapy for cancer, may disturb the host/microbial 6ora interactions. One of the easiest ways the host can influence the oral flora is by use of oral hygiene methods, such as tooth brushing. This produces a persistently young plaque containing many facultative anaerobic Gram-positive bacteria with limited numbers of obligate anaerobes, a flora which is compatible with oral health. However, in an effort to make plaque removal easier for patients, chemical agents have been introduced to reduce plaque build up.

## 1.7. Antiplaque agents

Three main approaches have been utilized for chemically interfering with the formation of dental plaque (Fig. 7).

| ANTI-PLAQUE AGENTS | |
|---|---|
| Mechanism of action | Examples |
| Antimicrobial | Chlorhexidine (also anti-adherent action) |
| Plaque disruption | Sodium lauryl sulphate (detergent action)<br>Delmopinol (plaque-loosening action)<br>Plaque-degrading enzymes, such as dextranase |
| Anti-adherent | Experimental compounds<br>Fluoride-containing compounds |

**Fig.7. Summary of the types of antiplaque agent available**

### 1.7.1. Antimicrobial agents

These agents prevent bacterial proliferation on the tooth surface. Currently the most effective anti-plaque agent is chlorhexidine. The molecule has a positive charge at either end and binds readily to negatively charged sites on the enamel pellicle, mucosal cells and bacterial cell wall structures. Once bound, the chlorhexidine can exert its antimicrobial effect by damaging the microbial cell membrane and precipitating the cell contents. Chlorhexidine also inhibits microbial adherence since it is able to adsorb onto a surface and is slowly released, maintaining its antimicrobial activity, a property known as substantivity.

### 1.7.2. Plaque disruption agents

Sodium lauryl sulphate is used commonly in toothpastes and mouth rinses as an anionic detergent which solubilizes plaque to reduce its accumulation. In addition, it has a moderate degree of substantivity and antimicrobial activity, although much less than chlorhexidine.

### 1.7.3. Anti-adhesive compounds

Anti-adhesive compounds are designed to alter the surface binding within the oral cavity, thus preventing or blocking interactions between bacteria and the oral environment. Many are still at the experimental stage and are currently unavailable as commercial oral hygiene products. Fluoride-containing compounds such as sodium fluoride and stannous fluoride are reported to have anti-adherent properties, although the mechanism of action is uncertain.

## 1.8. Defence mechanisms of the mouth

The general aspects of host defences have already been described early. In this short chapter, attention will be drawn to some of the specific aspects relating to immunity in the mouth. The key factors responsible for maintaining oral health are listed in Fig. 8.

CONTRIBUTORS TO ORAL HEALTH

- Integrity of oral mucosa
- Lymphoid tissue
- Saliva

**Fig. 8. The major biological factors contributing to maintenance of oral health**

### 1.8.1. Oral mucosa

Oral health is dependent on the integrity of the oral mucosa, which normally functions as an effective barrier against microorganisms. If this barrier becomes compromised, for example in cancer patients wits mucositis following chemotherapy, then infectious complications may ensue, including the risk of systemic infection. In addition, the oral mucosa is in continuity with a number of anatomical structures, such as the pharynx, which are vulnerable if the oral defences break down. A major area of risk is the junction between the gingiva and the tooth and the various forms of petiodontal disease encountered at this site are described in Part 3.

There are several factors which may prevent penetration of intact oral mucosa by microorganisms. These include keratinization in certain areas of the mouth, discharge of membrane-coating granules in the granular layer, formation of immune complexes by interaction of antigens with antibodies and the barrier function of the basement membrane. The small numbers of lymphoid cells adjacent to the basement membrane may help to deal with any organisms which pass through the overlying barriers.

### 1.8.2. Oral lymphoid tissues

Both extra-oral lymph nodes and intra-oral lymphoid aggregations are associated with the mouth.

Lymph capillaries originating superficially in the oral mucosa, gingivae and pulps of the teeth join to form larger lymphatics, which later join lymph vessels from a deep network in the other facial structures such as muscle of the tongue. These

vessels drain into the submandibular, submental, upper deep cervical and retro-pharyngeal lymph nodes in an ordered fashion. Microbes that have passed through oral epithelium into the lamina propria may enter lymphatics directly or be transported to them by phagocytic cells. The antigen will thereby reach the anatomically neighbouring lymph nodes where an immune response may be elicited.

There are four types of lymphoid aggregations in the mouth (Fig. 9). While the functions of the intra-oral lymphoid tissue are not fully understood, the tonsils are believed to guard the entry into the digestive and respiratory tracts, whilst the gingival lymphoid tissue responds to dental plaque. Secretory IgA, produced in the salivary glands, helps to prevent infection within the glands themselves but also protects the oral mucosa and tooth surfaces from microbial colonization.

| INTRAORAL LYMPHOID TISSUE | |
|---|---|
| Palatine and lingual tonsils | Classical structure of lymphoid follicles<br>B cells and perifollicular T cells<br>Antigen penetrates through covering epithelium<br>(no afferent lymphatics) |
| Salivary gland lymphoid tissue | Concerned mainly with synthesis of secretory IgA |
| Gingival lymphoid tissue | Plasma cells, lymphocytes, macrophages and polymorphs<br>Important in immunological response to dental plaque |
| Scattered submucosal lymphoid cells | |

**Fig. 9. Summary of the collections of intraoral lymphoid tissue**

### 1.8.3. Saliva

Saliva is a very important component of the oral defences, both by its mechanical washing activity and by means of the antimicrobial factors that it contains. The important antimicrobial activities and components of saliva are summarized in Fig. 10. Secretory IgA is by far the most important immunoglobulin in saliva. IgA is secreted by salivary gland plasma cells, two molecules of which are combined by means of a J chain, which is also secreted by local plasma cells. The resultant dimeric IgA is then complexed to the secretory component, synthesized by epithelial cells of the salivary acini, and the complete secretory IgA is transported into the duct lumen and then into the mouth. Secretory IgA is more resistant to proteolytic degradation than other immunoglobulins. It probably functions by combining with rnicroorganisms and preventing their adherence to host surfaces.

| ANTIMICROBIAL ACTIONS OF SALIVA | |
|---|---|
| Mechanical cleansing | Muscular movements, in conjunction with saliva, maintain hygiene in accessible areas of mouth<br>Swallowed microbes are inactivated in the stomach |
| Lysozyme | Bactericidal, by splitting the bond between *N*-acetyl glucosamine and *N*-acetyl muramic acid in the cell wall |
| Peroxidase | Heat-labile, anti-bacterial enzyme |
| Lactoferrin | Heat-stable protein, bacteriostatic to many micro-organisms |
| Leucocytes | Saliva contains many leucocytes (99% polymorphs)<br>Migrate from blood via gingival crevice |
| Secretory IgA | IgA is the predominant immunoglobulin in saliva<br>Produced by plasma cells within salivary glands<br>Mainly in dimeric form, complexed with secretory component<br>Functionally, secretory IgA prevents microbial adherence to host surfaces |

**Fig. 10. Summary of the major antimicrobial actions of saliva**

### 1.8.4. Gingival crevicular fluid

Blood components, including leucocytes, are able to reach the oral cavity via the flow of fluid through the functional epithelium of the gingival. The flow of this so-called gingival crevicular fluid (GCF) increases greatly with the inflammation accompanying periodontal disease. Experiments using radiolabelled IgG, IgM, IgA and neutrophils have shown that both humoral and cellular components from blood can reach the oral cavity in GCF.

In addition to immunoglobulins, complement components have been detected in GCF, suggesting that both the classical and alternative complement pathways may be activated in the gingival crevice. Other components include enzymes such as lysozyme, proteases and collagenases released by cells of both the host and bacteria. Specific proteases which inactivate IgA have been described.

The cellular component if GCF comprises mainly neutrophils, with small numbers of macrophages and B- and T-lymphocytes. These cells migrate continuously from the blood through the functional epithelium into the gingival crevice. Over 80% of neutrophils in the gingival crevice are functional and can phagocytose microorganisms.

It is clear, therefore, that tooth surface is influenced by both local salivary immune mechanisms, mediated largely through secretory IgA, and by systemic immunity involving all the varied immune components present in blood. The way in which these contributing factors interact to provide immunity within the oral cavity is illustrated in Fig. 11.

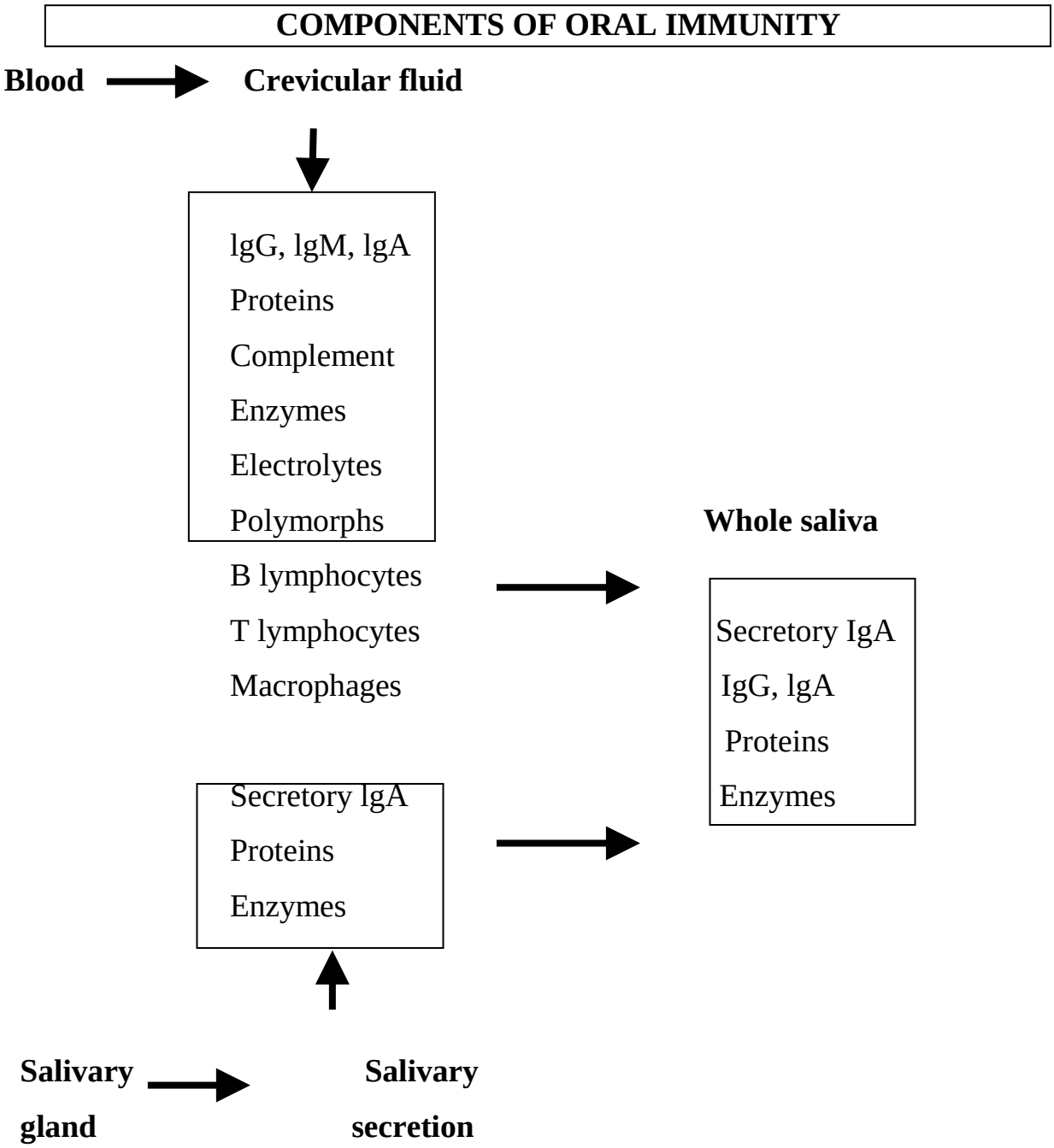


**Fig. 11. The main humoral and cellular components in gingival crevicular fluid, salivary gland secretion and whole saliva (Adapted from Lehner T., 1992)**

# Part 2

## Dental caries

Dental caries can be thought of as a chronic infection of enamel or dentine in which the microbial agents are members of the normal commensal flora. Lesions result from the demineralization of enamel or dentine by acids produced by plaque micro-organisms as they metabolize dietary carbohydrates. Once the surface layer of enamel has been lost, the infection invariably progresses via dentine, with the pulp becoming firstly inflammed and later necrotic. Dental caries occurs in all Western countries but there is an uneven distribution of decay in the population. For example, in Scotland towards the end of the twentieth century all of the decayed teeth were found in 54% of children and mote than half of the untreated caries was present in just 10% of children. In less developed countries where changes in diet, especially with respect to carbohydrate content, have occurred, the prevalence is rising.

There is a last literature about the aetiology, diagnosis, management and prevention of dental caries. In this chapter only the main factors are discussed.

### 2.1. Clinical presentation and diagnosis

Dental caries can be classified with respect to the site of the lesion. The main stages involved in enamel caries. The earliest clinical appearance of the disease is a well-demarcated chalky-white lesion in which the surface continuity of enamel is still intact. This so-called 'white spot' lesion can heal or remineralize with the result that this stage of the disease is reversible. However, as the lesion develops the surface becomes roughened and cavitation occurs. Depending on the rate of tissue destruction, caries can be described as rampant, slowly progressive or arrested. If the lesion is untreated, micro-organisms extend the disease into dentine, the pulp may become infected and die and there is a risk of subsequent periapical abscess formation.

Diagnosis is traditionally by a combination of direct observation and radiographs, but using these techniques alone, early white spot lesions may easily be missed. It is also possible for large carious lesions to develop in pits and fissures with very little clinical evidence of disease. Recent research has identified a number of innovative

methods of detecting caries, including laser fluorescence (buccal/lingual caries) and electrical resistance techniques (occlusal caries), both of which show promise. However, neither can be used routinely at present.

### 2.2. Aetiology

The main factors involved in dental caries are the tooth, saliva, supragingival plaque, the diet (especially sucrose intake) and the time necessary for caries development. These complex factors can interact in numerous different ways, but certain patterns of interrelationships are more likely than others to result in the initiation and progression of carious lesions or healing of an early white spot lesion.

### 2.3. Host factors

The two main host factors are the structures of enamel or dentine (root surface caries) and the composition and flow of saliva.

#### 2.3.1. Enamel

The susceptibility of different areas of enamel on the same tooth to a standard acid attack in vitro can vary markedly. This and other information strongly suggests that some areas of the same tooth are more susceptible to carious attack than others. Similarly, a microbial challenge to a susceptible surface may produce an early carious lesion whilst one on a more mineralized area may fail to initiate disease. Such interactions are often ignored when the role of micro-organisms in caries is studied in vivo or in vitro. Susceptibility to demineralization by acid is probably related to many factors including the mineral and fluoride content, together with the structure of particular areas of enamel.

#### 2.3.2. Saliva

Mixed or whole saliva consists of secretions from the major (parotid, submandibular and sublingual) and minor salivary glands, with a variable input from the gingival crevicular fluid. Also present are exfoliated epithelial cells, oral micro-organisms and their produces and food residues. The rate of secretion and composition of mixed saliva can be affected by a wide range of variables including age, sex, time of day and possibly genetic differences. Some of the constituents of saliva are shown in Fig. 12.

| MAIN CONSTITUENTS OF MIXED SALIVA | |
|---|---|
| Antimicrobial factors | IgA, histidin-rich proteins, cystatins, lysozyme, peroxidase system |
| Minerals | Sodium, chloride, fluoride, calcium, phosphate, bicarbonate |
| Other constituents | Amylase, glucose, urea, albumin |

**Fig. 12. Constituents of mixed saliva**

The pH and buffering capacity of saliva are determined by the bicarbonate and phosphate concentrations, the normal pH of mixed saliva ranging from 5.6-7.8 with a mean of 6.7. Saliva should be regarded as a slow-moving, thin film about 0.1 mm thick with a variable velocity related to site (0.8 mm/min in the upper labial area and 5.0-8.0 mm/min on the lingual surfaces of the lower incisors and molars when the salivary flow is unstimulated). The complex constituents of saliva are not well mixed in vivo and the thin mobile film both removes substances from and deposits them in dental plaque. Recent research suggests that saliva provides a series of distinctly different fluid environments, some of which interact with dental plaque to produce dental caries, while others favour calculus formation and remineralization of early carious lesions.

Saliva plays a number of important roles in maintaining oral and dental health, some of which are related to dental caries. For example, the mechanical washing action of saliva is a very effective mechanism for removing food debris and unattached oral microorganisms from the mouth. The protective role of saliva is highlighted in patients with severe Sjogren's syndrome (a degenerative disease of salivary glands) who have a very low salivary flow rate, retain food debris in their mouth for long periods and suffer from rampant dental caries. Saliva has a high buffering capacity, which tends to neutralize acids produced by plaque bacteria on tooth surfaces. It is also supersaturated with calcium and phosphorus which, together with fluoride, are important in the remineralization of white spot lesions. The precise roles of some of the other salivary

antimicrobial factors in dental caries, for example lysozyme, the lactoperoxidase system and immunoglobulins, are not clear.

### 2.3.3. Diet

A number of epidemiological studies have demonstrated clearly a direct relationship between dental caries and the intake of carbohydrate. The most cariogenic sugar is sucrose and the evidence for its central role in the initiation of dental caries includes the following:

• an increase in the caries prevalence of isolated populations
with the introduction of sucrose-rich diets;
• clinical association studies;
• short-term experiments in human volunteers using sucrose
rinses;
• experimental animal studies.

In addition, sucrose is highly soluble and diffuses easily into I dental plaque, acting as a substrate for the production of extracellular polysaccharide and acids. Streptococcus mutans produces water-insoluble glucans from sucrose and these polysaccharides contribute to plaque matrix, consolidate the attachment of bacterial cells to the tooth surface and many localize acidic fermentation products within plaque. The direct relationship between sucrose and dental caries is more complex than can be simply explained by the total amount of sugar consumed.

There is good evidence that the frequency of sugar intake, rather than the total sugar consumption, is of decisive importance in caries development. Also important are the stickiness and concentration of sucrose consumed, both factors influencing the period for which sugar is retained in the mouth in close contact with the tooth surface.

Carbohydrates other than sucrose are also cariogenic, for example glucose and fructose, but to a lesser degree. Carbohydrates with low cariogenicity also exist, for example mannitol, sorbitol and xylitol.

## 2.4. Microorganisms

Dental caries does not occur in vivo if microorganisms in the form of dental plaque are absent; it is clear that dental caries is a plaque-associated disease. However, over the years there has been debate about whether one or more specific bacteria are principally involved in the initiation of caries (specific plaque hypothesis) or if the disease is caused by a non-specific mixture of bacteria (nonspecific plaque hypothesis). In the former hypothesis, S. mutans is believed to initiate virtually all carious lesions in enamel, while in the latter, caries is not dependent on the presence of S. mutans. Whilst the evidence required to prove or disprove these different hypotheses is incomplete there are sufficient data to indicate each may be valid in specific circumstances. The microbial composition of supra-gingival plaque collected from the same site in the same mouth with respect to time can vary substantially and in view of the wide variability in plaque microbiology ir is unreasonable to expect that the initiation and progression of all carious lesions are associated with identical or even similar plaques either from a qualitative or quantitative point of view. However, rhere is good evidence that overall some bacteria (S. mutans, Lactobadllus spp., and perhaps Actinomyces spp.) are more important than others in enamel and root surface caries.

### 2.4.1. Streptococcus mutans

Most of the research performed in recent years into the role of micro-organisms in canes has concentrated on mutans streptococci, especially S. mutans.

The term mutans streptococci refers to a group of seven different species (S. mutans, S. sobrinus, S. cricetus, S. ferus, S. rattm, S. macacae and S. dowmt) and 8 serotypes (a—h). S. mutans (serotypes c/e/f) and S. sobrinus (serotypes d/g) are the species most commonly found in humans, with serotype c strains being most ftequently isolated, followed by d and e. The others are rarely encountered in man. The evidence for the aetiological role of S, mutans in dental caries is shown in Fig. 13.

The strongest correlation between S. mutans and human caries is for fissure caries, but its relation to all other forms of caries is also very substantial. Early studies implicated Actinomyces spp. in the aetiology of root surface caries but

more recent work has implicated S. mutans and possibly lactobacilli. The role of S.sobrinus in human caries is less certain and this is due mainly to the use of a selective culture medium containing bacitracin in clinical studies, which inhibits the growth of S. sobrinus but not S. mutans, and to a lack of studies in humans that distinguish the two species. However, it is commonly isolated from dental plaque, though usually at a lower frequency than S. mutans, and possesses many of the pathogenic characteristics believed to be necessary to cause caries.

Not all strains of S. mutans possess the complete range of properties described in Fig. 13 and therefore strains of S. mutans may vary in their potential to produce dental caries. It is possible that certain strains of S. mutans are more pathogenic than others and that in a small number of individuals caries may be an infectious disease, with a highly pathogenic strain being transmitted from one individual to another, for example during kissing.

| FACTORS RELATED TO CARIOGENICITY OF STREPTOCOCCUS MUTANS |
| --- |
| • Significant correlation in humans between S. mutans counts in saliva and plaque with the prevalence and incidence of caries<br>• S. mutans can be isolated from precise sites on the tooth surface before the development of caries<br>• Correlation between the progression of carious lesions and S. mutans counts<br>• Produces water-soluble and insoluble extracellular polysaccharides from sucrose which help in the colonization of tooth surfaces by consolidating microbial attachment<br>• Most effective streptococcus in experimental caries in animals (rodents and non-human primates)<br>• Ability to transport sugars rapidly in competition with other plaque bacteria even at low pH<br>• Ability to initiate and maintain microbial growth, metabolism and acid |

production in sites with a low pH

- Acidogenic (strongly acid producing) and aciduric (acid loving)
- Efficient and rapid metabolism of sugars to lactic and other organic acids
- Can attain the critical pH for enamel demineralization more rapidly than other common plaque bacteria
- Produces intracellular polysaccharide which can act as a food store for use when dietary carbohydrate is low
- Immunization of animals with S. mutans significantly reduces the incidence of caries

**Fig. 13. Factors related to the cariogenicity of mutans streptococci, especially Streptococcus mutans**

While there is little evidence to support this hypothesis, molecular typing techniques have indicated that strains of S. mutans are transmitted between mothers and children during the first 6 months of life and that some adults vary in the number of genotypes they carry in their oral microflora. Not all evidence supports the apparently strong relationship between S. mutans and the initiation and progression of caries.

However, there are many problems involved in clinical studies, for example difficulty in diagnosing approximal 'white spot' lesions accurately at an early stage, problems in obtaining plaque samples directly from the surface of a developing lesion free of surrounding plaque, and technical difficulties in the microbiological identification and enumeration of the plaque micro-flora. A combination of the new methods of diagnosing caries and innovative molecular biology techniques should enable important new knowledge about the natural history of caries to emerge.

### 2.4.2. Lactobacillus species

Lactobacilli can be divided into two groups: the homofermentative species which produce mainly lactic acid (> 65%) from glucose fermentation (for example L. acidophilus and L. casei) and the heterofermentative species which produce lactic acid as well as significant amounts of acetate (for example L. fermentum). The most

commonly isolated species from oral samples appear to be L. cam, L. fermentum and L. acidophilus although characterization of isolates to species level is rarely performed since existing tests are expensive with doubtful specificity.

For many years lactobacilli were believed to be the causative agents of dental caries. Although they possess some properties which would be valuable to a cariogenic organism (Fig. 14), their affinity for the tooth surface and their numbers in dental plaque associated with healthy sites or early carious lesions are usually low. At present the general opinion supports the concept that lactobacilli are not involved in the initiation of enamel caries, but mote in the progression of the lesion deep into enamel and dentine where they are the main pioneer organisms in the advancing carious process. Lactobacilli are also implicated in the aetiology of root surface caries.

| FACTORS RELATED TO CARIOGENICITY OF LACTOBACILLUS SPECIES |
| --- |
| • Present in increased numbers in most carious cavities affecting enamel and root surfaces<br>• Numbers in saliva correlate positively with caries activity<br>• A few strains produce caries in gnotobiotic rats<br>• Able to initiate and maintain growth at low pH levels (aciduric)<br>• Produce lactic acid in conditions below pH 5.0 (Acidogenic)<br>• Some strains synthesise extracellular polysaccharides |

**Fig. 14. Factors related to the cariogenicity of Lactobacillus species**

There is evidence from *in vivo* human studies that on a group basis, salivary lactobacillus counts are related statistically to caries activity. However, when the counts for individuals are examined, and used to predict activity, overall the level of statistical significance is relatively low and the results of such tests are difficult to interpret. The characterization of oral lactobacilli is poor and although substantial

changes in their classification have been suggested, including the subdivision of L. *acidophilum* into three new species, very few in-depth laboratory investigations of clinical isolates have been performed in recent years. Until much more information is available, the precise role of lactobacilli in the initiation and progression of dental caries cannot be defined clearly.

### 2.4.3. Actinomyces species

*Actinomyces* spp. form a major and complex part of the microflora of dental plaque, particularly at approximal sites and in the gingival crevice. In recent years, there have been changes in the classification of Actinomyces and a number of new species described, but very few detailed clinical studies employing these new data have been reported. Therefore the precise role of *Actinomyces* spp., especially at species level, in dental caries is uncertain. *Actinomyces odontolyticum* has been correlated with the very early stages of demineralization. *Actinomyces naeslundii* (especially genospecies 2) has been associated with the development of root surface caries, which is a disease of middle-aged and older adults. Gingival recession exposes the root surface to the mouth and microbial colonization follows, with subsequent demineralization. The lesions are clinically different from enamel caries, in that the calcified tissues are often softened without obvious cavitation. They tend to form on the buccal and lingual surfaces close to the gingival margin and slowly progress laterally round the neck of the tooth. Human isolates of A. *naeslundii* have been shown to cause root surface caries in gnotobiotic rats and hamsters. Although *Actinomyces* spp., especially *A. naeslundii,* are often the predominant organisms isolated, their role in the initiation and development of the disease remains uncertain. Some studies have tended to show strong associations between root surface caries and mutans streptococci and lactobacilli rather than with *Actinomyces* species. Furthermore, the sites from which *S. mutans* and lactobacilli were isolated appear to have a higher risk of developing root surface caries than other sites. Root surface caries appears to be polymicrobial with the advancing front containing various species including proteolytic Gram-negative rods e.g. *Prevotella* and *Capnocytohpaga* spp. Factors such as the role of diet, and sali-

vary flow rate and constituents, have received little or no detailed investigation in this form of dental decay, and the application of the new classification of Actinomyces to clinical studies to help clatify the role of specific microorganisms is at an early stage.

### 2.4.4.Veillonella species

There is some evidence to suggest that *Veillonella* spp., which are present in significant numbers in most supragingival plaque samples, may protect against dental caries. *Veillonella* spp. require lactate for growth, but are unable to metabolize carbohydrates. They therefore utilize lactate and other intermediate metabolites formed by plaque bacteria as energy sources and convert them into a range of weaker and probably less cariogenic organic acids, predominantly acetic and propionic. This protective effect has been *n vitro* and in animal experiments, but has not been described clinically.

### 2.4.5. Non-mutans streptococci (non-MS)

Recent studies have focused attention on the role of'low pH' non-mutans streptococci in the caries process. These organisms are often numerically dominant in supragingival plaque and belong to the *S. mitis* group (especially some strains of *S, mitts,* and *S. gordonii)* and *S. anginosus* group. Strains of S. *sanguis* are generally not acidogenic. While strains of *S. mutans* can produce a final pH of about 4, a number of non-MS can achieve a pH of about 4.25. The 'low pH' non-MS could affect the carious process by causing the initial stages of demineralization and lesion formation and/or by creating an acidogenic environment in plaque, suitable for the colonization and proliferation of mutans streptococci. This group of micro-organisms may play an important role in the ecological plaque hypothesis (Fig. 15).

## 2.5. Plaque metabolism

Saliva is the main source of nutrition for oral microorganisms. Carbohydrate is present in saliva as glycoproteins (for example mucin), but since no single bacterial species possesses the full complement of enzymes to utilise these substrates, synergistic activity is necessary. However, the rate of production of acid is slow and is unlikely to cause significant demineralization. Following a meal, salivary

carbohydrate increases dramatically and, in order to avoid possible toxic effects and to gain maximum benefit from these high levels of carbohydrate, oral bacteria have developed a number of regulatory mechanisms which act at three main levels:

- transport of sugar into the organisms;
- the glycolytic pathway;
- the conversion of pyruvate into metabolic end products.

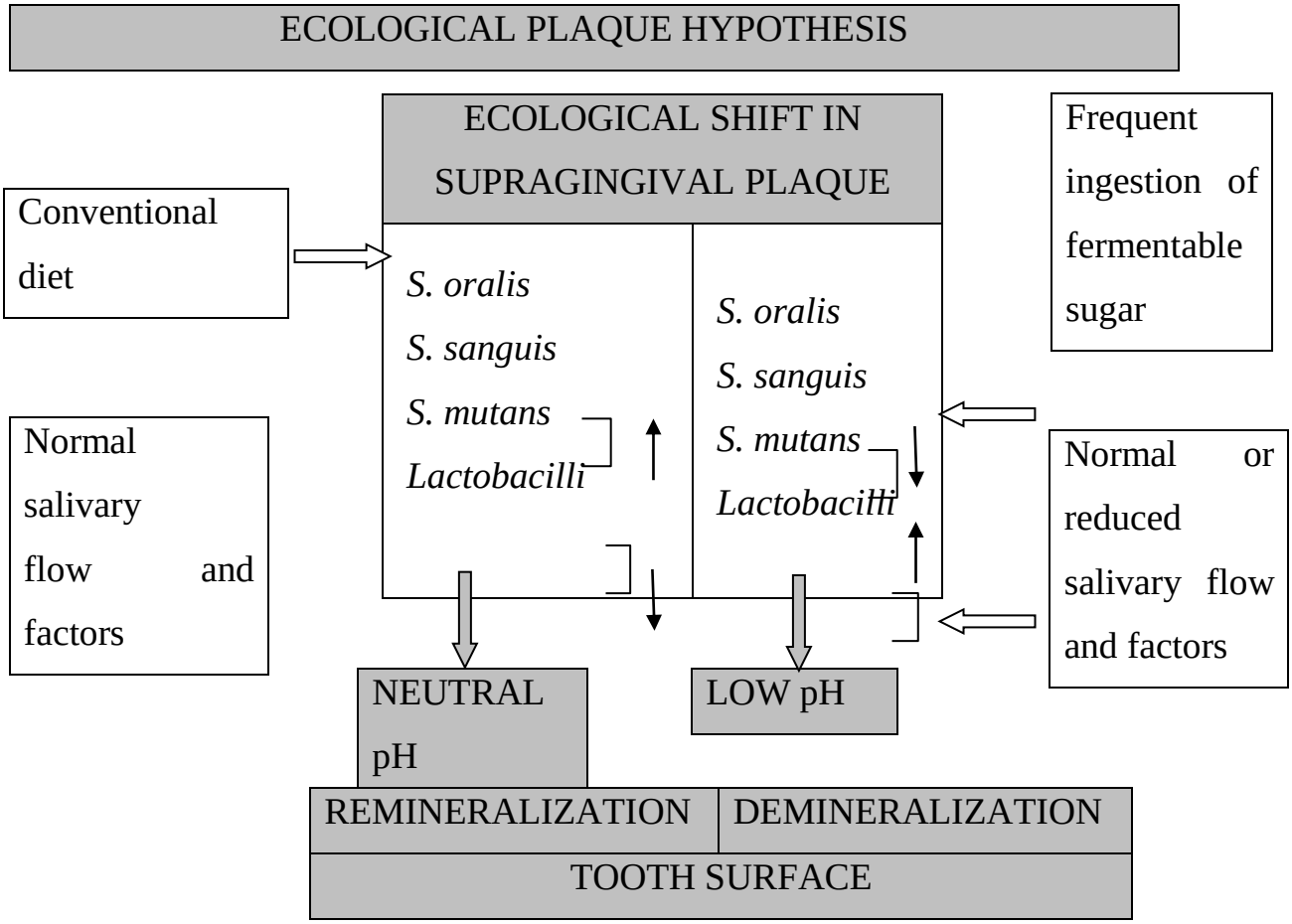


**Fig. 15. The Ecological Plaque Hypothesis in relation to dental caries**

The bacterial metabolism of carbohydrate, especially sucrose, which is consumed at levels of about 50 kg/person/year in many industrial countries, is important In the aetiology of caries since the acid end-products are responsible for enamel demineralization. The metabolic fate of dietary sucrose and other carbohydrates in the mouth is complex. Initially, sucrose is broken down by various bacterial extracellular enzymes (glucosyl- and fructosyl-transferases), with the release of glucose and fructose, some of which are polymerized into water-soluble or water-insoluble polysaccharides (glucans or fructans). The insoluble polysaccharides are

important in plaque formation, the consolidation of bacterial attachment to the teeth and as extracellular storage compounds. Some sucrose is transported intact into plaque bacteria as disaccharide or disaccharide phosphate and cleaved intracellularly by invertase or sucrose phosphate hydrolase to glucose and fructose. Most plaque bacteria catabolise these sugars internally by glycolysis to pyruvate for immediate energy needs, but can also store excess carbohydrate as intracellular polysaccharides (IPS). Sugars are also utilized in anabolic pathways to generate biomass. In glycolysis, most oral bacteria metabolize pyruvate anaerobically to organic acids. In the case of *S. mutans* this involves the conversion of pyruvate to lactate by lactate dehydrogenase when sugar is in excess - formate and acetate are also produced. As mentioned earlier, *S. mutans* is probably the most aciduric and acidogenic organism in plaque and can create environmental conditions that are lethal for other bacteria. When carbohydrate is scarce, bacteria chat form IPS can utilize these stores with the production of acid, which is sufficient to cause dissolution of enamel and dentine. Thus, overall the interaction of plaque bacteria and carbohydrate results in a rapid fall in plaque pH, which is usually followed by a slow return to the original pH value in about one hour.

Ecological plaque hypothesis has been developed by integrating the published data concerning the main factors discussed earlier, which are thought to be involved in dental caries (tooth surfaces, saliva, diet and plaque ecology), to explain the unpredictable and somewhat random pattern of dental caries that occurs *in vivo*. The main features of the hypothesis are represented in Fig. 15, and they can be summarized as follows. When salivary composition and function and fermentable sugar intake are within normal limits, plaque ecology favours bacterial species that are associated with a pH of about 6-7 *(S. oralis* and *S. sanguis),* and intact enamel and dentine surfaces. However, if the amount and frequency of intake of fermentable sugar increases markedly, with or without changes In salivary composition and function, plaque ecology favours acid-tolerating bacteria *(S. mutans* and *Lactobacillus* spp.) that are associated with low pH (less than 5) and demineralized tooth surfaces. Figure 15 is a simplified representation of a very complex process, and shows only

two extreme situations (health and disease) but in reality a very wide range of possible interactions can occur involving the main aetiological factors, some of which will tend towards remineralization and health, and others towards demineralization and disease. It follows that caries can be prevented not only by targeting the putative pathogens but also by interfering with the factors that help to select them.

### 2.6. Management of dental caries

The clinical management and prevention of dental caries is based on an understanding and practical application of the scientific information presented so far. In the past, the general approach in the treatment of dental caries was to remove diseased tissue and replace it with an inert restoration. This form of management made no attempt to cure the disease, and the patient often returned some 1-3 years later requiring further fillings due to new or recurrent caries.

The current philosophy in dental caries management highlights the importance of accurate early diagnosis, encouraging remineralization where appropriate, minimal cavity preparation techniques and active prevention. The end result of such measures should be that with the passage of time an individual patient will require less restorative work.

#### 2.6.1. Evaluation of patients

In patients with a low incidence of caries, a case history, together with clinical and radiographic examination, are probably sufficient for treatment planning. However, for patients with rampant or recurrent caries, or where extensive crown and bridge work is planned, additional investigations are necessary. These include assessment of dietary habits, determination of salivary flow rate and buffering capacity, and microbiological tests. It is outside the scope of this book to describe how these different factors are used to assess caries risk and subsequently incorporated into the treatment plan. However, the standard microbiological method is to enumerate the numbers of *S. mutans* and *Lactobacillus* spp. in mixed saliva from patients. Briefly, a paraffin-wax-stimulated sample of mixed saliva is collected and sent to the laboratory, where it is vortex-mixed, diluted, and cultured on selective

media for *S. mutans* (Mitis Salivarius Bacitracin Agar) and *Lactobacillus* spp. (Rogosa SL Agar). For each organism the count per millilitre of saliva is calculated and interpreted as follows:

High value >1 million *S. mutans* > 100,000 *Lactobacillus* spp.

Low value <100,000 S. *mutans* < 1,000 *Lactobacillus* spp.

Commercially available dip-slide kits are available for lactobacillus and mutans streptococcus counts which correlate well with laboratory plate counts. They can be performed in dental practice without the need for special facilities.

While there are good statistical correlations between caries prevalence and increment and laboratory counts of lactobacilli and mutans streptococci when data are analysed on a group basis, the correlations are less convincing when analysis involves diagnosis or prediction of disease on an individual basis. The presence of high salivary levels of mutans streptococci or lactobacilli does not necessarily mean that the patient has a high incidence or risk of developing dental caries because other factors, such as diet, buffering capacity, fluoride content of enamel and degree of oral hygiene, may combine to produce a protective effect, and thus tip the host-parasite balance from disease towards health. However, the identification of a patient who has an abnormally high oral count of lactobacilli or mutans streptococci allows this fact to be taken into account when assessing all the factors which may contribute to the caries experience of the individual and when deciding short- and long-term treatment. The tests can also be used subsequently to monitor the efficacy of preventive techniques, such as dietary and oral hygiene advice and chlorhexidine therapy.

### 2.6.2. Prevention of dental caries

The most common approaches used in caries prevention are shown in Fig. 16. The rationale for the use of the different procedures is as follows.

### 2.6.3. Sugar substitutes

The use of artificial sweeteners to replace fermentable sugars is based on the premise that they cannot be absorbed and metabolized by plaque bacteria to produce acid. Two main types of sugar substitutes are available: intensive

sweeteners, for example saccharine, which are extremely sweet and recommended for drinks, and bulk sweeteners such as xylitol, sorbitol and manitol that are used in the confectionery industry. Xylitol is effective in reducing caries by stimulating salivary flow, thereby encouraging remineralization, and also interferes with acid production by mutans streptococci.

### 2.6.4. Mechanical cleansing techniques

Conventional toothbrushing with fluoridated toothpaste, even though it depends very much on the motivation and skill of the patient, is related to an overall reduction in the incidence of caries. Other aids for plaque removal, for example interdental brushes, wood sticks and dental floss, may achieve some reduction in interdental caries, but there is no good evidence for this.

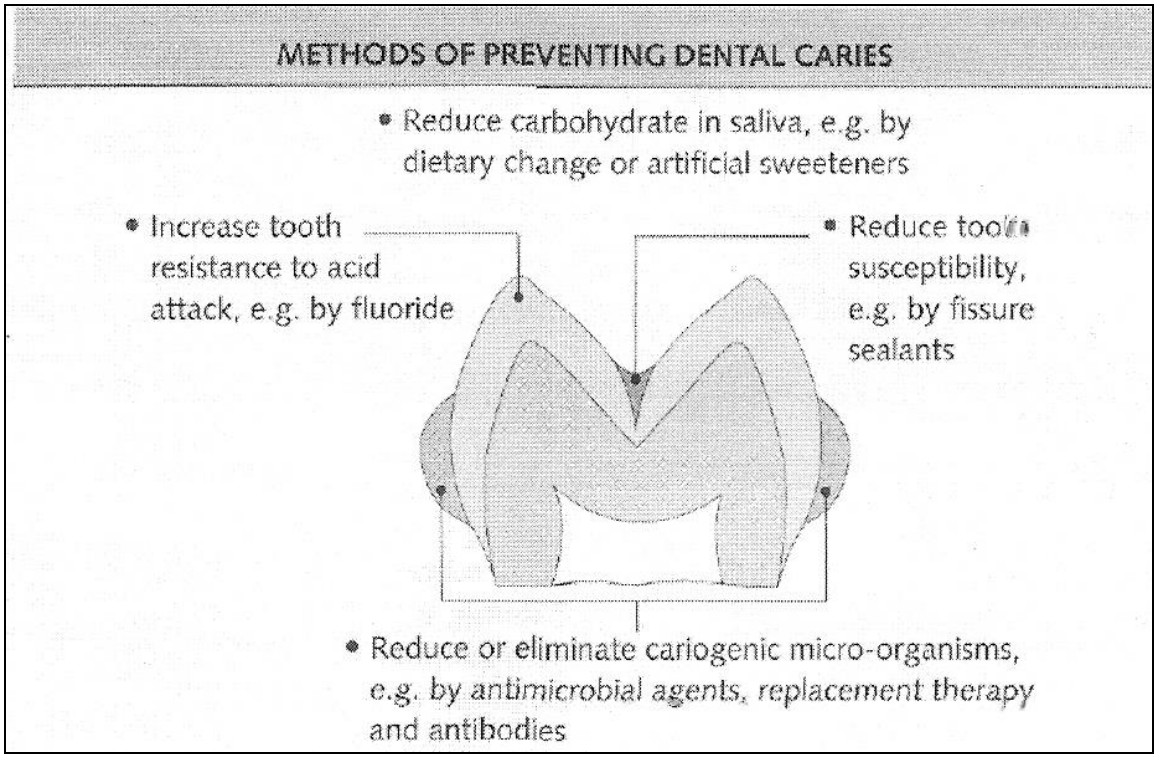


**Fig.16. Methods of dental caries preventing**

Certainly it is unlikely that mechanical cleansing methods alone will reduce or prevent caries significantly in fissures or pits.

### 2.6.5. Replacement therapy

The idea that non-pathogenic bacteria can be used to control pathogens and prevent disease has been around for about a century. Two approaches have been suggested for

caries and although no extensive studies have been attempted in humans, there is positive evidence from a mixture of laboratory and animal experiments. One approach is to inoculate the host at an early age with low-virulence strains of mutans streptococci, which colonize and exclude the colonization of virulent strains at a later date. The second approach is to develop a bacterial strain which, when inoculated into the host, can compete and displace a pre-existing pathogen; for example a strain of *S. salivarius* has successfully displaced *S. mutans* from the teeth of rats and inhibited subsequent carious arrack.

### 2.6.6. Antimicrobial agents

Chlorhexidine as a 0.12-0.2% mouthwash is by far the most effective agent in controlling dental plaque formation and has activity against many Gram-positive and Gram-negative oral bacteria. The antiseptic can also be applied to teeth in gel form contained in special trays or as a slow release varnish. At high concentrations the antiseptic is bactericidal by damaging cell membranes. Chlorhexidine also binds to oral surfaces (especially teeth) and is then slowly released into saliva over many hours at bacteriostatic concentrations that can reduce acid production in plaque by abolishing the activity of certain bacterial sugar transport systems. It is also possible that the presence of Chlorhexidine on enamel surfaces and in saliva interferes with the adherence of plaque-forming bacteria, thus reducing the rate of plaque accumulation. Mutans streptococci tend to be more sensitive to chlorhexidine than other streprococci commonly involved in plaque development, for example *S. sanguis.* This fact is convenient, in that the antiseptic not only reduces the numbers and effectively the metabolic end-products of the major group of cariogenic bacteria, but also tends to favour the growth of streptococci which are associated with health. However, due to the problems of tooth staining and unpleasant taste, combined with possible harmful effects on the oral microflora, chlorhexidine is used normally only for short term therapy. It may be used for longer periods in high-risk subjects, for example patients with xerostomia.

### 2.6.7. Vaccination

It is well established that immunization, with either cell-wall associated antigens or glucosyltransferases from *S. mutans*, is effective in reducing experimental dental caries in rats and primates. It is not entirely clear how the vaccine produces its protective effect, although the following have been suggested:

- inhibition, by secretory IgA, of bacterial colonization of
- enamel;
- interference with bacterial metabolism;
- enhancement of phagocytic activity in the gingival crevice area due to the opsonization of *S. mutans* with IgA or IgG antibodies.

However, convincing proof that any of these mechanisms prevent the development of dental caries *in vivo* is lacking. A number of cell-wall associated vaccines have been tested and all have produced good protection against caries in primates. Although potential vaccines against *S. mutans* have been manufactured to legally acceptable standards, no major field trials have been performed on humans. Some of the antigens tested elicited antibodies that cross-reacted with heart tissue, although this potential and undesirable problem has been eliminated with careful selection of individual purified antigens. However, theoretically, other side effects could emerge and this raises the question of balancing the risk of using a potentially hazardous vaccine in the prevention of a non-life threatening disease.

Another problem in instituting a vaccination programme is the fact that the incidence of dental caries has fallen dramatically in most industrialized countries, probably as a result of fluoride and vaccination is deemed unnecessary. However, it can be argued that a vaccine could be regarded as a benefit to particular high-risk groups in the population. Until immunization has been tested *in vivo* it can only be regarded as a potential method of preventing dental caries.

An interesting development is the use of passive immunization. There is evidence that passive immunization of human volunteers (previously rendered free of *S. mutans)* with monoclonal, secretory antibody produced by transgenic plants against

antigen I/II (a surface protein of *S. mutans),* can prevent oral recolonization of *S. mutans* for many months.

### 2.6.8. Fissure sealants

Fissure sealants prevent caries in pits and fissures by eliminating stagnation areas and blocking potential routes of infection by oral bacteria deep within the tooth. Early carious lesions in fissures that are sealed tend not to progress, probably because the source of microbial nutrition has been blocked. However, more extensive lesions will probably extend into the pulp, since the bacteria will obtain sufficient nutrients from the carious dentine.

### 2.6.9. Fluoride and tooth solubility

The various ways in which fluoride protects human teeth from carious attack are summarized in Fig. 17. Mutans streptococci are particularly sensitive to low levels of fluoride at moderately low pH values. However, in these circumstances mutans streptococci are not eliminated from the mouth but bacterial growth appears to be suppressed in plaques under environmental conditions in which it would otherwise be expected to be stimulated.

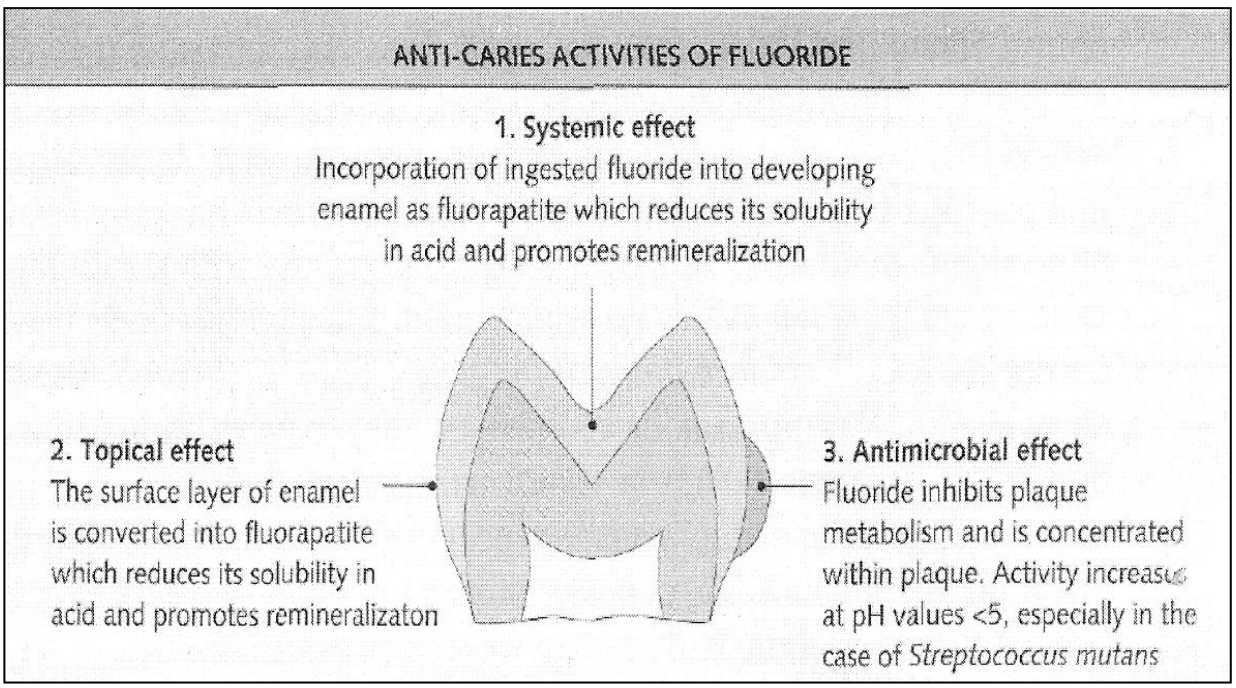


**Fig. 17. Simplified diagram of the anti-caries activities of fluoride**

# Part 3

# Periodontal diseases

Periodontal disease in its widest sense includes all disorders of the supporting structures of the teeth, namely the gingiva, periodontal ligament and supporting alveolar bone. This may vary from inflammation of the gingiva alone, termed gingivitis, to the severe inflammation of the periodontal ligament called periodontitis (Fig. 18), in which there is destruction of alveolar bone and eventual tooth loss.

Unlike many medical infections, periodontal diseases ate not caused by pathogens that have their primary habitat outside the host. Instead, they are associated with a shift in the balance of the resident microflora, a similar situation to dental caries. The microorganisms may produce disease directly, by invasion of the tissues, or indirectly via bacterial toxins. The host response to these challenges may be protective, fot example phagocytosis of invading bacteria, or destructive, for example immune complex activation of osteoclasts. Frequently it is a combination of both and the interaction between these components which determines the wide spectrum of disease that is seen clinically.

## 3.1. Gingivitis

As shown in Fig. 18, there are several types of gingivitis. The most common of these is plaque-associated chronic marginal gingivitis.

| **CLASSIFICATION OF GINGIVITIS** | |
|---|---|
| **Type of gingivitis** | **Comments and examples** |
| **Chronic marginal gingivitis** | Non-specific inflammatory response to dental plaque involving the gingival margins. Early gingivitis associated with *Streptococcus* spp. and *Actinomyces* spp. Longstanding gingivitis has more Gram-negative anaerobes and spirochaetes |

| | |
|---|---|
| **Acute ulcerative gingivitis (AUG)** | An acute gingival infection characterized by necrosis of tips of the gingival papillae, spontaneous bleeding, pain and halitosis. Predisposing factors include stress and cigarette smoking. Micro-organisms can be seen invading the gingival tissues and studies have identified large numbers of spirochaetes and fusiform bacteria. Other bacteria cultured are *Prevotella intermedia, Veillonella* spp. and *Fusobacterium* spp. |
| **Steroid hormone-induced gingivitis** | Characterized clinically by an exaggerated response to plaque, leading to intense inflammation, redness, oedema and enlargement. May occur during puberty, pregnancy and with steroid therapy. Subgingival growth of *Porphyromonas gingivalis* may be enhanced when steroid hormones are elevated |
| **Medication influenced gingivitis** | Begins as small spherical enlargements of the gingival margin and papillae. May progress until most of the tooth surface is covered, forming false periodontal pockets. Induced by phenytoin, cyclosporin and nifedipine |
| **Gingivitis associated with systemic disease** | Acute leukaemia may present clinically with intense gingival redness, swelling and bleeding |
| **Acute herpetic gingivostomatitis** | One of the commonest causes of acute gingivitis is herpes simplex virus. Presents clinically with well-defined vesicles succeeded by ulcers |
| **Desquamative gingivitis** | Characterized by desquamation of the gingival epithelium, leaving *an* intensely red surface. Most cases represent oral manifestations of dermatological diseases, such as lichen planus, pemphigus vulgaris and pemphigoid |

**Fig. 18. A summary of the common forms of gingivitis**

### 3.1.1. Plaque-associated gingivitis

The microflora of the healthy gingival crevice is relatively sparse and composed mainly of Gram-positive cocci, especially *Streptococcus* spp. The crevice has a lower redox potential than most sites within the oral cavity, which encourages initially the growth of *Actinomyces* spp. and an increase in capnophilic (carbon dioxide-requiting) bacteria such as *Actinobacillus actinomycetemcomitans.* Toxins released by these bacteria induce an inflammatory response in the gingival tissues with a resultant increase in gingival crevicular fluid. How and the provision of nutrients essential to the changing needs of the plaque flora. The environment ultimately changes to one that can support the growth of obligately anaerobic bacteria and spirochaetes. The inflammatory reaction in the gingiva progresses, with resultant chronic marginal gingivitis. Clinically, gingivitis is characterized by redness, gingival bleeding and oedema.

There is strong evidence for a bacterial aetiology of gingivitis. Both cross-sectional and longitudinal oral hygiene studies, in particular the experimental gingivitis studies of Lo'e in the 1960s, demonstrated that the development and accumulation of dental plaque can be correlated with clinically demonstrable gingivitis. However, it is the presence of dental plaque *per se* that correlates with gingivitis and there is no evidence to suggest that any particular bacterial species is responsible.

Acute ulcerative gingivitis is a specific form of gingivitis in which there is necrosis of the tips of the gingival papillae, spontaneous bleeding, pain and halitosis. Diagnosis is based on demonstration of the characteristic fusospirochaetal complex in a deep gingival smear.

Among the immunocompromised, gingivitis often presents in clinically atypical forms. Thus, patients with acute leukemia may develop sudden-onset gingival swelling, ulceration and bleeding in conjunction with other oral manifestations such as petechial haemorrhages. HIV-associated gingivitis is an atypical gingivitis which is characterized by a band-like

marginal erythema, usually accompanied by diffuse redness which extends onto the vestibular mucosa.

### 3.1.2. Stages in the development of gingivitis

Plaque-associated gingivitis has been separated into three stages based on the sequence of histopathological events which occur when plaque is allowed to accumulate at the gingival margin.

**STAGE 1: THE INITIAL LESION.** This develops within 4 days of plaque accumulation. The micro-flora consists mostly of Gram-positive cocci *(Streptococcus* spp.). Histologically, there is an acute inflammatory reaction. The lesion is characterized by increased flow of gingival crevicular fluid and migration of polymorphonuclear leukocytes into the gingival sulcus from the local vasculature. Adjacent to the functional and sulcular epithelia, the inflammatory infiltrate occupies approximately 5-10% of the gingival connective tissue. This initial lesion is not visible clinically.

**STAGE 2: THE EARLY LESION.** The early lesion appears after approximately 7 days of plaque accumulation and is detectable clinically as gingivitis. The environment now has a lower oxygen tension and the plaque flora shifts to contain more *Actinomyces* spp., spirochaetes and capnophilic organisms. Histologically, the gingival infiltrate in the early lesion is dominated by lymphocytes (75%) and macro-phages, with some plasma cells located at the periphery of the lesion. The infiltrated area occupies approximately 15% of the marginal gingival connective tissue, with some local destruction of collagen. Migration of polymorphonuclear leukocytes into the gingival sulcus and crevicular fluid peaks at 6 to 12 days following the onset of clinically detectable gingivitis.

**STAGE 3: THE ESTABLISHED LESION.** After a variable period of time the subgingival microflora develops into an environment that can support the growth of obligate anaerobes such as *Porphyromonas gingivalis* and *Prevotella intermedia.* Histologically, there is a further increase in the size of the

inflammatory lesion within the affected gingiva, with a shift to a predominance of plasma cells and B-lymphocytes. A periodontal pocket lined with pocket epithelium may be present. The functional and pocket epithelia are heavily infiltrated with neutrophils. Plasma cells are found at the periphery of the lesion, while macrophages and lymphocytes are present in the lamina propria of the pocket wall. Established lesions may persist for months or years without progression to periodontitis.

### 3.2. Periodontitis

Periodontitis may be defined clinically as inflammation of the supporting tissues of the teeth. It can be subdivided clinically into several groups, the commonest of which is adult periodontitis.

The lesion of adult periodontitis maintains all the features of the established lesion of gingivitis, with additional migration of the functional epithelium down the root surface, alveolar bone resorption and subsequent pocket formation (Fig. 19). In addition it is characterized by progressively destructive changes which destroy alveolar bone and periodontal ligament, with an attachment loss of mote than 3 mm. Histologically, the conversion of the established lesion of gingivitis into periodontitis is characterized by destruction of the connective tissue attachment to the toot surface and by alveolar bone loss. The exact mechanism for the transition from gingivitis to periodontitis is unknown.

Formation of a periodontal pocket creates an environment that is highly anaerobic. The pH shifts from 6.9 to approximately 7.4-7.8 and the pocket is continually bathed by the protein-rich solution of gingival crevicular fluid, which encourages growth of proteolytic bacteria. Subgingival plaque appears to have a dense zone of mostly Gram-positive bacteria attached to the tooth surface and a less densely packed zone of mainly Gram-negative organisms next to the gingival surface. Subgingival plaque may undergo calcification to form subgingival calculus. Clinically, subgingival calculus is darker in colour and more firmly attached to the root surface than its supragingival counterpart. Subgingival calculus is covered by a

layer of microorganisms and its porous nature serves as a reservoir for bacterial antigens, toxins and enzymes.

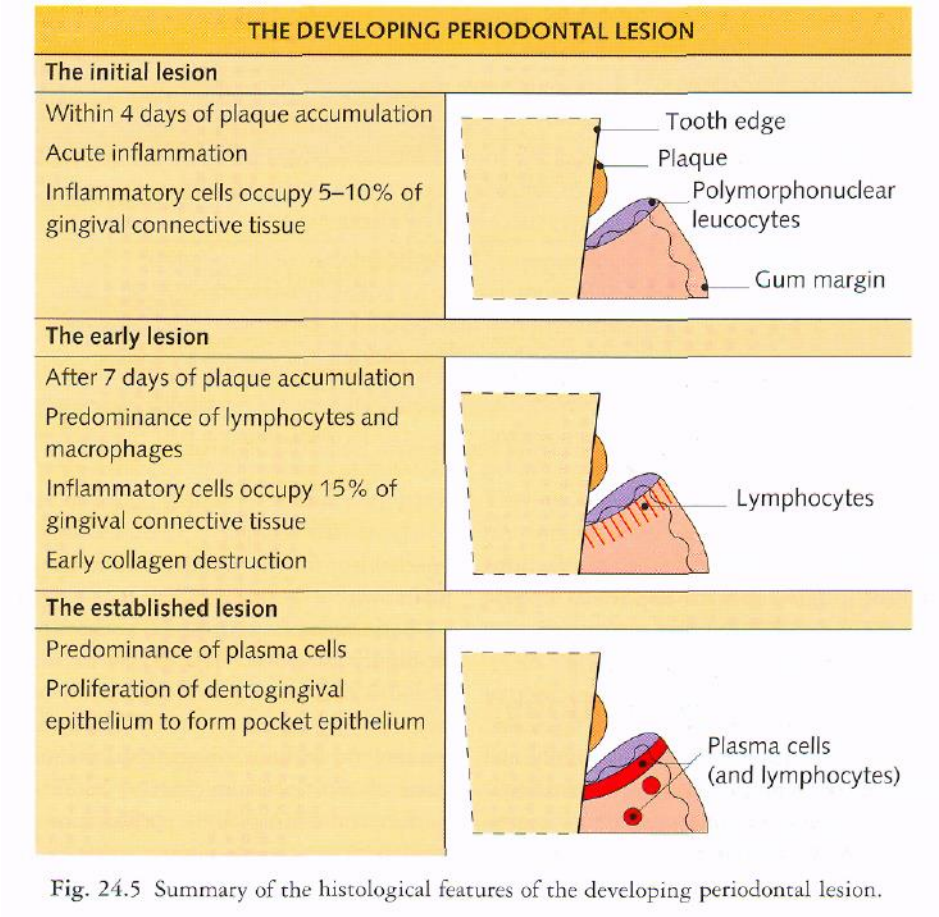

Fig. 24.5 Summary of the histological features of the developing periodontal lesion.

**Fig.19. Summary of the histological features of the developing periodontal lesions**

### 3.3. The aetiology of periodontal disease

The search for the causative agent(s) of periodontal disease has been dogged by difficulties. These have included:

- technical problems, for example obtaining uncontaminated plaque samples during the active stages of periodontal
  disease and the difficulty of culturing and discriminating between the 300 or more candidate species.
- inadequate understanding of the progression of periodontal diseases.

- inability to apply Koch's postulates since the causative organisms are likely to be part of the normal flora.
- the lack of an adequate animal model for periodontal disease.

In this section, a summary will be given of the present state of knowledge, though it must be recognized that this is currently incomplete.

### 3.3.1. Host and microbial factors

The search for the aetiology of periodontal disease must consider both host and microbial factors. The exact roles of each remain unclear but, as with most infections, it seems likely that the clinical outcome in periodontal disease is a result of the complex interactions between a wide range of host and microbial factors.

For infectious disease to occur, the host must be susceptible to the relevant pathogen. Some of the factors which may increase host susceptibility to infection include inadequate of unregulated host immune response, diabetes mellitus, stress and tobacco use. Many of these are relevant to periodontal diseases, as summarized in Fig. 20.

| HOST FACTORS IN PERIODONTAL DISEASE | | |
|---|---|---|
| Host factor | Beneficial effects | Harmful effects |
| Immuno globulins | Ig G enhances phagocytosis by opsonizatiosis of bacteria Ig A decreases bacterial adherence | Antibody/antigen complexes may lead to type 3 hypersensivity reactions.The attracted leucocytes release enzymes resulting in tissue damage |
| Comple ment proteins | Endotoxin or antigen-antibody complexes can activate complement proteins. This initiates inflammatory reactions leading to lysis of bacteria,chemotaxis and activation of neutrophils and macrophage degranulation | Type 2 hypersensivity reactions may follow activation of complement |
| Cytokine s | Have a multitude of activities. For example, IL-2 recruits other members of the immune system | Cell mediated tissue destruction may occur via the release of cytokines such as osteoclast activating factor |
| Polymor phs and macroph ages | Phagocytose bacteria | Release of neutral proteases and reactive oxygen metabolites may lead to tissue damage |
| T cells | T helper cells cooperate with B cells in antibody production | |
| B cells | Produce antibodies against a wide range of periodontal pathogens | |

**Fig. 20. Host factors in periodontal disease**

The important bacterial factors relevant to the role of microorganisms in periodonral disease are summarized in Fig. 21.

### 3.3.2. The role of microorganisms in periodontal disease

Studies on dogs have shown that chronic plaque-associated gingivitis can progress to periodontitis. However, epidemiological studies in humans have demonstrated that while 85-96% of the population have gingivitis, only a small proportion (12%) suffer from severe periodontitis. It remains unclear whether gingivitis is a necessary prerequisite for the development of periodontitis in humans.

| Bacterial factor | Examples and comments |
|---|---|
| Attachment to host issues | Mediated by fimbriae and capsules |
| Multiplication at a susceptible site | Inhibitor production, for example bacteriocins |
| Evasion of host defenses | Capsules and slimes inhibit phagocytosis |
| Enzymes | Microbial collagenases have been implicated in destruction of collagen in periodontal ligament<br>*Porphyromonas gingivalis* produces a wide range of proteases including trypsin-like protease (gingivain), collagenase, fibrinolysin, hualuronidase and heparitinase |
| Endotoxin (lipopolysachharide) | Produced by Gram-negative bacteria. May initiate an inflammatory response via complement activation, mediate bone resorption and kill macrophages |
| Leukotoxins | Kill polymorphs. Produced by some strains of *Actinobacillus actinomycetemcomitans* |
| IgA and IgG proteases | Degrade IgA and IgG. Produced by *Streptococcus oralis*, *Porphyromonas gingivalis* and *Capnocytophaga* spp. |

| | |
|---|---|
| Cytotoxins | Butyric and propionic acids produced by *Porphyromonas gingivalis* |
| Indirect effects | The induction of an inflammatory response and IL-1 production in response to plaque antigens may cause indirect activation of host collagenases and stromolysins which degrade connective tissues |
| Superoxide dismutase | Protects aerobic bacteria from harmful oxygen products such as hydroxyl radicals |

**Fig. 21. Bacterial factor in periodontal disease**

Adult periodontitis may have its onset in adolescence and continue for the life of the individual, the severity increasing with age. Early work suggested that the course of the disease was a slow, constant and progressive destruction of the tissues. However, more recently it has been proposed that the disease occurs in short periods (bursts) of destruction followed by periods of inactivity, these occurring randomly with respect to time and site within an individual. There is currently much interest in developing methods to detect exactly when periodontal disease is active. The efficiency of periodontal disease prevention could be greatly increased and treatment better focused if the clinician or public health administrator were able to identify, in advance, those sites, subjects or groups who would experience periodontal disease activity. Periodontal disease activity refers specifically to the dynamic stage of the disease characterized clinically by loss of supporting bone and connective tissue attachment.

### 3.3.3. Specific and non-specific plaque hypotheses

Periodontal disease occurs in sites normally inhabited by numerous bacteria, where 300-400 different species have been described. Even this figure is thought to be an under-estimate, since a large number of species have not yet been cultured. However, there is disagreement over the precise role of plaque bacteria in periodontal

disease and several hypotheses have evolved to explain the part played by microorganisms.

**The specific plaque hypothesis**. Cross-sectional and longitudinal studies of the predominant cultivable microflora have revealed that of the 300-400 bacterial species that can inhabit the oral cavity, only a small number are regularly associated with periodontal diseases. According to the specific plaque hypothesis, particular species of microorganism are responsible for causing each type of periodontal disease. For example, early workers observed large numbers of a spirochaetes in sections of tissue from acute necrotizing ulceracive gingivitis, and believed this organism to play a major role. Later, studies on localized juvenile periodontitis implicated *Actinobacillus actinomycetemcomitans* as a possible pathogen in this disease while, more recently,

| **PERIODONTAL PATHOGEN** |
|---|
| • The organism is present in high numbers in periodontal disease compared with either the absence of the micro-organism or its presence in much smaller numbers (carrier state) in periodontally normal subjects |
| • Patients infected with the periodontal pathogen demonstrate specific antibodies in serum, saliva and gingival crevicular fluid and may also develop a cell mediated immune response to the putative pathogen |
| • The organism demonstrates *in vitro* production of virulence factors that can be correlated with clinical histopathology |
| • Experimental implantation of the organism into the gingival crevice of an appropriate animal model leads to the development of at least some characteristics of the naturally occurring disease, for example, inflammation, connective tissue disruption, and bone loss |
| • Clinical treatment that eliminates the organism from periodontal lesions should result in clinical improvement |

**Fig. 22. A modified set of criteria, based upon Koch's Postulates, for the categorization of an organism as a periodontal pathogen**

*Porphyromonas gingivalis* has been suggested as an important agent in adult periodontitis. Owing to the difficulties in identifying aetiological organisms in periodontal disease, a modified set of criteria has been developed for a specific microorganism to be considered as a periodontal pathogen (Fig. 22). The species that have been implicated in periodontal disease by various workers are summarized in Fig. 23, though *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Bacteroides forsythus* and *Prevotella intermedia* are currently viewed as the mainstream periodontal pathogens.

**The non-specific plaque hypothesis** proposes that bacteria have 'collectively' the total complement of virulence factors required to cause destruction of the periodontal tissues and that some microorganisms can substitute for others which are not present in the pathogenic consortia. It implies that plaque will cause disease regardless of its composition. The wide range of species that have been associated with periodontal disease (Fig. 23) may reflect this view.

| **BACTERIA ISOLATED FROM DESTRUCTIVE PERIODONTAL DISEASE** | |
|---|---|
| **Gram-positive** | *Eubacterium brachy*<br>*Eubacterium nodatum*<br>*Eubacterium timidum*<br>*Peptostreptococcus micros* |
| **Gram-negative** | *Actinobacillus actinomycetemcomitans*<br>*Porphyromonas gingivalis*<br>*Bacterioides forsythus*<br>*Fusobacterium nucleatum*<br>*Prevotella intermedia*<br>*Capnocytophaga spp.*<br>*Selenomonas spp.*<br>Spirochaetes |

**Fig. 23. The bacteria commonly isolated from periodontal pockets of patients with destructive periodontal disease**

**The ecological plaque hypothesis.** This hypothesis suggests that environmental conditions within the periodontal pocket allow the expression of microbial virulence factors and/or overgrowth of certain organisms already present in low numbers and that this shift in balance predisposes the site to disease (Fig. 24).

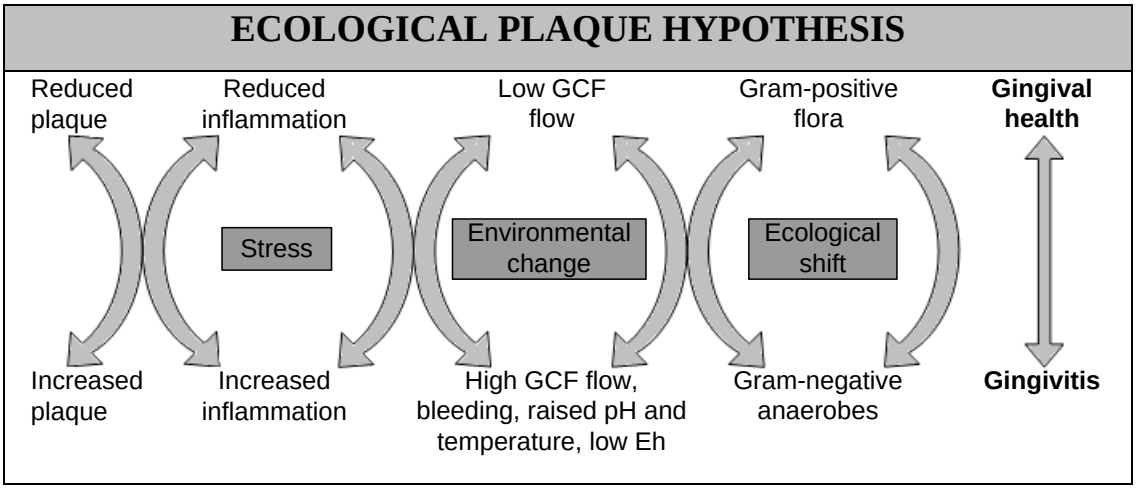


**Fig. 24. The ecological plaque hypothesis for periodontal diseases**

This theory may be viewed as a combination of the specific and non-specific plaque hypotheses, but the ecological plaque hypothesis also helps to explain some of the current findings relating to periodontal disease activity. Thus, if favourable ecological conditions develop within a site, this allows the selection of a range of periodontal pathogens. These organisms will produce virulence factors sufficient to overwhelm the host defences for a period of time, resulting in a period of tissue destruction or disease activity. These conditions are continually changing *in vivo* and the irregular pattern of disease progression in periodontal disease may reflect changes in the ecosystem within the periodontal pocket. The hypothesis predicts that any microbial species with the relevant growth and survival characteristics could contribute to the disease process.

The validity of otherwise of these hypotheses is relevant to the appropriate treatment of periodontal disease. The non-specific plaque hypothesis and the ecological plaque hypothesis imply that the appropriate treatment for periodontal disease is to achieve total plaque control, or to encourage an 'environmentally friendly'

periodontal plaque that does not encourage the proliferation of putative pathogens. The specific plaque hypothesis suggests that treatment should be directed towards elimination of the specific pathogen(s), or their products and that ideally laboratory tests for their detection and quantification should be made available (Fig. 25). Tests would be used to assess disease activity in treatment planning, monitor the effects of treatment, identify sites of patients that are refractory to treatment and identify antibiotic sensitivity patterns of organisms that prove difficult to eradicate by conventional means.

| **ANALYSYS OF PERIODONTAL MICROFLORA** | |
|---|---|
| **Detection of:** | **Examples and comments** |
| **Viable bacteria** | The reference method for determining microbial composition of plaque is bacterial culture.<br>Disadvantages: potential errors in sampling, plaque dispersion, culture and counting. Time-consuming, labour-intensive and requires immediate access to laboratories |
| **Microbial enzymes** | *Treponema dentiocola, Porphyromonas gingivalis, Bacteriodies forsythus* and some *Capnocytophaga* strains prossess an enzyme which hydrolyses the synthetic peptide benzoyl-DL-arginine-naphthylamide (BANA) from a colourless substrate to a blue/black colour. This enzyme activity is detectable in subgingival plaque samples and has been associated with the levels and proportions of spirochaetes and anaerobes in the plaque and with pocket probing depth |
| **Microbial antigens** | Entails use of antibodies directed against specific bacterial antigens. The antigen-antibody complex may then be detected by, for example, a fluorescent labeling technique. These methods rely on recognition of specific antigen(s) which may be blocked or missing in certain strains and are therefore open to error. In addition, cross-reaction with other similar antigens may also |

| | |
|---|---|
| | occur giving rise to false negative or positive results |
| **Microbial DNA/RNA** | DNA/RNA probes are sequences of DNA or RNA with a known specificity, labeled with a chemiluminescent marker. They are used to probe plaque samples for the presence of a specific organism. If the organism is present, the DNA probe will be retained and detected. These probes can be species-specific and the technique does not depend on bacteria remaining viable. PCR techniques are being applied to analysis of the periodontal microflora |

**Fig. 25. Summary of the laboratory methods available for detection of specific microorganism in dental plaque**

Whichever hypothesis turns out to be correct, recent data suggest that periodontitis results from the activity of mixtures of interacting bacteria. All studies agree that the disease can vary in degree from person-to-person and site-to-site, and that there is a progressive change in the composition of the flora from health to gingivitis to periodontitis. This is reflected by a switch from aerobic, non-motile, Gram-positive cocci (gingivitis) to anaerobic, motile, Gram-negative bacilli (periodontitis).

### 3.4. Treatment of periodontal disease

Whilst the exact aetiology of the various forms of periodontal disease has not been fully identified there is still a need to provide treatment. The main methods for preventing and treating periodontal disease can be summarized as follows:

- supragingival plaque control, root surface debridement;
- surgery, if improved access is required;
- consideration of adjunctive antimicrobial agents.

# Part 4

# Infections of the pulp, periapical tissues and bone of the jaw

As discussed in previous chapters, bacteria are responsible for both dental caries and periodontal diseases. Extension of these diseases commonly causes infection in the adjacent tissues, notably the pulp, periapical area and oro-facial soft tissues. More rarely, infection may become established in the bone of the jaw to cause osteomyelitis. These infections, which are usually acute and are among the most common seen by dentists, will be covered in this part.

## 4.1. Pulpitis

Inflammation of the pulp (pulpitis) may follow exposure to a range of irritants. These include thermal, mechanical or chemical stimuli, in addition to micro-organisms which are the focus of this chapter. Since the pulp is enclosed within the hard tissues of the tooth, it is unable to expand during the acute inflammatory phase of pulpitis, with a resultant rise in internal pressure. This not only results in severe pain but also impairs the circulation within the inflamed pulp, which may cause pulpal necrosis and subsequent periapical disease. The possible outcomes are illustrated in Fig. 26. Whilst the most common cause of pulpal necrosis is dental caries, others include accidental trauma to the tooth, exposure of the pulp during instrumentation and spread of infection from a deep periodontal pocket.

### 4.1.1. Pulpitis following dental caries

Gram-positive bacteria, especially lactobacilli and certain streptococci, predominate in the advancing front of a cariotic lesion. Whilst bacterial penetration of the tubules is slow, acids and toxic products of the organisms diffuse quickly, causing damage to the odontoblasts and local pulp tissue. Providing the bacteria have not actually infected the pulp, these effects may be transient. Once the pulp tissue becomes invaded by bacteria (initially lactobacilli and streptococci) the organisms

multiply and large numbers of polymorphonuclear leucocytes appear. Microabscesses will develop and enlarge, with ultimate death and liquefaction of pulp tissue.

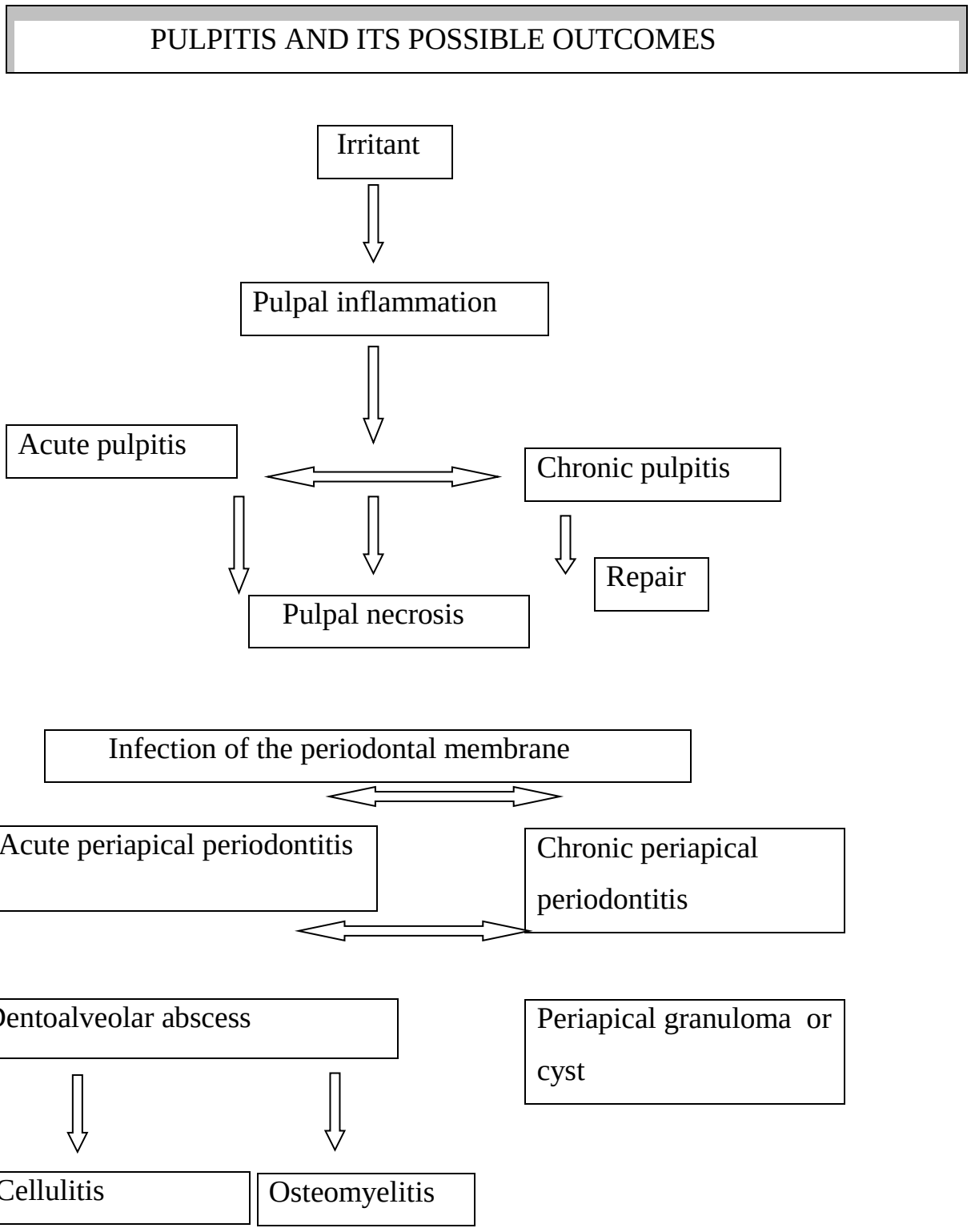


**Fig.26. Flow chart illustration the possible outcomes of pulpitis**

### 4.1.2. Pulpitis through an open cavity

If the pulp becomes exposed to the mouth, either through dental decay, instrumentation or other trauma, several types of bacteria establish themselves and produce even higher concentrations of toxic products, which diffuse throughout the pulp. Bacteria themselves may spread through the entire tissue, resulting in rapid disintegration and liquefaction of the pulp. A mixed, mainly anaerobic flora is often identified in such cases (Fig. 27).

### 4.1.3. Pulpitis through the apical foramen

The pulp may become infected via the apical foramen. This can occur from a lateral canal in communication with a deep periodontal pocket (a 'perio-endo' lesion), from an adjacent periapical lesion or through haematological spread. An impaired state of the pulp is a prerequisite for this type of infection to establish and rapid pulpal necrosis often follows.

### 4.1.4. Pulpal necrosis

A necrotic pulp may remain sterile for varying periods of time, but it can become infected very readily with rapid bacterial spread, because of the lack of host defences in such tissue. The possible routes of infection arc the same as those for a vital pulp. A necrotic pulp in contact with the mouth microflora usually becomes infected with several bacterial species, with obligate anaerobes playing an important role. The main genera commonly isolated from infected necrotic pulps are shown in Fig. 27.

| **BACTERIA ISOLATED FROM NECROTIC PULPS** | |
|---|---|
| **Category** | **Genus** |
| **Obligate anaerobes:** | |
| Gram-positive cocci | Peptostreptococcus |
| Gram-negative cocci | Veillonella |
| Gram-positive rods | Eubacterium |
| | Propionibacterium |

| | |
|---|---|
| Gram-negative rods | Arachnia<br>Porphyromonas<br>Prevotella<br>Fusobacterium<br>Campylobacter<br>Wolinella |
| **Facultative anaerobes:**<br>Gram-positive cocci<br>Gram-positive rods<br>Gram-negative rods | <br>Streptococcus<br>Lactobacillus<br>Eikenella<br>Capnocytophaga |

**Fig. 27. The most common genera of bacteria isolated from necrotic dental pulps. Obligate anaerobes predominate**

### 4.2. Dentoalveolar abscess

This common infection develops typically at the apices of the roots of teeth, following necrosis of the pulp (Fig. 28). The clinical presentation is largely dependent on the local anatomy, but is also influenced by the pathogenicity of the infecting organisms and by the adequacy of treatment.

Abscesses may arise *de novo* or may develop within a pre-existing granuloma. The abscess may remain localized within the alveolar bone, in which case the tooth is usually very tender to pressure. Alternatively, the infection may burst through the alveolar bone and into the soft tissues. This may result in intra- or extra-oral swelling or in potentially dangerous spread of infection through fascial planes, as described later.

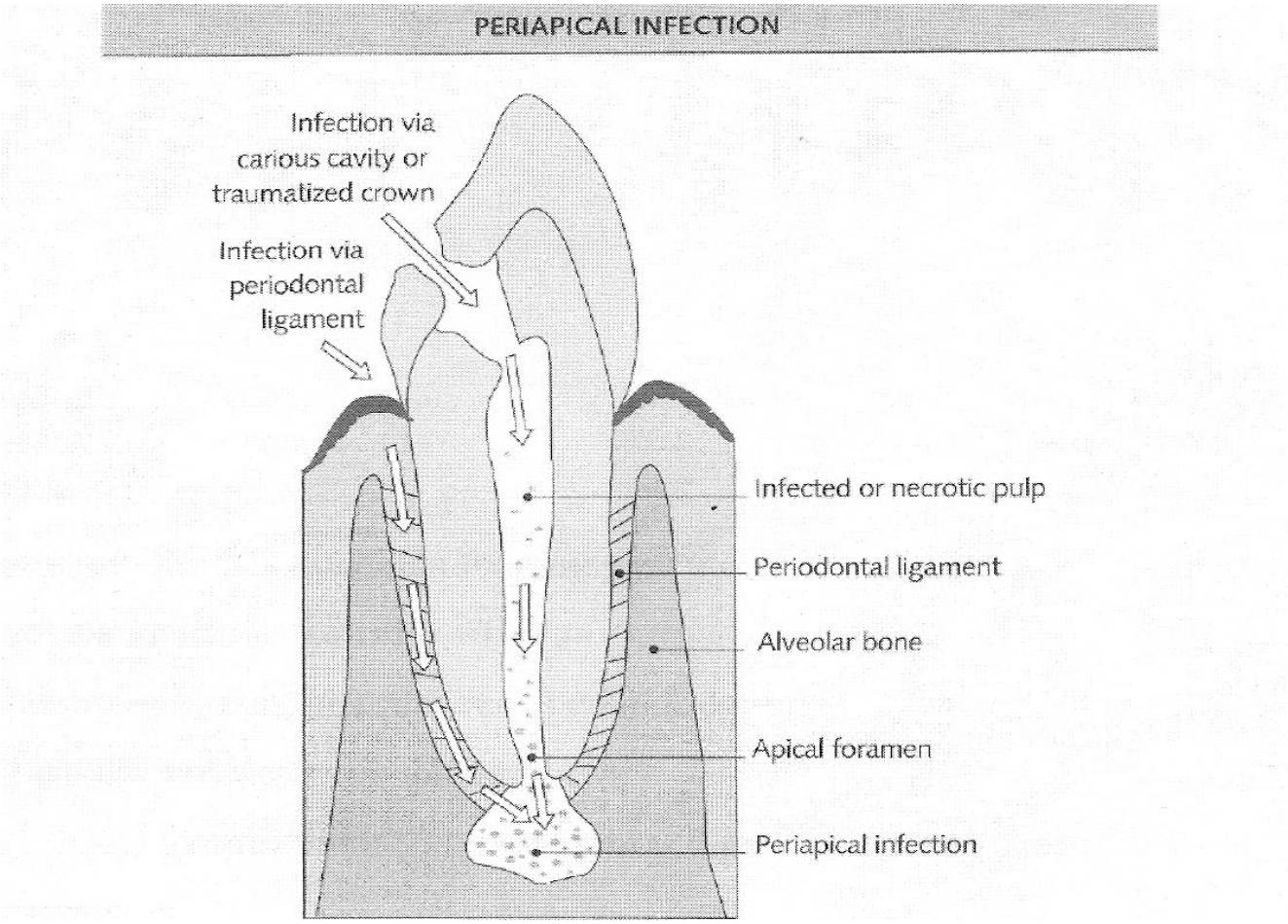


**Fig.28. Diagram illustrating the development of a dentoalveolar abscess at the tooth apex. Infection arises most commonly via the pulp chamber**

### 4.2.1. Microbiology

The microbiology of dentoalveolar abscesses (Fig. 29) has become better understood in recent years through the application of improved sampling methods and anaerobic culture techniques. Overall the related microflora is similar to that isolated from necrotic pulps (Fig. 27). Lesions are typically caused by organisms which comprise part of the normal oral flora (endogenous infections). A mixture of bacteria is usually isolated, often including obligate anaerobes. Facultative anaerobes, particularly those of the anginosus group of streptococci *(S. anginosis*, *S. intermedium* and *S. constellatus),* are also found frequently.

More recently, researchers have applied molecular biological approaches to study of the microflora involved in endodontic infections and dentoalveolar abscesses.

Large numbers of unculturable organisms have been detected, suggesting that the microbiology of these infections is more complex than traditional culture methods had implied.

### 4.2.2. Specimen collection

Collection of the correct specimen is critical if microbiological analysis of pus from dentoalveolar infections is to be attempted. Swabs have often been employed in the past, but this is entirely inappropriate for two reasons. First, since these infections are typically endogenous, contamination of the swab with salivary organisms confuses the interpretation of culture results. Second, obligate anaerobes are very sensitive to the effects of oxygen and die rapidly on the surface of a swab.

The specimen of choice, which overcomes these problems of contamination and oxygen contact, is an aspirate of pus collected by means of a needle and syringe. The syringe and its contents are then submitted to the laboratory, after the needle has been carefully removed and a cap placed over the hub.

### 4.2.3. Treatment

The essential element of treatment is to establish drainage of the pus. This can be achieved in several ways, depending on the clinical circumstances. If the tooth is expendable, then extraction will allow drainage. For teeth which are to be retained, drainage should be established through the root canal and by incision of any residual fluctuant collections of pus, for example in the buccal sulcus.

| **MICROBIOLOGY OF DENTAL ABSCESSES** |
|---|
| - Endogenous infections<br>- Often mixed infections<br>- Strict anaerobes importans |
| **Ideal specimen: aspirated pus** |

**Fig. 29. Key features in the microbiology of dentoalveolar abscesses**

Antimicrobial agents are not required in many cases. They are useful as an initial approach to treat patients with gross facial swelling for whom drainage cannot be established immediately and are important adjuncts to drainage in patients who are febrile. Amoxicillin or metronidazole are used commonly.

### 4.3. Periodontal abscess

Periodontal abscesses usually occur in patients with established periodontal pockets. The associated tooth may be vital or non-vital. It is believed that occlusion of the opening of the pocket prevents normal drainage and results in an acute episode. Impaction of foreign bodies in the periodontium may also play a role in the aetiology. The periodontal abscess is of sudden onset. There is usually swelling, redness and tenderness of the overlying gingiva. These abscesses frequently drain themselves along the root surface to the pocket opening, but if occlusion of the pocket is complete there may be local spread of infection with destruction of bone and soft tissue.

#### 4.3.1. Microbiology

It is extremely difficult to collect an uncontaminated specimen of pus from a periodontal abscess. The related microflora is not, therefore, well characterized and routine microbiological examination is not undertaken. Subgingival plaque is the source of the organisms in periodontal abscesses and those believed to play a role include anaerobic Gram-negative rods, alpha haemolytic and anaerobic streptococci together with others such as spirochaetes.

#### 4.3.2. Treatment

This should form part of an overall clinical assessment of the patient's dentition. The options include extraction of the tooth or drainage of the abscess followed by appropriate periodontal treatment. Antibiotics may be considered as an adjunct to treatment, as described earlier in the management of dentoalveolar abscesses.

### 4.4. Osteomyelitis of the jaws

Though once a fairly common disease, osteomyelitis of the jaws is now encountered only rarely. Osteomyelitis is defined as inflammation of the medullary cavity of bone, but it usually spreads to involve the cortical bone and periosteum as well. Following ischaemia, the infected bone becomes necrotic. Osreomyelitis may present as an acute or chronic infection and is much commoner in the mandible than the maxilla.

One specific form of osteomyelitis which causes particular problems in those who have received radiotherapy to the head and neck region, particularly the mandible, is osteoradionecrosis. This complication, which results largely from reduction in the blood supply to the affected area, typically occurs within the first three years after radiotherapy, but patients remain at risk indefinitely. The management can be very difficult and sometimes unsuccessful, with significant added morbidity for patients. Thorough dental assessment and treatment prior to radiotherapy, followed by careful rules to oral hygiene, are essential to prevent: the need for subsequent extraction of teeth and osteoradionecrosis.

#### 4.4.1. Aetiology and predisposing factors

Odontogenic infections are common and in view of the close relationship of the teeth to the medullary cavity it is surprising that osteomyelitis of the jaws is so rare. This is thought to relate to host resistance and it is well recognized that systemic diseases which reduce host defences, for example diabetes or agranulocytosis, predispose to the infection. The vascularity of bone is an essential part of the defence system and any conditions that reduce this vascularity, for example head and neck radiotherapy or Paget's disease, with increase the risk of osteomyelitis.

When the organisms reach the medullary cavity they proliferate and stimulate an acute inflammatory response. There is hyperaemia, increased capillary permeability, infiltration by granulocytes and tissue necrosis. Pus accumulates, increasing the intramedullary pressure, with resultant venous stasis and ischaemia. Pus may then travel through the haversian and nutrient canals and accumulate beneath the

periosteum, further compromising the blood supply. Eventually the periosteum is penetrated and mucosal or cutaneous abscesses and fistulae often develop. If left untreated the infection may proceed to chronic osteornyelitis with, for example, new bone formation and loss of dead bone by sequestration.

### 4.4.2. Clinical features

In early, acute, suppurative osteomyelitis of the mandible the four key features are intense pain, high and intermittent fever, paraesthesia or anaesthesia of the mental nerve and, finally, a clearly defined aetiology. At this point there is minimal swelling

If untreated the condition will progress to established suppurative osteomyelitis. Patients complain of deep pain, malaise, fever and anorexia. Teeth in the involved area become loose and tender to percussion and pus may exude from the gingival sulcos or through fistulae. The patient is febrile, regional lymph nodes are enlarged and there may be cellulitis of the cheek and trismus.

Radiographs show no significant abnormalities in the early stages of acute osteomyelitis. The full extent of bone destruction is seen radiographically about three weeks after osteomyelitis develops, and is described as a 'moth-eaten' appearance.

### 4.4.3. Microbiology

Historically, staphylococci were implicated as important organisms in osteomyelitis of the jaws. More modern studies indicate that members of the normal oral flora, particularly anaerobic Gram-negative rods and anaerobic streptococci, are usually the organisms of importance. The infections are typically mixed.

Since a wide range of organisms may be isolated, culture and sensitivity tests are an important part of the management of acute osteomyelitis, although it may be difficult to obtain a specimen in the early stages. In the later stages, pus can be collected, but great care must be taken to avoid contamination with organisms of the normal skin and oral flora.

### 4.4.4. Treatment

Both medical and surgical treatments are usually required in the management of osteomyelitis of the jaws. Successful treatment is based on early diagnosis, drainage of pus, bacterial culture and sensitivity testing, antibiotic therapy, supportive treatment, debridement and, if necessary, surgical reconstruction. Attention must also be paid to any predisposing factors.

Antibiotics of value in the management of osteomyelitis include amoxicillin-clavulanate and clindamycin. In the early stages, before a pus sample can be collected, empirical Treatment is provided, for example with an penicillinase-resistant penicillin. Thereafter, the antibiotic regimen should be based on the results of microbiological examination.

### 4.5. Actinomycosis

The cervicofacial region is the most common site for actinomycosis (Fig. 30), accounting for approximately 90% of the recorded cases. Most of the remaining cases are abdominal. The disease is usually a chronic, long-standing infection, sometimes with a history of mild preceding trauma such as a tooth extraction, and is a good example of an endogenous infection.

| **CERVICOFACIAL ACTINOMYCOSIS** | |
|---|---|
| **Aetiology** | Actinomyces israelii other organisms,<br>e. g. Acninobacillus actinomycetemcomitans<br>Trauma |
| **Clinical features** | Younger patients, more commonly male<br>Swelling, typically at angle of jaw<br>Discharging sinuses<br>Dental focus of infection |
| **Laboratory diagnosis** | Gram stained film of sulphur granules in pus:<br>Gram-positive branching filaments<br>Anaerobic culture |

| | |
|---|---|
| **Treatment** | Extraction of dental focus of infection<br>Surgical drainage<br>Extended course of penicillin |

**Fig. 30. Summary of the important features of cervicofacial actinomycosis**

It presents typically as a swelling, often at the angle of the lower jaw and is commoner in young people, particularly males. If left untreated, multiple draining sinuses will develop. The exudate from these sinuses contains visible, yellow particles known as 'sulphur granules', which are aggregates of actinomyces filaments that may have a calcified centre. The slow growing *Actinomyces* species induce a granulomacous-type reaction at the periphery of the lesions, resulting in formation of fibrous walls in and around the swellings. These must be broken down if treatment is to be effective.

### 4.5.1. Microbiology

The most frequent isolate is *Actinomyces israelii,* though *A. naeslundii* and *A. bovis* may also be detected. Other organisms are commonly present in addition to *Actinomyces* species, including *A. actinomycetemcomitans, Haemophilus* species and obligate anaerobes.

### 4.5.2. Diagnosis

The ideal specimen for diagnosis is an uncontaminated sample of pus collected by needle aspiration. This is examined macroscopically in the laboratory for the presence of 'sulphur granules'. If granules are detected they can be squashed between two glass microscope slides and Gram-stained. This will reveal a mass of Gram-positive branching filaments, allowing a pre-sumptive diagnosis of actinomycosis. The diagnosis can be confirmed by anaerobic culture of the pus. *Actinomyces israelii* is usually a strict anaerobe whilst the remaining *Actinomyces* species are facultative anaerobes. On agar plates the colonies, which take several days to appear, have morphology

similar to 'molar teeth'. Antibiotic sensitivity tests can also be undertaken once the organism has been isolated.

### 4.5.3. Treatment

Whilst *Actinomyces* species are sensitive *in vitro* to a wide range of antibiotics, the bacterial cells within sulphur granules and in locules of pus surrounded by fibrous septa may be protected from and survive antibiotic treatment *in vivo.* The treatment of actinomycosis therefore includes thorough surgical drainage and removal of dead tissue in addition to long-term administration of an antibiotic, typically a penicillin or erythromycin.

## 4.6. Ludwig's angina

Ludwig's angina is a bilateral infection of the sublingual and sub-mandibular spaces. The infection often represents cellulitis of the fascial spaces, rather than true abscess formation. The key clinical features are a brawny oedema with elevation of the tongue, airway obstruction and very little pus. Although uncommon, the mortality is close to 100% in patients who do not receive treatment. Dental infection is the causative factor in up to 90% of cases, though Ludwig's angina may be secondary to other infections, for example submandibular sialadenitis.

A wide range of organisms has been reported from these infections, including staphylococci, streptococci and enterobacteria. However, oral commensal bacteria, especially anaerobic Gram-negative bacilli and anaerobic streptococci, are most commonly isolated. Like dentoalveolar abscesses, the infections are usually mixed.

Ludwig's angina is a life-the eaten in infection, requiring urgent treatment. The key elements of management are early diagnosis, maintenance of the airway, high dose antibiotic treatment, removal of the source of infection (usually tooth extraction), parenteral hydration and early surgical drainage. A pus sample should be collected if possible for microbiological examination. A parenteral broad-spectrum antibiotic tegirnen, such as ceftriaxone with metronidazole, would be appropriate, but may be changed in the light of the microbiological results.

# Part 5

# Oral fungal infections

Fungal infections in the oral and perioral regions occur either as primary localized lesions or as manifestations of systemic mycoses. By far the most common group of fungal infections that dental practitioners diagnose and treat are caused by *Candida* spp.. Some of the rarer mycoses with oral manifestations, such as histoplasmosis, are found almost exclusively in the USA, while others such as mucormycosis are found particularly in immuno-compromised individuals. Accordingly, this chapter will concentrate on Candida infections, with brief notes about a selection of other less common fungal diseases.

## 5.1. Candida. Carriage in the oral cavity

The carriage rate of *Candida* spp. in the oral cavity is relatively high but only a few individuals develop oral candidosis. The transition from carrier state to infection appears to depend on environmental factors and changes in the host defences that allow some yeast cells to express virulence factors which are normally repressed. Wide variations have been reported in the oral carriage rare of *Candida* spp.; in healthy volunteers 2-71% (median 35%) and around 13-76% (median 55%) when hospitalized patients or individuals with oral prostheses have been studied. The dorsum of the tongue is the primary oral reservoir of the organism in carriers, although *Candida* spp. can also be found in dental plaque and on intra-oral appliances. Eight *Candida* species are of medical importance, of which *C. albicans, C. glabrata, C. dubliniensis, C. tropicalis,* and *C. krusei* are the most frequently isolated. *Candida albicans* is better adapted than other species for growth in the mouth, particularly through its ability to adhere to oral and acrylic surfaces, and is the most common species present in health and disease. *Candida dubliniensis,*

usually in combination with other *Candida* spp., has been associated with AIDS patients, although its role in infections in other groups of patients is uncertain.

### 5.1.1. Factors that affect the carriage of Candida and predispose to infection

The main host factors that predispose the oral mucosa to infection with *Candida* spp. are in Fig 31. The more predisposing factors an individual possesses, the more likely he or she will be colonized by *C. albicans* which can then express its virulence factors and produce oral candidosis.

| **Predisposing factor** | **Effects on host defenses** | **Possible host changes** |
|---|---|---|
| **Prosthesis** | Epithelial shedding and mechanical washing action of saliva compromised | Mucosal atrophy, hyperplasia and inflammation |
| **Sjögren's syndrome**<br>**Radiotherapy**<br>**Cytotoxic drugs** | Washing action of saliva and associated defense mechanisms depressed | Xerostomia<br>Mucosal atrophy, e.g. tongue<br>Mucositis |
| **High sugar intake**<br>**Diabetes** | Loss of competitive inhibition between yeasts and bacteria due to nutrient limitatioin | Increased numbers of candida within more acidic enviroment |
| **Antibiotics** | Inhibition of commensal bacteria antagonistic to candida | Increased numbers of candida |
| **Malignant disease, cytotoxic drugs** | Phagocytosis by neutrophils and macrophages impaired | Neutropenia and oral ulceration |

**Fig 31. Factors that predispose to oral candidosis**

### 5.1.2. Antifungal drugs

Information relevant to the treatment and prophylaxis of oral candidosis is presented in Fig. 32. Nystatin, amphotericin B and miconazole are prescribed as topical drugs, which are non-absorbable and are available in a number of different formulations that deliver and release the active agent to the oral mucosa. They are effective in the treatment of most forms of oral candidosis in non-immunocompromised hosts, though compliance can be a problem. Azole drugs (for example fiuconazole and itraconazole) are more effective in compromised patients and are usually administered systemically by the oral route, although itraconazole is also available as a solution rhar is applied topically then swallowed giving a combined topical and systemic effect. Some species of Candida (e.g. *C. kruzei)* are intrinsically resistant to fluconazole and itraconazole, while other species that are usually sensitive, including *C. albicans,* can acquire resistance following long-term azole Treatment for oral or pharyngeal candidosis. If a patient is unresponsive to antifungal treatment, susceptibility testing should be performed and the drug therapy changed as necessary.

| | **TREATMENT OF ORAL CANDIDOSIS** |
|---|---|
| **Treatment** | Details and comments |
| **Oral hygiene measures**<br>**-Denture hygiene**<br>**-Brushing** | Dentures act as a reservoir for infection and should be:<br>• cleaned daily with a soft brush<br>• removed at night and soaked in disinfectant ,<br>e.g. dilute hypochlorite ( plastic dentures only ) or chlorhexidine<br>Brushing the oral mucosa with a soft brush may aid resolution and prevent relapse |
| **Dietary advice** | A high carbohydrate intake encourages plaque and candidal growth and should be reduced |
| **Denture trauma** | The quality of existing dentures should be reviewed and new dentures constructed after resolution of clinical |

| | |
|---|---|
| | symptoms |
| **Other systemic factors** | Attention must be paid to contributing factors such as drugs, endocrine disease, immunodeficiency, nutritional deficiency and smoking |
| **Antifungal events** | Used as an adjunct to local treatment. Topical, e.g. nystatin and amphotericin B, or systemic, e.g. fluconazole. |

**Fig 32. Summary of measures that should be taken to treat oral candidosis**

### 5.2. Oral candidosis

Candida infections confined to the mouth are relatively common and can be classified as shown in Fig. 33. Cases of generalized candidosis with oral manifestations, however, are uncommon.

| CLASSIFICATION OF ORAL CANDIDOSIS | |
|---|---|
| **Confined to mouth and comissure** | |
| Pseudomembranous | - thrush |
| Erythematous | - trophic (e.g. HIV related) |
| - | - denture related |
| Hyperplastic | - candidal leukoplakia |
| Angular cheilities | |
| **Generalized candidosis with oral manifestations** | |
| Chronic mucocutaneous | |

**Fig. 33. Classification of oral candidosis**

### 5.2.1. Pseudomembranous candidosis (PMC)

This form of candidosis, also known as thrush, is prevalent in infants, the elderly and debilirated patients and may occur as an acute or chronic infection. Between the extremes of age it is an important marker of underlying disease. Predisposing factors include malignancy, AIDS, diabetes mellitus, radiation therapy of the head and neck and the use of aerosol steroid inhalers. The disease is present in asymptomatic HIV-1 infection and in 50-90% of AIDS patients, although in recent years the use of anti-retroviral drugs has reduced these figures by inducing a recovery in the patients' immunity. PMC is characterized by the presence of creamy-white plaques (pseudomernbranes), consisting of superficial mucosal cells, neutrophils and yeasts, which are found on the surface of the tongue, soft palate, cheek, gingivae or pharynx and are easily rubbed off to leave red, raw and bleeding areas underneath. The lesions vary in size from small discrete areas to confluent white patches covering a wide area. Symptoms are uncommon but patients may complain of dryness or roughness of the mucosa and pain, especially if the lesions extend into the pharynx and oesophagus.

Systemic or topical antifungals can be prescribed. In severe cases of infection in immunocompromised patients, for example those with AIDS, a systemic antifungal agent such as fluconazole is required. Resolution usually occurs quickly with treatment, but patients who fail to respond should be investigated further by clinical and laboratory means for unsuspected underlying disease or other predisposing factors.

### 5.2.2. Erythernatous candidosis and denture-related candidosis

**Erythematous candidosis**. This form of candidosis may arise as a consequence of a number of different factors and local conditions:

- following acute pseudomembranous candidosis after the white plaques are shed and infection persists;
- *de nova* in patients with AIDS;

in patients receiving prolonged drug therapy, for example topical steroids or broad-spectrum antibiotics;

- most commonly related to denture wearing.

The lesions of erythernatous candidosis consist of red areas of varying sizes and can appear on any part of the oral mucosa. The dorsum of the tongue is commonly affected in non-denture-related infections and lesions may be painful, fiery-red, and shiny with evidence of marked depapillation. While atrophic changes characterize some of these erythernatous lesions this is not a constant feature and therefore the use of the term 'atrophic' in the classification of this form of candidosis has not been used here. The duration and severity of erythernatous candidosis is very variable and there seems little value in diagnosing lesions as either acute or chronic when they can persist for many weeks or months, if untreated.

Erythematous candidosis related to dentures is the most common form of oral candidosis and is present in about 50% of denture wearers. It is also associated with patients who wear orthodontic appliances or an obturator for cleft palate. It is sometimes called 'denture sore mouth', which is a misnomer as the patient is usually unaware of the condition. The affected area presents as a red, swollen, inflamed mucosa, commonly involving the palatal mucosa beneath the fitting surface of both complete and partial upper dentures. The lower ridge is seldom affected. The palatal lesions have been categorized into three types depending on seventy:

- Type 1 as localized pinpoint hyperaemia;
- Type 2 as diffuse erythema and oedema of the denture-bearing area of palatal mucosa;
- Type 3 as inflamed hyperplastic epithelium.

The factors that predispose to denture-related candidosis are largely local, for example trauma, poor denture hygiene and carbohydrate-rich diets. Occasionally other factors such as xerostomia, iron and folate deficiency and diabetes mellitus may be involved.

The samples required for the laboratory diagnosis of erythematous candidosis are described. The trearment of erythematous candidosis requires the prescription of anti-fungal agents and the correction of the factors involved in its aetiology, for example considering amendment of current antibiotic or steroid drug treatment, the correction of any haematological deficiences, and the introduction of denture hygiene regimens. In denture-related candidosis the fitting surface of the denture is the main reservoir for *Candida* spp.. Patients should be encouraged to clean the fitting surface thoroughly with a toothbrush each evening and soak the denture overnight in an antiseptic solution such as dilute hypochlorite for acrylic dentures or 2% chlorhexidine for metal dentures. Patients should also be discouraged from wearing dentures during sleep. In addition, anti-fungal therapy should be instituted and topical therapy sustained for at least 3-4 weeks.

### 5.2.3. Angular cheilitis

This disease can be associated with any type of oral candidosis but is most frequently seen as a complication of denture-related candidosis in edentulous patients. However, dentate young adults can also present with this condition. As with all forms of oral candidosis, angular cheilitis has a multifactorial aetiology, though the relative importance of the different factors remains uncertain. Maceration of the epithelium at the angles of the mouth by saliva trapped in mucosal folds appears to be an important factor, especially in denture-related forms of rhe disease. The clinical signs vary from areas of inflammation at the angles of the mouth to ulcerated and crusted fissures. The presence of distinctive yellow crusts, not unlike the typical lesions of impetigo, may suggest involvement of *Staphylococcus aureus.* Since the lesions are usually only mildly irritating, most patients do not seek medical or dental treatment. The importance of *Candida* species, *S. aureus* and |beta-haemolytic streptococci in the aetiology of the lesions is not clear but in many cases the use of specific antimicrobial agents leads to considerable improvement in the condition. The source of these micro-organisms is mainly from the mouth or also the nose in the case of *S. aureus.*

Elimination of the reservoirs of infection and the factors that predispose to the disease, for example inadequate dentures, is necessary for successful management. If intra-oral candidosis is present, local and any systemic predisposing factors should be corrected, the appropriate antifungal therapy employed together with antifungal ointment applied topically to the affected angles of the mouth. Miconazole gel, which has both antifungal and anti-staphylococcal activity, can be used in mixed infections or when the infecting microorganisms are unknown.

If the disease does not resolve with normal treatment then both patient compliance and the possible presence of underlying systemic disease, such as iron deficiency anaemia, should be considered. In addition, the possibility of chronic nose-mouth transfer of staphylococci should be determined.

### 5.2.4. Chronic hyperplastic candidosis (candidal leukoplakia)

This form of candidosis usually presents as individual lesions on the oral mucosa of the cheek near the commissure, at the angles of the mouth, or on the surface of the tongue. The white patches cannot be rubbed off, in contrast to the lesions of pseudomembranous candidosis, and are indistinguishable from leukoplakias due to other causes. The presence of speckled, red-white areas in the lesion has clinical importance, since areas with this appearance have a higher chance of malignant transformation. Histologically the surface epithelium is parakeratlnized and markedly hyperplastic, with candidal hyphae invading the parakeratinized layer at right angles to the surface but remaining relatively superficial. The role of *C. albicans* in the aetiology of these epithelial changes remains unresolved. *Candida* spp. may be a co-factor in epithelial hyperplasia, play a part in the malignant transformation of cells, or simply super-infect an already thickened area of abnormal epithelium. The fact that prolonged antifungal therapy leads to resolution of some of these lesions suggests that Candida may play a causative role in at least some cases. An accurate diagnosis of candidal leukoplakia is important, since 5-11% of the lesions can become malignant. After the laboratory diagnosis is made,

general measures to reduce predisposing factors, for example tobacco smoking, folic acid or iron deficiency, should be instituted. Long-term antifungal therapy should be prescribed until the lesions are removed by surgery, cryotherapy or laser, depending on which procedure is most appropriate. Long-term review of patients is essential due to the risk of malignant change.

### 5.2.5. Miscellaneous oral candidoses

There are a number of oral and perioral lesions in which *Candida* spp. seem to play a major role, mainly on the basis that clinically they respond well to antifungal therapy. These include cheilocandidosis, juvenile candidosis, chronic oral multifocal candidosis and median rhomboid glossitis.

## 5.3. Chronic mucocutaneous candidosis

This is a rare group of disorders characterized by persistent superficial candidal infection of the mouth, other mucosal surfaces, the skin and nails. The oral lesions resemble those of chronic hyper-plastic candidosis and can involve any part of the mucosa. The clinical patterns of presentation can be classified in a number of ways but four main subgroups are identified, based on clinical features and age of onset. Chronic mucocutaneous candidosis (CMC) must be confirmed by taking swabs and smears from the lesions and by histological examination of biopsies (Fig. 34). In addition, appropriate clinical and laboratory investigations should be performed to define the extent of immunological or endocrine dysfunction.

CMC is probably the most difficult candidal infection to eradicate. Due to the complex aetiology of these conditions, the management is a combination of different approaches to remove predisposing factors and reduce the numbers of, if not eradicate, *Candida* spp.. While attempts have been made to correct immune defects, for example with *Candida-specific* transfer factor, few appear to have long-term benefit, although the endocrinopathies associated with the disease do respond to conventional endocrine therapies. Systemic azole antifungal drugs are a key element in the treatment of CMC.

| CHRONIC MUCOCUTANEOUS CANDIDOSIS (CMC) SYNDROMES | |
|---|---|
| Type | **Features** |
| **Familial CMC** | First decade- persistent candidosis: mouth, nails, skin. Iron deficiency |
| **Diffuse CMC (Candida granuloma)** | First 5 years-chronic candidosis: mouth, nails, skin, pharynx.<br>Susceptible to bacterial infections |
| **Candidosis-endocrinopathy syndrome** | Hypothyroidism, hypoadrenocorticism and mild chronic hyperplastic candidosis involving the mouth |
| **Candidosis-thyhoma syndrome** | Haematological disorders<br>Pseudomembranous or hyperplastic candidosis: mouth, skin, nails |

**Fig.34. Chronic mucocutaneous candidosis (CMC) syndromes**

### 5.4. Oral manifestations of systemic mycoses

Fungi chat infect the lower respiratory tract are described in Fig. 35. Many are caused by dimorphic fungi and are extremely rare in Europe but are endemic in different parts of the Americas. In most instances the oral lesions are secondary to the primary infections, typically granulomatous lesions found in the lungs and on the skin. The oral lesions may, however, be the initial presenting sign of the disease, as is the case for histoplasmosis. In general, the main habitat for these organisms is the soil and infection is usually acquired by inhalation, with the primary lesions occurring in the lungs. In the majority of cases these heal without causing illness, but in progressive disease, sometimes related to lung cavitation, infection disseminates to

the skin, mucous membranes and internal organs. The lesions tend to be chronic granulomas, and diagnosis is by direct demonstration of the yeast-like form of the fungus in smears of sputum or in biopsy specimens. Culture and identification of pathogens from clinical samples is useful in diagnosis, as is serology in certain infections. Many of the dimorphic fungi are sensitive to amphotericin B but azole drugs, for example fluconazole, are replacing amphotericin for some infections.

| **ORAL MANIFESTATIONS OF SELECTED SYSTEMIC MYCOSES** | | | |
|---|---|---|---|
| | **Histoplasmosis** | **Paracoccidiomycosis** | **Mucormycosis** |
| **Organism** | **Hystoplasma *capsulatum*** | **Paracoccidioides *brasiliensis*** | ***Mucor* spp.** |
| **Type of fungus** | **Dimorphic** | **Dimorphic** | **Mould** |
| **Main sites affected** | **Oral mucosa, tongue, palate, gingiva, periapical area** | **Hard and soft palate, gingiva, tongue** | **Extension from maxillary sinus through palate into the mouth** |
| **Major manifestations** | **Nodular, indurated or granular masses of tissue destruction with bone erosion** | **Papules or vesicles leading to ulcers. Extensive local destruction** | **Sloughing ulcers with grey eschar and exposed bone (especially maxilla). Unilateral facial pain** |
| **Frequency of oral infection** | **40% of cases** | **Common** | **Common** |
| **Antifungal therapy** | **Amphotericin B ltraconazole** | **Amphotericin B ltraconazole** | **Amphotericin B** |

**Fig. 35. Oral manifestations of selected systemic mycoses.**

# Part 6

# Bacterial infections of the oral mucosa

Specific bacterial infections of the oral mucosa are uncommon in the USA and Europe and many are manifestations of systemic diseases, for example syphilis, gonorrhoea or tuberculosis. Such infections are seen more frequently in many developing countries.

## 6.1. Gonorrhoea

The microbiology of this sexually transmitted disease, caused by *Neisseria gonorrhoeae (N. gonorrhoeae),* has been discussed in this part. When lesions are present in the oral cavity (Fig. 36) they are found most frequently in the pharynx, though any part of the oral mucosa may be affected. The main risk factor for gonococcal pharyngitis is oro-genital sexual contact. Thus, the oral lesions are more commonly associated with primary infection of the mouth than with spread of N. *gonorrhoeae* from a distant site.

| **ORAL GONORRHOEA** | |
|---|---|
| **Primary infection** | Orogenital contact |
| **Commonest site** | Pharynx |
| **Clinical features** | Oral lesions variable –<br>inflammation, oedema,<br>vesiculation, ulceration,<br>pseudjmembranes<br>Submandibular<br>lymphadenopathy<br>Pain |
| **Diagnosis** | Culture |
| **Treatment** | Penicillin or tetracycline |

**Fig. 36. The features of oral infection with Neisseria gonorrhoeae**

### 6.1.1. Clinical features

Patients complain of an initial burning sensation in the mouth. Within 1-2 days the mouth becomes acutely painful and the sub-mandibular lymph nodes enlarge. The intra-oral lesions have a variable appearance, showing signs of inflammation, oedema, vesiculation, ulceration and pseudo-membranes. Oral functions such as speech and swallowing become very painful.

### 6.1.2. Diagnosis

In view of the variable clinical appearances of the oral lesions of gonorrhoea, laboratory tests are essential. Direct examination of a Gram-stained smear from oral lesions may show the presence of Gram-negative intracellular diplococci, though the large numbers of commensal *Neisseria* spp. in the mouth are a complicating factor. Swabs taken from the lesions should be placed in bacteriological transport medium and sent rapidly to the laboratory for culture on an appropriate semi-selective medium such as Thayer-Martin agar. Isolates can be identified on the basis of a positive oxidase test followed by carbohydrate utilisation or fluorescent antibody tests. Evidence of uro-genital infection should be sought.

### 6.1.3. Treatment

The choice of antibiotic depends to a large extent on local resistance patterns. Oro-pharyngeal gonorrhoea can be treated with a single dose of cefttiaxone, ciprofloxacin or ofloxacin.

## 6.2. Syphilis

### 6.2.1. Clinical features

Syphilis may have a variety of oral manifestations (Fig. 37). These include the dental abnormalities associated with infection of the developing tooth germs by *T. pallidum.* Since the deciduous teeth ate usually well developed by the time the spirochaetes invade the developing dental tissues, these teeth are minimally affected.

The first permanent molar teeth ate usually involved and have roughened hypoplastic occlusal surfaces with poorly developed cusps and are smaller in size than normal. The upper central incisors may also be affected (Hutchinson's incisors), with crescentic notches in the middle of their incisal edge and a greater width gingivally than at the incisal edge, giving a 'screwdtivet' appearance.

| **SYPHILIS** | |
|---|---|
| **Oral manifestations** | |
| **Primary syphilis** | Chancre — typically on lip<br>Mucous patches on mucosa<br>Snail track ulcers |
| **Secondary syphilis** | Rubbery, enelarged cervical Lymph nodes<br>Gumma – ofter of palate<br>Glossitis<br>Syphilitic leukoplakia |
| **Tertiary syphilis** | Serological<br>Penicillin or tetracycline |
| **Diagnosis** | |
| **Treatment** | |

**Fig. 37. The oral manifestations at each stage of syphilis**

The clinical course of syphilis can be divided into three main stages, all of which may have oral features:

1. The characteristic lesion of primary syphilis is the chancre. Extra-genital chancres occur most commonly on the lip, though intra-oral chancres may also be seen. They are usually a result of transmission of *T. pallidum* by oro-genital sexual practices. These lesions are highly infectious, contain many motile spirochaetes and heal 1-5 weeks after appearing. There is enlargement of the regional lymph nodes.
2. About 6 weeks later the secondary stage of syphilis begins. The oral lesions are glistening, greyish-white patches on the oral mucosa, some of which may combine to produce so-called 'snail track ulcers'. The cervical lymph nodes are enlarged and rubbery. Secondary syphilitic lesions are infectious and heal within 6 weeks.
3. Tertiary syphilis appears 3-10 years after initial infection and as a result of modern treatment is now seen very rarely. The gumma is the characteristic lesion, in which ulceration of an initial raised lesion is followed by necrosis. In the mouth the most common site is the hard palate and from this site there may be perforation into the nasal cavity. Atrophic glossitis and syphilitic leukoplakia on the dorsum of the tongue are other late stage features, rarely seen today.

### 6.2.2. Diagnosis

Laboratory tests are essential to the diagnosis of syphilis. Dark ground microscopy is of limited value for the diagnosis of oral lesions of syphilis due to the presence of endogenous spirochaetes. The diagnosis is usually based on serological investigations.

### 6.2.3. Treatment

Penicillin is the treatment of choice for all stages of syphilis, but doxycycline can be used for penicillin-allergic patients.

## 6.3. Tuberculosis

*Mycobacterium tuberculosis* can infect any organ in the body and Fig. 38 summarizes the key features of oral tuberculosis. Primary infections of the oral

mucosa are rare in humans and oral lesions are usually secondary to primary lung infection.

### 6.3.1. Clinical features

The clinical presentation of tuberculous lesions of the oral mucosa is varied, but ulceration and pain are common. The tongue is affected most commonly, but lesions have been reported at all intra-oral sites, particularly in the posterior part of the mourn. This may be related to the distribution of lymphoid tissue.

Tuberculous lymphadenitis commonly affects the cervical lymph nodes. The swelling, which may be several centimetres in diameter, is initially firm but mobile. Later it becomes fixed, with abscess and sinus formation. The atypical mycobacteria, for example *Mycobacterium avium-intracellulare*, are frequently involved in cervical lymphadenitis among children, while *M. tuberculosis* is more common in adults.

| ORAL TUBERCULOSIS | |
|---|---|
| **Clinical features** | Primary infection usually in lungs<br>Oral lesions variable – ulceration and pain are common<br>Tongue is most common site<br>Cervical lymphadenopathy |
| **Diagnosis** | Biopsy, culture and skin testing |
| **Treatment** | Combination chemotherapy with antituberculous drugs |

**Fig. 38. Features of the oral lesions of tuberculosis**

### 6.3.2. Diagnosis

Tuberculous lesions of the oral mucosa are difficult to diagnose, and a biopsy is usually undertaken. If tuberculosis is suspected at the time of biopsy, half of

the specimen should be placed in normal saline for culture, and the remainder placed in formal saline for histological examination. Culture of mycobacteria is undertaken on Lowenstein-Jensen medium. Extended incubation for up to 3 months is necessary before colonies appear.

Histological examination of the formalin-fixed tissue will reveal caseating granulomata and Ziehl-Neelsen stained sections may show the presence of acid- and alcohol-fast bacilli.

The Mantoux test is sometimes helpful in the diagnosis of oral lesions of tuberculosis, and differential testing may be of value for diagnosing cervical lymphadenitis in children. Appropriate radiographic examination, including a chest radiograph, is obligatory in all patients with oral tuberculosis.

### 6.3.3. Treatment

All patients with tuberculosis must be referred to an experienced physician for evaluation and treatment. Combinations of anti-tuberculous drugs, for example rifampicin, isoniazid, ethambutol and pyrazinamicle are used for periods of several months. In the case of multidrug-resistant strains of M. *tuberculosis,* drug treatment should be guided by local knowledge of sensitivity patterns until formal sensitivity resting has been completed. The atypical mycobacteria are frequently resistant to standard anti-tuberculous drug regimens and in children with cervical lymphadenitis caused by these organisms, surgical excision of the node is usually a more appropriate treatment.

## 6.4. Staphylococcal mucositis

One bacterial pathogen that can cause oral mucosal infection among immunocompromised hosts is *Staphylococcus aureus.* This bacterium, often in conjunction with *Candida albicans,* has long been associated with angular cheilitis. More recently, oral mucosal infection with *S. aureus* has been incriminated as a cause of severe mucositis in some groups with systemic disease, including dependent elderly patients who are semi-comatose,

dehydrated and receiving intravenous fluids, and patients with Crohn's disease. The clinical presentation starts with oral discomfort and mucosal erythema, progressing to widespread crusting and bleeding of the oral mucosa. In addition to the local discomfort, there is also a serious risk of aspiration of the infected fibrious crust and subsequent aspiration pneumonia. Staphylococcal mucositis responds to regular oral lavage and, if necessary, treatment with an anti-staphylococcal antibiotic such as flucloxacillin. In dependent patients this condition is largely preventable if patients receive a high standard of oral care.

# Part 7

# Viral infections of the oral mucosa

Viral infections of the oral mucosa are common. The viruses most frequently involved are listed in Fig. 39.

| VIRAL INFECTIONS OF ORAL MUCOSA |
| --- |
| - HIV<br>- Herpes simplex virus<br>- Varicella zoster virus<br>- Epstein-Barr virus<br>- Group A coxsackie viruses<br>- Measles virus<br>- Papilloma viruses |

**Fig. 39. Major viruses which infect the oral mucosa**

## 7.1. HIV infection

The currently used staging scheme for HIV-associated disease was published by the Centers for Disease Control (CDC) in the USA in 1993. Patients are classified into one of nine categories, based on the presence of clinical conditions associated with HIV infection and the CD4 T-lymphocyte count.

The acute seroconvension illness, which is recognized in up to 60% of those infected, has an incubation period of about one month and resembles mild glandular fever. Antibodies may take several months to develop and cytotoxic T cells are also formed. The disease then becomes quiescent. Persistent generalized lymphadenopathy is present in up to 30% of those who are otherwise asymptomatic.

As the disease progresses, patients develop other features including weight loss, fever, oral candidosis and diarrhoea. Viral replication continues until the development of full-blown AIDS, which is defined as the presence of HIV and one or more AIDS-defining diseases. These include Kaposi's sarcoma and *Pneumocystis jiroveci* pneumonia. If untreated, the median survival from time of diagnosis is 1 year, and 95% are dead within 5 years of diagnosis.

AIDS is an epidemic immunosuppressive viral disease. The clinical features are dominated by susceptibility to life-threatening infections, the development of tumours and neurological disease, typically sub-acute encephalitis, often with dementia.

The oral manifestations have been classified by the strength of their association with HIV infection. Those that are strongly associated with HIV infection are listed in Fig. 40.

| ORAL LESIONS STRONGLY ASSOCIATED WITH HIV INFECTION | |
|---|---|
| Candidosis | Erythematous<br>Pseudomembranons |
| Hairy leukoplakia | |
| Kaposi’s sarcoma | |
| Non-Hodgkin’s lymphoma | |
| Periodontal disease | Linear gingival<br>Erythema<br>Necrotizing (ulcerative)<br>Gingivitis<br>Necrotizing (ulcerative)<br>periodontitis |

**Fig. 40. Oral lesions strongly associated with HIV infection**

Oral candidosis is a very common feature of HIV infection. Erythematous candidosis appears as red areas commonly found on the hard and soft palate, buccal mucosa and tongue. Pseudomembranous candidosis (thrush) presents as creamy white plaques that can be wiped off the mucosa to reveal a granular, erythematous base. Angular cheilitis may also be seen and is often secondary to intra-oral candidosis.

Oral hairy leukoplakia, an Epstein-Barr virus-associated lesion, is an asymptomatic, white, hyperkeratotic lesion, usually presenting on the lateral margins of the tongue. Classically it has vertical corrugations. Kaposi's sarcoma arises from endothelial cells of blood vessels and presents as purple/dark blue macules or nodules, most commonly on the palate. Kaposi's sarcoma is more common in homosexual men than in other groups with HIV infection and is associated with human herpes virus 8 (HHV-8) infection. Non-Hodgkin's lymphoma appears as a rapidly growing swelling or intractable ulceration, which may occur anywhere in the mouth. Periodontal manifestations of HIV infection are divided into three groups. Linear gingival erythema presents as a localized red band on the marginal gingiva, often in the presence of good oral hygiene. Necrotizing ulcerative gingivitis involves localized ulcerative destruction of the gingiva with pain and spontaneous gingival bleeding. Finally, in necrotizing ulcerative periodontitis there is rapid, localized, ulcerative destruction of periodontal tissue, including bone.

Other miscellaneous oral lesions seen in HIV infection include recurrent intra-oral herpes simplex infections, cytomegalovirus-associated oral ulceration and parotid gland enlargement, the latter often in association with oral dryness.

### 7.1.1. Laboratory diagnosis of HIV infection

A specific virological diagnosis of HIV infection can be achieved in several ways (Fig. 41) but, in practice, current laboratory tests depend on antibody detection. Patients must always be given appropriate counselling by a senior clinician or by a professionally trained counsellor, before blood is submitted for resting. An enzyme linked immunosorbent assay (ELISA) test is performed initially for detection of HIV antibody. Positive results are always confirmed by examining a

further blood sample from the same patient using a range of different test formats such as radioimmunoassay or immunofluorescence. This ensures that no false positives are reported.

| LABORATORY DIAGNOSIS OF HIV INFECTION | |
|---|---|
| Serology | Demonstration of specific anti-HIV antibodies<br>Mainstay of clinical diagnosis |
| Viral culture | Slow process (3-6 weeks)<br>Not routinely available |
| Viral antigen (p24) | Present briefly at time of infection<br>Reappears late in the infection<br>Correlates with degree of viraemia<br>Not routinely available |
| Viral nucleic acid | Polymerase chain reaction (PCR) useful in patients with indeterminate serological results<br>May have role in confirming infection in babies born to carrier mothers |

**Fig. 41. Laboratory diagnosis of HIV infection**

### 7.1.2. Prevention of HIV infection

The emphasis in controlling this infection must be on risk reduction. Public education programmes have concentrated on the need for changes in sexual behaviour, particularly the use of barrier contraceptives. The problem of spread among the intravenous drug using population has been approached in some areas by the distribution of free sterile needles and syringes.

The risk of transmission to healthcare workers is low and the use of protective workwear, together with measures to avoid needlestick accidents, will minimize the possibilities of infection.

Despite intense research efforts, the likelihood of a vaccine being developed in the near future seems remote. Many of the biological properties of HIV, including its high variability, integration into the host cell genome and high replication rate provide major challenges to vaccine development. There is a need to design immunogens that will elicit neutralizing antibodies that are reactive against a wide variety of HIV isolates. Furthermore, vaccine-elicited T cells must be better at controlling HIV replication than those responses that occur during natural HIV infection. Nevertheless, progress is being made and a number of DNA vaccines, recombinant viral vector vaccines and recombinant protein sub-unit vaccines ate undergoing development.

### 7.1.3. Treatment

The management of patients with advanced HIV infection is complex, but the main aspects of treatment are outlined in Fig. 42.

MANAGEMENT OF AIDS

- **Treat opportunistic infections**

  Examples: Fluconazole for candidosis

  Pentamidine for *Pneumocystis jirovcci* Ganciclovir for cytomegalovirus

- **Treat Kaposi's sarcoma and other malignancy**
- Example: locally administered cytotoxic drugs
- **Highly active anti-retroviral therapy (HAART)**

  Combinations of nucleoside analogues (e.g azidothymidine) and protease inhibitors (e.g ritonavir)

- **Supportive medicine**

  Psychosocial

**Fig. 42. Management of AIDS**

In recent years, a range of anti-retroviral drugs have been developed. These include the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (Pis) and fusion inhibirors. It has been shown rhat combinations of these different classes of drugs have a dramatic and positive effect on those with HIV infection, resulting in rapid falls in plasma HIV load and rises in CD4 cell counts. Such combination treatment is known as highly active anti-retroviral therapy (HAART). There are a number of important side-effects of these drugs, for example altered fat distribution, and development of drug resistance is a problem. The drugs are not a cure and have to be taken for life, but the improvement in overall quality of life and longevity for HIV infected patients has been dramatic.

### 7.2. Herpes virus infections

Primary herpetic gingivostomatitis is the most common viral infection of the mouth. It is usually caused by herpes simplex virus (HSV) type I, though a small number are caused by HSV type II, which is the usual isolate from genital herpes. The virus is spread by direct contact with infected saliva or reactivation lesions. The incubation period is about five days. Infection in early childhood often results in a subclinical infection, but in older children and adults the symptoms are more severe. Initially there is a fever, together with enlarged cervical lymph nodes and intra-oral pain. Vesicles then develop on the oral mucosa, particularly the gingiva, tongue and buccal mucosa. These vesicles are intraepithelial and rupture quickly to form superficial ulcers with erythematous margins on greyish-yellow bases.

The mouth is painful, making eating and swallowing difficult. The lips may also be swollen and covered in a blood-stained crust.

Bed rest, maintenance of fluid intake and provision of antipyretics ate important elements of treatment. In the immunocompetent, the lesions are self-limiting and heal within 10 days without scarring. The prescribing of aciclovir at an early stage in the infection may shorten its course and reduce the severity of symptoms.

About one-third of patients who have been infected with HSV develop secondary infections later in life, due to reactivation of virus lying latent in the trigeminal ganglion. A number of factors have been associated with reactivation of HSV, including sun exposure and menstruation. The most common lesion is herpes labialis, also known as a 'cold sore', which appears on the mucocutaneous junction of the lip or on the skin adjacent to the nostril. There is a premonitory burning sensation for 24 hours before the vesicles develop, rupture, crust over and heal within 10-14 days. Treatment with topical application of aciclovir or penciclovir creams, starring during the premonitory burning sensation, may reduce the severity of the lesions.

Intra-oral reactivation lesions have been described, but are uncommon in the immunocompetent. They present as small clusters of lesions, typically involving the palatal mucosa.

Like many of the herpes viruses, HSV is an important pathogen in the immunosuppressed. The oral lesions in this group usually represent reactivation of latent virus as a consequence of the altered host-parasite relationship. The clinical presentation is often atypical and a high index of suspicion is required for a diagnosis to be made. Treatment should be commenced urgently with systemic aciclovir and laboratory tests employed to confirm the clinical diagnosis.

HSV infection may be confirmed by viral culture, antigen detection tests, serology or by PCR.

### 7.3. Varicella zoster virus infections

Primary infection with varicella zoster virus (VZV) causes chickenpox and the reactivation disease is shingles.

#### 7.3.1. Chickenpox

Before development of the skin rash, oral lesions may be detectable, especially on the hard palate, pillars of the fauces and uvula. The oral lesions are small ulcers, 2-4 mm in diameter, surrounded by an erythematous halo.

### 7.3.2. Shingles

Shingles of the face and mouth results from reactivation of VZV lying latent in the trigeminal ganglion. If the maxillary or mandibular divisions are affected, then the lesions of shingles may affect both skin and oral mucosa. Local severe pain and paraesthesia commonly precede the appearance of the skin eruption by several days and at this early stage the diagnosis is extremely difficult to make. Indeed the severe prodromal pain may be misdiagnosed as toothache. However, the subsequent appearance of the skin lesions, which present as groups of vesicles on an erythematous base in a strictly unilateral distribution, clarifies the diagnosis (Fig. 43). The vesicles dry within a few days to form scabs, which separate and heal without scatring. Subsequently a proportion of patients, particularly the elderly, may suffer from an intractable form of facial pain known as post-herpetic neuralgia.

| EBV AND ORAL DISEASE |
| --- |
| Infectious mononucleosis |
| Cervical lymphadenopathy |
| Pharyngeal inflammation |
| Tonsillar pseudomembrane |
| Palatal petechiae |
| Burkitt’s lymphoma |
| Nasopharyngeal carcinoma |
| Oral hairy leukoplakia |

**Fig. 43. The various forms of oral disease associated with Epstein-Barr virus**

Diagnosis of shingles is usually made clinically. However, if necessary the diagnosis can be confirmed by submitting vesicle fluid for electron microscopy and virus isolation, smears for immunofluorescence and serum for detection of specific IgM antibodies.

Traditionally, high dose aciclovir (800 mg five times daily) has been recommended for treatment. However, famciclovir (500 mg three times daily) or valadclovir (1000 mg three times daily) are more conveniently dosed and achieve higher plasma concentrations than oral aciclovir. The chosen antiviral agent should be prescribed as soon as possible, ideally before the skin eruption appears, though this is often precluded by the difficulties of diagnosis in the early stages.

### 7.4. Epstein-Barr virus infection

Epstein-Barr virus (EBV) is associated with a range of pathologies in the oral cavity. Most importantly it is responsible for infectious mononucleosis (glandular fever).

**INFECTIOUS MONONUCLEOSIS.** In those with clinical disease, the classic features are lymph node enlargement, fever and pharyngeal inflammation. Intra-orally, the throat may be painful and congested in the early stages. Clusters of fine petechial haemotrhages may be seen at the junction of the hard and soft palate. Later, a white pseudomembrane may develop on the tonsil.

The diagnosis of infectious mononucleosis is based on laboratory tests.

**EBV AND OTHER ORAL MUCOSAL DISORDER.** EBV is an oncogenic virus and plays a role in the pathogenesis of Burkitt's lymphoma, an aggressive tumour of the jaws seen in certain parts of the world where malaria is endemic. It is also linked to nasopharyngeal carcinoma, particularly in Southern China.

Finally, EBV is of interest to dentists because of its association with oral hairy leukoplakia in patients with HIV infection and other forms of immunosuppression.

**OTHER HERPES VIRUS INFECTIONS.** Cytomegalovirus (CMV) causes a potentially fatal congenital infection called cytomegalic inclusion disease, with

widely disseminated organ involvement including salivary gland enlargement. There have also been several reports of CMV-related oral ulcerative lesions in those with AIDS and in transplant patients.

Human herpes virus 8 has been described very recently and is believed to play a role in the aetiology of Kaposi's sarcoma. This tumour is an important oral manifestation of HIV infection.

### 7.5. Coxsackievirus infections

Members of the group A Coxsackie viruses are responsible for hand, foot and mouth disease and for herpangina, both of which have oral manifestations (Fig. 44).

| **COXSACKIEVIRUS INFECTIONS** | |
|---|---|
| **Hand, foot and mouth disease** | |
| **Cause** | Coxsackie A (usually type A16) |
| **Clinical features** | Epidemics<br>Mainly children<br>Intra-oral vesicles and ulcers (any site)<br>Skin lesions: palmar surfaces of hands plantar surfaces of feet<br>Mild illness, lasting 5-8 days |
| **Treatment** | Supportive |
| **Herpangina** | |
| **Cause** | Coxsackie A (types A2, A4, A5, A6, A8) |
| **Clinical features** | Fever and sore throat<br>Pharyngeal hyperaemia<br>Vesicles and ulcers in pharynx and back of mouth<br>Mild illness, lasting 3-4 days |
| **Treatment** | Supportive |

**Fig. 44. Clinical features of hand, foot and mouth disease and herpangina**

### 7.5.1. Hand, foot and mouth disease

This infection occurs in small localized epidemics, particularly among children. The disease is usually very mild. An early symptom is facial pain, together with tenderness along the path of the parotid duct and small vesicles around the duct opening. There is a variable degree of systemic upset. The oral lesions appear as bright red macules which become vesicular and burst, resulting in small shallow ulcers with an erythematous margin. Any intra-oral site may be affected.

The palpar surfaces of the hands and plantar surfaces of the feet are also involved. The diagnosis is usually clinical, but if laboratory confirmation is required, the virus can be isolated from saliva, vesicle fluid or feces. A significant rise in neutralizing antibody titre is also evident during the course of the illness.

### 7.5.2. Herpangina

This systemic viral infection, which lasts for 3-4 days, is most common in children. Clinically, there is sudden onset of fever and sore throat followed by the appearance of oral and pharyngeal lesions. Other symptoms may include anorexia, vomiting and abdominal pains.

Intra-orally, small papulovesicular lesions develop on the mucosa of the anterior pillars of the fauces, hard and soft palate, tongue, uvula, pharyngeal wall and tonsils. This typical distribution at the back of the mouth is useful diagnostically.

As described for hand, foot and mouth disease, laboratory confirmation of the diagnosis may be made by viral culture or serology.

## 7.6. Morbillivirus infection

Measles is one of the common childhood infections. The virus is spread by droplet infection.

The disease begins with a catarrhal stage. The buccal mucosa during this stage is erythemarous and after about 2 days tiny, bluish-white spots surrounded by red margins appear on the buccal mucosa opposite the molar teeth. These are called Koplik's spots and last for only 1-2 days. As the red, maculopapular skin rash

appears, 3-4 days after the catarrhal stage, the Koplik's spots disappear. The skin rash lasts for 2-3 days and then fades, after which recovery is rapid.

### 7.7. Papillomavirus infections

More than 70 types of the human papillomavirus (HPV) have been identified. They give rise to warty lesions of skin and mucous membranes. Most of these lesions are benign, but some malignant lesions, for example carcinoma of the cervix, have been associated with certain types of HPV.

The common wart (verruca vulgaris) frequently affects skin and may be seen on the lips of intra-orally, particularly in children when they may be associated with auto-inoculation from the fingers. The lesions are typically white, because of the surface keratinization. Common warts are usually associated with HPV types 2 or 4.

Venereal warts (condyloma acuminatum) may also be seen intra-orally and form soft, pink papillary lesions. These are usually associated with HPV types 6, 11 and 16.

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