# Surgical pathology of the mouth and jaws

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## 10. Epithelial tumours and cancer of the mouth

### Papilloma

Squamous cell papillomas are relatively common oral mucosal tumours and usually clinically recognizable by their warty surfaces or long, papillary finger-like processes. They are white when keratinized or pink if not. Adults between the ages of 20 and 50 years are predominantly affected, but their age and site distribution and other characteristics have been analysed in detail by Abbey et al (1980).

Human papilloma virus (particularly HPV 6 or 11) can be isolated from papillomas by DNA hybridization. However, unlike infective warts discussed below, evidence of viral proliferation is not seen by light microscopy. Moreover, simple papillomas appear not to be infective and have no tendency to spread by auto-inoculation to other sites.

### Microscopy

Papillomas have a branching structure consisting of a vascular connective tissue core, supporting a thick hyperplastic epithelium, which is often heavily keratinized. Occasionally, the epithelium shows mitotic activity but malignant change in oral papillomas is virtually unknown.

### Management

Excision is curative. For patients reluctant to accept surgery, cryotherapy is equally effective but often followed by severe postoperative oedema.

### Florid oral papillomatosis

This is a rare condition of widespread oral papilloma formation, which may involve the whole of the buccal mucosa, lip or other sites which become pebbly in character. It has been reported in Down's syndrome (Eversole and Sorenson, 1974), and massive oropharyngeal papillomatosis causing obstructive sleep apnoea in a child has been reported by Brodsky et al (1987). Surgical excision may be justified, particularly for effects such as the latter, or for cosmetic reasons when the lips are affected, but the condition is otherwise benign.

It should be differentiated particularly from naevus unius lateris.

### Papillary hyperplasia of the palate

Palatal papillary hyperplasia consists of multiple soft tissue nodules giving a coarsely granular or cobblestone texture to the vault of the palate. It is frequently regarded as response to trauma from or infection under a denture. However, it may occasionally be seen in the

absence of a denture, but the latter aggravates the condition, particularly when harbour *Candida albicans.* The papillae are then red and oedematous.

*Microscopically,* papillary hyperplasia consists of multiple, closely set, rounded nodules of connective tissue covered by hyperplastic epithelium and infiltrated by varying numbers of chronic inflammatory cells.

### Management

If a denture is worn, the main requirement is to correct any defects and to treat candidal infection, if present, with topical nystatin or miconazole. There is little or no justification for surgical intervention.

## Cowden's (multiple hamartoma) syndrome

Cowden's syndrome is a rare autosomal dominant, genetic disorder characterized by hamartomas in almost any site and, later, of malignant neoplasms. The mouth, skin, thyroid, breast, gastrointestinal tract and reproductive system are most frequently involved and papular facial lesions may bring the patient to seek attention.

*Clinically,* the disease often remains unrecognized until middle age, though the patient may have had treatment for what seemed to be disparate conditions for several years. Skin lesions are concentrated round the centre of the face and consist of fine, hyperkeratotic papular lesions which can give a toad-skin appearance. Oral lesions are present in most patients and consist of multiple, often almost confluent, small papules on the lips, buccal mucosa, gingivae, tongue or uvula, resembling florid oral papillomatosis. The tongue may also be scrotal. The papules are initially painless, but may be so many as to interfere with mastication and if abraded become sore. Due to incomplete penetrance, relatives may have minor manifestations such as telangiectasia. The oral and systemic manifestations have been reviewed by Swart et al (1985).

*Microscopically,* the oral papules consist of a fibrous core which may be highly vascular, covered by acanthotic epithelium

### Management

Diagnosis depends on the clinical orofacial features and usually also a history of removal of multiple, initially benign tumours, particularly in the sites mentioned earlier. Oral lesions require no treatment unless they trouble the patient. If so they can be excised, but Devlin et al (1992) reported persistent bleeding as a complication. Continued observation is required to enable internal cancers to be recognized and treated as early as possible.

## Verruca vulgaris

Infective warts occasionally affect the oral mucosa, particularly in children with warts of the fingers.

*Clinically,* oral warts are white and similar in appearance to papillomas. HPV 2a-e can be found in common warts and HPV 6a-f can be found in oral warts.

### Microscopy

Warts are similar to papillomas, but distinguishable by the presence of intranuclear inclusion bodies.

Excision is treatment of choice, but further lesions may develop as a result of repeated autoinoculation.

## Condyloma acuminatum

Condyloma acuminatum is a sexually transmitted lesion seen mainly in the anogenital region. It is rare in the mouth but increasingly frequently seen in the mouth in patients with AIDS as an opportunistic infection, probably transmitted by orogenital contact. DNA of HPV 6 and 11 has been identified in 85% of condylomata acuminata by DNA hybridization, though HPV 11 may be found in all types of papilliferous lesions.

*Clinically,* condyloma acuminatum appears as a white or pink nodule with prominent papillary processes, larger and broader than those of papillomas. It is usually sessile and may be single or multipe.

### Microscopy

The epithelium is thrown up into folds or broad papilla, giving a clefted appearance, and supported by a vascular stroma with a scanty, chronic inflammatory infiltrate. There is parakeratosis with a clear zone in the upper levels of the epithelium due to vacuolated koilocytic cells with pyknotic nuclei. Acanthosis is characterized by broad, long rete ridges. However, there are no reliable histological criteria for distinguishing condyloma acuminatum from infective warts.

## Molluscum contagiosum

The molluscum contagiosum virus is a member of the poxvirus family and spreads by contact. It causes pearly umbilicated nodules on the skin, particularly of the neck, limbs and trunk. The nodules can reach 1 cm in diameter. They are exceedingly rare in the mouth (Barsh, 1966), but may be seen in the perioral region in those with HIV infection.

*Microscopically,* molluscum contagiosum consists of a goblet-shaped mass. The proliferating epithelium forms compressed papillae pushing down into the corium and surrounding a central cavity open to the surface. The superficial epithelial cells are distended by molluscum bodies which are large, hyaline, eosinophilic inclusion bodies containing enormous numbers of the virus. The contents of the central cavity are mainly desquamating kerating with molluscum bodies.

## Verruciform xanthoma

This rare lesion can appear as a papilloma-like warty swelling with a whitish surface, but is readily recognizable histologically by the large subepithelial xanthoma cells (Chapter 9).

## Focal epithelial hyperplasia (Heck's disease)

Focal epithelial hyperplasia is an HPV-associated disease, but possibly dependent on a genetic predisposition. It was first noted among American Indians and an Eskimo boy. The reported incidence in various racial groups was reviewed by Praetorius-Clausen (1973), who showed that it may be seen in up to 20% of Grenlandic Eskimos and nearly 34% of Venezuelan Indians. It is rare in Britain, but isolated cases have been reported from many parts of the world including Africa. HPV 13 and HPV 32 appear to be virtually specific to this disease.

*Clinically,* focal epithelial hyperplasia appears as creamy, slightly elevated, nodular, soft masses usually about 6-7 mm across. Thet are asymptomatic and frequently noticed by chance. The labial and buccal mucosa are typical sites, but the palate appears to be spared. Almost any age and either sex may be affected.

### Microscopy

The epithelium is hyperplastic, mildly parakeratotic and with vacuolated, koilocyte-like cells with pyknotic nuclei just below the surface. The rete ridges are broad and often confluent. Virus-like particles can be identified by electron microscopy and viral protein identified by DNA hybridization.

### Management

The diagnosis is confirmed by biopsy. Treatment is not normally required and may be impractical if lesions are widespread. Spontaneous resolution has also been seen.

## Adenomas and adenocarcinomas

These tumours arise from minor intra-oral salivary glands and can, therefore, appear in the oral mucosa as submucosal nodules or swellings, most commonly on the palate, in the lip or buccal mucosa. They are discussed in Chapter 12.

## Cancer and precancerous lesions

### Definitions

Cancer refers here to squamous cell carcinoma which is by far the most common oral mucosal malignant tumour. However, the definition of premalignant lesions is more difficult. In practice, lesions can only be termed precancerous after malignant change has developed, since there is, as yet, no means of identifying with certainty the risk of cancerous transformation before the event. Cancerous change is well recognized, but by no means

inevitable, in chronic white or red lesions. Even severely dysplastic lesions can undergo spontaneous regression as discussed earlier (Chapter 9). The histological findings, therefore, indicate no more than that a lesion has a malignant potential, but cannot be used as a firm prediction that malignant change will develop.

Clinically, the main lesions with malignant potential are idiopathic keratoses, speckled leucoplakias and erythroplasias. Microscopically, the main predictive feature is epithelial dysplasia.

## Epidemilogical aspects

Oral cancer is a disease of the elderly, having a peak incidence in the sixth or seventh decades. Overall, mouth cancer is uncommon in the UK, when compared with other sites. Although there are regional variations, oral cancer is also uncommon in most parts of the world where reliable data is available. The main exception is the Indian sub-continent, where the figure reaches 40% in some areas, and the mouth is one of the most common sites of cancer in any part of the body.

*Incidence.* In England and Wales, in 1984 (latest available figures), the number of registrations for intra-oral cancer was 1329 and for cancer of the lip was 250. Together these accounted for 2.4% of all malignant neoplasms.

For comparative purposes, it is more useful to express incidence rates as annual age-adjusted rates per 100.000 population. Where reliable national cancer registries exist, these figures may be used for international comparisons. However, in India, were oral cancer has been reported to account for 40% of all cancers, this does not apply to all areas and figures for the country as a whole may not be reliable. Within Europe, the incidence varies from 2.5 in southern Britain to 16.5 per 100.000 in Malta where there is an unusually high incidence of lip cancer, probably due to the strong sunlight. The different incidence rates for rural and metropolitan Poland and Spain are probably similarly explained by the exposure of rural workers to sunlight. Binnie et al (1972) remarked on the exceptionally high mortality from oral cancer in France, where there appeared to be an association between oral cancer, cirrhosis and the consumption of immature pot-still spirits containing toxic by-products of distillation.

In Norther America and Canada there appear to be even greater variations in incidence than in Europe. Newfoundland has the highest rate for oral cancer in the Western world. Again, this high incidence may be explained by the high rate of lip cancer among fishermen in Canada. The chances of a fisherman in Newfoundland of developing lip cancer is 4.4 times higher than that of a comparable male in other occupations. In the USA the incidence of oral cancer varies considerably between States and between Whites and Blacks. This might be explained by the low incidence of lip cancer among Blacks. National figures are not, however, available for the USA.

As previously mentioned, figures for Asia are also less reliable due to the absence of national cancer registries. Waterhouse et al (1976) quote an incidence of only 19.6 per 100.000 for Bombay. This figure is considerably lower than that quoted by other studies undertaken in different areas of India such as 33 in Ernakulam, 25.2 in Gujarat, 22 in Srikakulam and 21.4 in Uttar Pradesh. There are conspicuous differences in incidence rates

between the various races in Singapore, with the highest rate among Indians. Though this may be due to tobacco and betel chewing, submucous fibrosis (Chapter 7) or genetic factors cannot be excluded.

## Age

Oral cancer is largely a disease of the elderly. Seventy-seven per cent of all oral cancers develop between the ages of 55 years and 77 years. In Britain, the mean age for oral cancer is 64 years for males and 61 for females.

## Sex incidence and trends

Cancer of the mouth is traditionally regarded as a disease predominantly of males. The Registrar General's figure for 1921, for example, showed that the male to female ratio for deaths from mouth cancer was 13 to 1 in England and Wales. The magnitude of this difference is all the more remarkable if account is taken of the heavier female predominance in the population as a whole at that time, as a result of the losses in the 1914-1918 war.

Recent figures for Enland and Wales, however, show, for cancer of the tongue, a male to female ratio of no more than 1.5 to 1. Moreover, in most sites within the mouth, this ratio is even smaller, but for cancer of the floor of the mouth, the male to female ratio is 2.7 to 1. This change is due to a fall in the incidence in males, while the incidence in females has remained virtually constant.

## Site

The floor of the mouth, bounded by the lateral and ventral aspects of the tongue and the mandibular alveolus, forms a horseshoe-shaped sump into which any soluble carcinogens could pool. Although this area is only 30% of the surface area of the oral cavity, it accounts for 70% of carcinomas and this fact suggests that an exogenous carcinogen may operate.

By contrast, cancer is so rare in the centre of the vault of the palate as to be a clinical curiosity. Cancer of the centre of the dorsum of the tongue is also rare that an isolated case is sufficiently remarkable to be reported in the international literatue, and a retrospective survey of the microscopy of six such cases (Ogus and Bennett, 1978-79) showed that the histological diagnosis had been incorrect in all of them.

Though squamous cell carcinoma of the mouth does not show any significant variation in its histological features in different areas of the mouth, there are differences in behaviour and in prognosis according to the site. The following sites are usually, therefore, identified.

- lip (vermilion border) (ICD 140)
- tongue (ICD 141)
- alveolar ridge or gingival margin (ICD 143)
- floor of the mouth (ICD 144)
- buccal mucosa
- palate.

For cancer registration and data on a national or international scale, the International Classification of Diseases is used, and in Britain at least, only the first four of these sites are considered in terms of incidence and survival. The remaining two sites are categorized as 'Other and unspecified' (ICD 145)

## Frequency in different sites

The tongue is the single most frequently affected site. In women, the lip is one of the least frequently affected sites. The reason for the considerable and persistent difference in the incidence of cancer of the floor of the mouth between men and women is unknown.

In the South Thames Cancer Registry area (covering a population of approximately 6.uke million), of 589 mouth cancers registered in one year, 83% of the tongue tunmours were histologically confirmed squamous cell carcinomas, while for the gum and floor of the mouth and other unspecificed sites the figures were 78%, 83% and 60%, respectively. These figures are slightly low because not all diagnoses were histologically verified, and in some cases the type of carcinoma was not specifically categorized as epidermoid.

## Aetiology

Much has been written about, but relatively little is known for certain, of the aetiology of cancer of the mouth or of precancerous conditions. Though the two are discussed together here, it must be emphasized that oral carcinoma developing in an identifiable precancerous lesion is found in only a minority of cases. In a careful study of 77 patients over the period 1935 to 1984, of the association between leucoplakia and cancer, Bouquot et al (1988) found leucoplakia juxtaposed to intra-oral carcinoma in 1-9% of cases according to the site, though they found juxtaposition to be more frequent (66%) on the vermilion border of the lip. More puzzling is that in a study of 212 patients with oral cancer, Hogewin et al (1989) found that 48% of them had *separate* white lesions. Moreover, as discussed earlier (Chapter 9), precancerous (dysplastic) lesions are usually of unknown cause.

The matter has been greatly confused by use of the term 'head and neck' cancer. To lump together such diverse types of neoplasia as mouth, salivary gland, nasopharyngeal, laryngeal or thyroid neoplasms - to name but a few - in terms of aetiology is, to say the least, to confuse the issue. Nevertheless, it is common to refer to 'head and neck' cancer without specifying which precise sites are being examined, both in epidemiological as well as clinical studies. Cancers, even in sites so close as the lip and intra-oral tissues, have different aetiologies and epidemiological studies on 'head and neck' cancer as a consequence often have little, if any, meaning.

Conditions or factors related to or thought to be involved in the aetiology of cancer of the mouth include the following:

- Possible carcinogens, direct or indirect:

    Tobacco
    Alcohol
    Areca ('betel') nut

Experimental carcinogens
Industrial hazards:

woolen textile work
some chemical industries.

- Infections (possibly with co-carcinogens):

Syphilis
Candidosis
Viruses.

- Genetic (specific syndromes):

Dyskeratosis congenita
Fanconi's anaemia.

- Mucosal or mucocutaneous diseases:

Iron deficiency (Paterson Kelly syndrome)
Lichen planus
Lupus erythematosus
Oral submucous fibrosis (Chapter 7)
Dysplastic leucoplakias and erythroplakias.

- Physical agents: sunlight (lip cancer only).

**Race and actinic radiation**

Dark-skinned ethnic groups have very low lip cancer rates in comparison with fair-skinned people living in the same areas. Anderson (1971) has shown that melanin acts as a protector, either as a physical barrier which blocks the passage of ultraviolet rays or by the chemical absorption of carcinogens released by ultraviolet radiation. This protective influence of melanin is not confined to Blacks. Belamarie (1969) reported that among the Chinese in Hong Kong the incidence of lip cancer formed only 4% of mouth cancers in contrast to 25-30% reported in the Western world.

Dorn and Cutler (1959) also showed that the incidence of lip cancer in the USA increased from the north-eastern States to the south-western States in line with the sunnier weather. This finding has been generally confirmed in countries such as America and Australia where immigrant populations with fair complexions are exposed to stronger sunlight than in their country of origin. The protective function of skin pigmentation is suggested by the lower incidence of lip and skin cancer in such countries among the indigenous populations.

In Britain, lip cancer has a higher incidence in Scotland than in England and Wales, and this too may possibly be explained by the higher proportion of fair- and red-haired Scots than English or Welsh. The amount of exposure to sunshine or the degree of protection from

it among outdoor workers is nevertheless difficult to assess. Thus, there are many fewer hours of strong sunshine durnig the year in Britain than in Texas, but in Texas the wearing of an unusually broad-brimmed ('ten gallon') hat is traditional. By contrast, Lindquist and Teppo (1978) have reported an inverse relationship between the mean annual amount of solar radiation and lip cancer incidence in Finland, but this is exceptional and unexplained. In general, therefore, the incidence of lip cancer is greater in rural than in urban populations living in the same area, and outdoor occupational workers carry a higher risk of developing lip cancer. Sunlight is usually implicated as the causative factor and microscopically cancer of the lip is typically associated with a wider area of actinic damage (solar elastosis, cholastic change).

Though genetically determined racial skin pigmentation has a protective effect against lip and skin cancer in tropical climates, a genetic factor in some races may confer susceptibility to intra-oral cancer. This is suggested by the exceptionally high incidence of oral cancer in the Indial subcontinent. Oral submucous fibrosis contributes to some extent to this high incidence and a genetic influence is suggested by the high frequency of HLA10, DR3 and DR7 (Caniff et al, 1986). Murti et al (1985) report a malignant transformation rate of 7.6% in 66 patients with oral submucous fibrosis, observed over a median period of 10 years.

## Tobacco use

### Pipe smoking

Historically, it has been claimed that there is a link between clay pipe smoking and lip cancer. For example, the decline in pipe smoking in Britain has been associated with a steady decline in mouth cancer in males. However, as this habit is now rare in most countries, evidence is lacking to prove or refute this claim. A high incidence of lip cancer in one region of Czechoslovakia has been attributed to a combination of actinic radiation, spicy food and the use of tschibut, a short-stemmed clay pipe.

In Gujarat, India, the hookly, a short-stemmed clay pipe, is widely used. Mehta et al (1969) noted that 7% of hookli smokers developed labial leucoplakia as a result of this habit.

Conventional pipe smoking can also cause a characteristic leucoplakia of the palate, but as discussed earlier (see Chapter 9), any associated carcinoma develops in another part of the mouth.

### Cigarette smoking

Unfortunaly, few workers have attempted to distinguish between the effects of cigarette smoking and other tobacco habits in the aetiology of mouth cancer. Wynder et al (1957) and Keller (1967) both demonstrated a relationship between tongue and floor of mouth cancer and total tobacco smoked. Martinez (1969) estimated that in Puerto Rico the risk of developing oral cancer was 2.5-5 times higher for heavy smokers than for non-smokers, but no distinction was made between different smoking habits. Graham et al (1977), in the USA, have shown that heavy smokers (more than 20 cigarettes or 5 cigars daily) are six times more likely to develop oral cancer than those who do not smoke.

Although cigarette smoking is widely believed to play a major role in the onset of oral cancer, its influence must be limited. In several countries, the incidence of oral cancer has been declining during the same period when cigarette smoking has increased. In Britain, in particular, where detailed and accurate national data are available, the steady increase in cigarette smoking since the beginning of the century has been associated with a steady decline in the incidence of mouth cancer in males and no increase in this disease in females.

Moreover, unlike pipe smoking, there is no recognized or consistently found lesion caused by long-term cigarette smoking. Detailed follow-up studies have also shown that malignant change in leucoplakias is more common in non-smokers than in smokers.

More recently, data from several countries has suggested that there has been a significant but unexplained rise in the incidence of tongue cancer, particularly in persons under 45 years old.

## Other smoking habits

Wynder et al (1957) have also presented some evidence to link pipe and cigar smoking and oral cancer. Cheroot smoking is a common habit among Danish females, and Pindborg et al (1972) have shown that floor of the mouth leucoplakia is associated with cheroot smoking.

In the Indian sub-continent, cancer of the hard palate is common and this has been linked with the reverse smoking of chuttas, with the burning end in the oral cavity. However, in the Caribbean, where a similar habit is practised, there is no link with oral cancer.

Bidi smoking, as practised in India, is related to oropharyngealcancer. A bidi consists of a small amount of Nipani tobacco rolled up in a dried temburni leaf. Hoffman et al (1974) have shown that bidi smoke has a higher content of carbon monoxide, ammonia, hydrogen cyanide, phenol and carcinogenic hydrocarbons than cigarette smoke. Pindborg et al (1967) have shown a high incidence of commissural leucoplakia with bidi smoking and that 16% of bidi smokers had leucoplakia.

## Tobacco chewing

There is a high prevalence of oral cancer in India, where chewing a betel quid containing tobacco is widespread. Attempts have therefore been made to assess the role of this habit. There is a greater prevalence of oral cancer:

- among individuals who chew betel quid compared with those who do not

- in the site where betel quid is habitually held

- among individuals who used betel for prolonged periods or particularly frequently.

Hirayama (1966) has confirmed that oral cancers form at the sites where the quid is habitually held.

The composition of the betel quid also varies from district to district, but usually contains tobacco, slaked lime, catachu and areca nut wrapped in a betel leaf. Recent epidemiological surveys have shown that it is only in those areas where tobacco is present in the quid that oral cancer is associated with the habit, though potential carcinogens such as arecoline have been identified in areca nuts.

Jaftarey and Zaidi (1976) have shown that in Pakistan the combination of betel chewing (with tobacco) and smoking enhances the risk of developing oral cancer by 23 times in men and 35 times in women. Others have shown a relationship between smokeless tobacco and oral cancer in the USA, as discussed below.

## Snuff dipping and use of smokeless tobacco

In the south-eastern States of the USA, lower gingival and alveolar ridge carcinoma is common and women account for 45% of such cases (Winn and Blott, 1985). This has been linked with the widespread habit of so-called snuff dipping among women, over many years. Relatively recently, Skoal Bandits (small permeable paper bags, resembling teabags but containing tobacco) have been introduced.

Link et al (1992) compared oral carcinomas in a small group of smokeless tobacco users with those in non-users. Among 874 patients with squamous cell carcinomas, 1.4% were smokeless tobacco users, while of 129 patients with verrucous carcinomas, 7.% were smokeless tobacco users. The numbers at risk from smokeless tobacco use are unknown, but it is noticeable that, as Link and colleagues confirmed, both squamous cell and verrucous carcinomas far more frequently affect the buccal mucosa where the tobacco was held. More remarkably, they found that cancers developed later in users than in non-users. The mean age of smokeless tobacco users developing either type of carcinoma was 70.5 years and of non-users was 64.2 years. Moreover, the squamous cell carcinomas in users were, overall, better differentiated than those in non-users. Any carcinogenic potential for smokeless tobacco, therefore, appears to be low. Indeed, in Sweden where the use of smokeless tobacco is reputedly heaviest, Larsson et al (1991), in reporting the findings from no fewer than 252 biopsies from regular snuff dippers, emphasized that over a period of many years they have never seen a carcinoma developing in a pre-existing snuff dipper's lesion. In short, despite the fact that tobacco-specific carcinogens can be identified, a relatively low proportion of long-term snuff users develop carcinomas. If malignant change develops, it is only likely to follow several decades of use.

## Alcohol

Wynder et al (1957) calculated that heavy drinkers (more than 6 ounces daily of spirits or equivalent) had a 10 times higher risk of developing oral cancer than occasional drinkers. However, it should be realized that many heavy drinkers are also heavy smokers. It is difficult to separate these risks and Lemon et al (1964) found a low mortality from oral cancer among Seventh Day Adventists, a group who abstain from both alcohol and tobacco. By contrast, Binnie et al (1972) noted that there was no association in Britain between alcohol consumption and oral cancer. Both alcohol and tobacco consumption had grown considerably during the previous 40 years, but during this time the incidence of oral cancer had been progressively falling in Britain. Binnie (1976) also noted that any association between alcohol

consumption and oral cancer in the USA and France could be related to consumption of unmatured pot-stilled spirits containing toxic by-products.

Other authors have found an associated between cirrhosis and oral cancer. They have suggested that alcohol-induced liver damage helps to initiate or accelerate malignant changes in the oral mucosa. Protzel et al (1964) have shown, in animal experiments, that alcohol may be an aetiological factor in oral cancer through a systemic effect and that other substances which damage the liver can potentiate the action of carcinogens on the oral mucosa.

### Infections and immunological factors

Syphilitic leucoplakia holds pride of place as a precancerous disease, in that reports suggest a rate of malignant change between 30% and 100%. However, the condition has become so rare that investigation of possible mechanisms has not become impossible.

The role of chronic candidosis is also obscure. The evidence rests on the facts that, first, *Candida albicans* is an intracellular parasite (Cawson and Rajasingham, 1972) and also candidal infection induces epithelial hyperplasia experimentally (Cawson, 1973). Secondly, chronic candidosis (candidal leucoplakia) is frequently speckled in character clinically and dysplasia is frequently associated. Thirdly, Cawson (1966) found that in randomly selected leucoplakias, in which the microscopic features of chronic candidosis were later found, the incidence of malignant change had been exceptionally high. Finally, cancer developing in cases of chronic candidosis have been reported. The possible role of candidosis in the aetiology of oral cancer has been summarised by Cawson and Binnie (1980), but even if chronic candidosis does promote malignant change, it accounts for relatively few cases.

Currently, there is active consideration of the oncogenic potential of viruses and some evidence has been produced to suggest the herpes virus genome or more recently human papilloma virus (particularly HPV 16) genomes can be found, incorporated into mouth cancer cells. The importance of this finding is as yet unclear, especially as HPV is equally frequently found in normal mucosa.

There is no evidence of any increased susceptibility to intra-oral cancer among patients who are deeply immunosuppressed or who have AIDS. However, the former have high rates of lip cancer if exposed to strong sunshine.

Various immunological abnormalities have been described among 'head and neck cancer' patients, but again their significance is as yet uncertain.

### Genetic syndromes and oncogenes

The susceptibility to mouth cancer is significantly increased in dyskeratosis congenita (Chapter 9) and Fanconi's anaemia, as mentioned earlier, and is occasionally seen in Bloom's syndrome (telangiectatic erythema with growth retardation). A strain of rat with a high genetic susceptibility to cancer has also been described. However, the low incidence of mouth cancer in the population at large suggests that any genetic component in the aetiology is insignificant, though the possibility cannot be discounted that it may contribute to the high incidence of the disease in the Indian subcontinent.

## Fanconi's anaemia

Fanconi's anaemia is a rare genetic chromosomal defect typically characterized by progressive bone marrow failure leading to pancytopenia and various congenital anomalies. Oral squamous cell carcinomas developed in 57% of 14 cases reviewed by Kennedy and Hart (1982). Carcinomas affected the oesophagus or other sites in the remainder.

Bone marrow failure usually starts to become apparent before the age of 10 and most die of anaemia or leukaemia within the next 10 years. In those where the marrow failure is mild or less rapidly progressive, carcinomas appear in the teens and usually before the age of 30.

Treatment of the oral carcinomas is according to accepted protocols but the long-term prognosis is probably limited by marrow failure which if mild at first may be accelerated by stress such as infection.

## Oncogenes and anti-oncogenes

Currently, there is great interest in the p53 tumour-suppressor gene which may undergo mutation to contribute to the development of cancer. Mutant p53 proteins are stable and their concentration in cancer cells is considerably higher than that of normal p53 protein in non-neoplastic cells. Ogden et al (1992) found that 55% of 20 oral cancers expressed the stable p53 protein, but failed to identify it in what they termed normal, benign or premalignant mucosa.

## Dental factors

Poor oral hygiene, rough restorations, sharp edges of teeth and ill-fitting dentures have often been implicated in the aetiology of oral cancer, particularly in the past. Indeed, it is uncommon to find a patient with oral cancer with a well-preserved dentition. However, the incidence of these dental irritants is so high that it is hard to prove a causal relationship with oral cancer.

Renstrup et al (1962) have demonstrated that chronic irritation enhances oral carcinogenesis in experimental animals. Graham et al (1977) attempted to assess dental status using a 'Dentition Index', and they found a greater risk of oral cancer to be associated with a low dental status. They found that men who smoked heavily, drank large quantities of alcohol and had a poor dentition had a risk eight times higher than matched controls.

The well-established improvement in dental health over the years in Britain has also been associated with an overall decline in oral cancer, though strangely not in women. Also, the lowest socioeconomic groups who have the lowest standards of dental health also are at highest risk for oral cancer. However, like so much of the data already discussed, any evidence for the role of oral sepsis in the aetiology of mouth cancer is circumstantial.

## Mucosal diseases

The precancerous potential of various mucosal diseases has been discussed earlier (Chapter 8). Of these, the only common condition with a small but significant risk of malignant change is lichen planus. In the less frequently seen diseases lupus erythematosus and epidermolysis bullosa, there is also a risk of malignant change, but the overall contribution of such diseases to oral cancer must be small. Of other diseases listed, Paterson-Kelly syndrome appears to have strong precancerous potential, both for the mouth and oesophagus, but the importance of iron or other haematinic deficiency in this process is unclear. Moreover, the condition has become rare both in Britain and Sweden, and both this and other mucosal diseases, in so far as they may be premalignant, contribute little to the incidence of mouth cancer overall.

## Clinical presentation of oral cancer

The clinical diagnosis of oral cancer is usually straightforward. Compared with most other sites within the body, the oral cavity is relatively easily examined without special equipment. Oral tumours, unlike many other sites, also cause early symptoms, and patients can become aware of, and often complain about, minute lesions within the mouth. Nevertheless, between 27% and 50% of patients present for treatment with late lesions. Many of these patients are elderly and frail, and therefore delay the effort of visiting their doctor or dentist. Many such patients wear dentures and may accept discomfort or ulceration and see no urgency in seeking treatment. Furthermore, the practitioner himself may not be suspicious that a lesion is malignant, and initial empirical treatment with antifungal therapy, antibiotics, steroids or mouth-washes may delay confirmation of the diagnosis and treatment. One survey suggested that medical practitioners are more likely to do this than dental practitioners.

It is essential that any clinician should use a thorough and methodical technique for examining the oral cavity. All areas of the oral mucosa should be inspected meticulously, and any suspicious lesion palpated for texture, tethering to adjacent structures and induration of underlying tissues.

Finally, the neck from the submandibular region to the clavicles should be carefully palpated in order to detect any lymphadenopathy.

## Clinical presentation by site

*Tongue*. The majority of tongue cancers affect the middle third of the lateral margin and extend early in the course of the disease into the ventral aspect and floor of the mouth. Approximately 25% affect the posterior third of the tongue, 20% the anterior third and only 4% the dorsum. Rare cancers of the dorsum of the tongue are usually secondary to syphilitic glossitis.

Early tongue cancer may manifest itself in a variety of ways, but is typically painless at first. Often the growth is exophytic with areas of ulceration. It may appear as an ulcer in the depths of a fissure, or as an erosion, sometimes with infiltration into underlying muscle. White patches may or may not be associated with the primary lesion. A minority of tongue

cancers may be asymptomatic but arise in an atrophic depapillated area with an erythroplastic patch or peripheral streaks or areas of leucoplakia.

Later, a more typical malignant ulcer usually develops and may reach several centimetres in diameter. The ulcer is hard, with heaped-up and often everted egdes. The floor is granular, indurated and bleeds readily. Often there are areas of necrosis. The growth infiltrates the tongue progressively with increasing pain and stiffening, causing difficulty with speech and swallowing. By this stage pain is often severe and constant, radiating to the neck and ears. Lymph node metastases at this stage are common and 50% may have palpable nodes at presentation. The lymphatics from the tip of the tongue drain first to the submentalnodes and from there directly to the jugulodigastric nodes deep in the neck. From the dorsum and lateral margins drainage is via the submandibular glands to the jugulodigastric group of nodes. The posterior third of the tongue drains via the jugulodigastric nodes to the upper deep cervical glands. Carcinoma on the tip, dorsum and posterior third may metastasize quite readily to the contralateral side. Due to the tendency to early lymphatic spread of tongue cancer, 12% of patients may present with no symptoms other than a lump in the neck.

*Floor of the mouth.* The floor of the mouth is the second most common site for intra-oral cancer, and accounts for 17% of cases in England and Wales. Most tumours in this site affect the anterior segment of the floor of the mouth to one side of the midline. Although arising in an anatomically distinct area, namely the U-shaped area between the lower alveolar ridge and the ventral surface of the tongue, carcinomas in this site quickly involve the tongue and lingual aspects of the mandible. This early involvement of the tongue often leads to a characteristic slurring of speech. The lesion usually starts as an indurated mass which ulcerates early. The clinical extent of infiltration is deceptive but may reach the gums, tongue and genioglossus muscle. Subperiosteal spread is rapid once the mandible is reached. Lymphatic metastasis, although early, is less common than with tongue cancers. Spread is usually to the submandibular and jugulodigastric nodes and may be bilateral.

More commonly than at other sites, oral carcinoma at this site is associated with pre-existing leucoplakia. Kramer et al (1978) have reported that leucoplakia in the floor of the mouth has a much greater frequency of malignant transformation than those at other sites, though this has not been widely confirmed.

*Gingiva and alveolar ridge.* Few authors distinguish between carcinomas arising from the alveolar mucosa and those arising from the gingival margins. However, they have quite different clinical presentations. In England and Wales, carcinoma of the 'gum' (ICD 143) accounts for about 20% of oral cancers, is rather more frequent in males, and is three times more frequent in the mandible than the maxilla. The disease is more common in the USA and particularly in the south-eastern States where women account for 45% of cases, particularly those with the habit of snuff dipping.

In the dentate patient, gingival carcinoma is likely to be misdiagnosed by the dentist as the signs may closely mimic dental sepsis and periodontal disease, even when radiographs show bone destruction. The usual features are soft tissue proliferation at the gingival margin or superficial gingival ulceration. Loosening of the related teeth due to early spread of the tumour along the periodontal ligament can follow.

On the edentulous ridge, a carcinoma often appears as an indolent superficial ulcer adjacent to or within an area of leucoplakia. Occasionally, the lesion may be proliferative and again mimic fibrous denture hyperplasia. Because of these presentations, gingival and alveolar carcinomas are frequently unrecognized and often there is a history of extraction in an attempt to resolve so-called dental sepsis. Even in the absence of radiographic changes, the underlying bone is invaded in 50% of cases and this has important consequences for management.

Regional metastases are common at presentation and found in 30-84% of cases.

*Buccal mucosa.* The buccal mucosa extends from the upper down to the lower alveolar ridge, and from the commissure anteriorly to the ramus and retromolar region posteriorly. In general, the prognosis for this site is probably better than elsewhere in the oral cavity. This may be due to several factors. Bone is involved late in the disease, and unlike other sites, fewer tumours are typical squamous cell carcinomas. Verrucous carcinoma, although accounting for only about 5% of oral cancers overall, most frequently affects this site.

The majority of carcinomas of the buccal mucosa are posteriorly situated. The onset of the disease may then be insidious, with trismus due to deep infiltration of the buccinator muscle. The tumours are also subject to occlusal trauma, with consequent early ulceration and secondary infection. Extension posteriorly involves the anterior pillar of the fauces and soft palate with consequent worsening of the prognosis.

Infiltrative lesions can later involve the overlying skin of the cheek, resulting in multiple sinuses, and metastasize to the submental, submandibular, parotid and lateral pharyngeal nodes.

## Microscopy

Approximately 90% of cancers of the mouth are squamous cell carcinomas, and are usually well differentiated. The characteristic microscopic feautures are the retention of an obvious epidermoid character (sheets of polygonal cells with intercellular bridges) by all but the most peripheral cells of the tumour processes, loss of definition or disappearance of the basal lamina, nuclear pleomorphism and hyperchromatism, deep cell keratinization and invasion of normal structures in the tumour's path. There is almost invariably an inflammatory reaction (predominantly lymphoplasmacytic) around the tumour margins, and many believe that this represents an immunological defence against the disease.

Abnormal keratinization frequently leads to formation of whorls of keratin (cell nests) within the tumour processes. In addition to deep keratinization, these tumours, in their earlier stages at least, occasionally produce significant amounts of surface keratin and this can cause them to be mistaken clinically for leucoplakia.

As tissue destruction progresses, the surface usually ulcerates, and the ulcer typically has thickened margins infiltrated by the tumour.

In less well-differentiated neoplasms, cell nests are absent, prickle cells become less obvious and there is increasing atypia. The most obvious features of the latter are the increased nuclear cytoplasmic ratio, so that the tumour may consist largely of closely packed,

hyperchromatic nuclei of variable shape and size. However, there is frequently variation in the degree of differentiation from one area of the tumour to another, and this inevitably makes grading - a subjective assessment at best - even more difficult, as discussed later.

Anaplastic carcinomas are rare in the mouth and, by definition, lack features indicative of their epidermoid origin, and prickle cells cannot be identified. They can, therefore, be difficult to distinguish by light microscopy, from metastases, or even from lymphomas. However, with the use of immunocytochemistry and epithelial markers, particularly cytokeratins, it is possible to identify epithelial tumours with more certainty.

Examples of these variations in microscopic differentiation are more satisfactorily illustrated than described.

## Classification, staging and prognosis

The practice of dividing cancer cases into stages arose from the finding that survival was better when the tumour was localized than for those which had extended beyond the immediate site of origin. Subsequent observation suggested that even for a tumour confined to its site of origin, its dimensions also influenced the prognosis. Small, localized tumours are referred to as 'early' cases, though this implies that all cancers grow at the same rate.

There are many possible bases for classification, such as the anatomical site and size of the tumour, the duration of symptoms or signs, the sex and age of the patient, or the histological grade. All of these variables influence the outcome of the disease.

The TNM classification is based on clinical assessment of the anatomical extent of disease, and as a consequence, subjective and dependent upon the personal experience and skills of the clinician. The TNM classification had as its primary aim the clinical staging of tumours without additional diagnostic aids. This was achieved by recording the size and degree of infiltration of the primary tumour (T), the presence and condition of the associated regional lymph nodes (N) and the presence or absence of distant metastases (M). When precisely evaluated, these variables should give an indication of the prognosis and help the clinician in his choice of treatment.

After more than 10 years of research, the TNM classification, although extensively modified, faces essentially the same problems that were inherent in the original method, namely:

1. Is it possible to evaluate with sufficient accuracy the dimensions of the primary tumour, involvement of the regional lymph nodes and any metastases?

2. Are these criteria sufficient to formulate a prognosis, and if so, how accurately?

3. As most clinical cancer research is based upon retrospective rather than prospective studies, are the recorded data sufficiently detailed and reliable?

4. How consistent is the quality of the data from different centres, even when the same criteria are apparently used?

## The need for staging

Before starting treatment for a patient with oral cancer, the patient's disease must be fully evaluated. Assessment includes an exhaustive history, physical examination, and laboratory and imaging studies, to determine the extent of the tumour and the presence or absence of lymph node or distant metastases. Every tumour should be biopsied and the histopathological diagnosis must be confirmed before the start of treatment. Because carcinomas arising from different sites in the oral cavity have distinctive clinical features, courses and prognoses, the therapeutic approach must be tailored to each patient. The many approaches to oral cancer suggest that a universally applicable form of treatment does not exist. The selection of the most effective treatment for a specific tumour at a particular stage, in any individual patient, is entirely dependent upon a meaningful comparison of the end results of adequate numbers of similar cases reported from different centres. For these reasons a classification system is essential, but it has to be admitted that, though the TNM system is widely used, an ideal system does not as yet exist, as discussed earlier.

Modality of treatment must be presumed to affect the outcome, and data have been available on a national scale for the survival rates for surgery as opposed to radiotherapy. However, such information is biased by selection, since cases too advanced or too unfit for surgery are likely to receive radiotherapy. Moreover, there are so many other unmeasurable variables, such as the skill of the operator and the thoroughness of the excision, that it may not be possible to draw any conclusions from different published series except to note that from some centres better results are reported than from others. However, personal series, though usually too small to overcome the inherent variables affecting prognosis, may be of value, because more details about both the tumours and patients are available.

*The size of the sample.* As discussed below, so many variables affect survival rates that when this aspect is under consideration, data on anything less than several thousand cases are rarely of value.

*The country of origin.* It is common to extrapolate data from the USA to Britain, but though this may be justified, the wide variations in site, sex and other aspects of cancer in different countries make such extrapolations difficult to validate. Some differences may be related to genetic factors, but environmental influences are likely also to play a part.

*Accuracy of site identification.* This is one of the most common sources of confusion, since, as mentioned earler, 'head and neck cancer' encompasses a wide variety of tumours, most of which are likely to have different aetiologies, and certainly have different survival rates. Frequently, because overall numbers are small, cancer registries find it convenient to include pharyngeal cancer with mouth cancers (oropharyngeal cancer) and may even include lip and salivary gland tumours. Aetiologies and survival times certainly vary widely even for this relatively restricted group of sites. Often these facts are not made clear, and it may be assumed that the data applies to mouth cancer only. In addition, it has been shown that even for oral cancer there are significant variations in survival times according to the site within the mouth. Broadly speaking, the further posteriorly the tumour, the poorer the prognosis.

*Tumour size.* Few surgeons make more than an approximate visual assessment of the maximum diameter of a tumour. In addition to any inaccuracies in such assessments, they can

only take account of the visible surface of the tumour and cannot take into account the extent to which it may be undermining the surrounding tissues and extending deeply. Moore et al (1986), for example, found that with tumours between 2 and 4 cm in surface diameter, there was little correlation with behaviour as depth of invasion was not taken into account. It seems inescapable that invasion has a significant impact on survival, but such information is not available until the specimen is examined histologically.

## Reliability of histological grading methods

It is considered virtually axiomatic that well-differentiated tumours do better than poorly differentiated ones. Any staging procedure should logically, therefore, take the histological grade into account. The difficulty is that assessments of grade are also largely subjective and different systems take into account different microscopic features. Further, a biopsy may provide an unrepresentative area since the cell populations of tumours are frequently heterogeneous. For this last reason, the long-established Broders' 1927 classification has been reported to be unreliable, but the number of grading systems published since then testifies to the difficulties involved. In addition to attempting to assess degrees of differentiation, other microscopic variables such as intravascular invasion may be taken into account. The latter has been correlated with the incidence of lymph node metastases (Close et al, 1987) and more recently has been found to have a considerable impact on survival as well as on the incidence of recurrence or metastases.

Anneroth et al (1987) have carried out a detailed comparison of histological grading systems since Broders' contribution, and proposed yet another. The latter provides a point system for assessing degrees of (a) keratinization, (b) nuclear pleomorphism, and (c) numbers of mitosis. In addition, assessment is also made of tumour-host relationship in terms of (a) pattern of invasion, (b) depth of invasion, and (c) lymphoplasmacytic response. Anneroth et al (1987) also recommended exclusion of assessment of vascular invasion because of the difficulties in defining and recognizing it.

More recently still, Bryine et al (1989) proposed a grading system modified from that proposed by Anneroth et al (1987) and applied only to the most invasive areas of the tumour. Using this method for 68 oral carcinomas, these workers found a strong correlation between the histological score and survival. By contrast, they found no correlation between Broders' grade and survival. The site and size of the tumour were also found to affect the outcome.

As more refined techniques develop, so further methods of grading tumours must be anticipated. In a study of 176 oral carcinomas by Tytor and Olofsson (1992), the findings from DNA cytometry were compared with more conventional staging procedures and correlated with outcome. In brief, their findings were that a high microscopic malignancy grading correlated withDNA non-diploidy and with a higher frequency of lymph node metastasis and bone invasion. Non-diploid tumours also had a shorter history. Aneuploid tumours responded better to preoperative radiotherapy than diploid or polyploid tumours. Bryne (1991) reviewed the various molecular and cellular factors used to assess the prognosis of oral carcinomas. He suggested that histopathological grading, tumour thickness and tumour DNA content formed independent markers for prognosis which might be useful clinically and that the features of cells from the invading margins were probably of greater prognostic value than others. He also summarized the research on other cellular and serum markers at that

time. However, in contrast to many earlier reports, Stell (1992), on the basis of an unusually large personal series of 842 tumours of the oral cavity, of which 512 were histologically proven squamous cell carcinomas, found that the histological grade appeared to be unimportant and that the only identifiable host factors determining survival were greater age and worsening performance status, although survival was similar for either sex.

Earlier, in an attempt to overcome the deficiencies of TNM classifications and their modifications. Rapidis et al (1977) and Langdon et al (1977) proposed an expanded classification applicable primarily to tumours of the oral cavity. They also developed a staging system which circumvented the problems of having large subgroups of the permutations of T, N and M and aimed to provide a more accurate indication of the prognosis.

Rapidis et al (1976) proposed a revised classification, for intra-oral carcinoma, consisting of S (site), T (tumour dimensions), N (lymph node involvement, M (distant metastases) and P (histopathology), and therefore termed the STNMP system. In this, the anatomical site of the primary tumour (S) was subdivided into nine different categories, although only five of these (tongue, cheek, palate, floor of mouth and alveolar process) were intra-oral.

The STNMP classification has since been applied to a larger series of patients and compared with the TNM classification. Evans et al (1982) developed a new statistical approach, using life tables and applying actuarial methods to compute survival times and confirmed that the STNMP scoring system was an accurate predictor of survival and was a significant improvement over TNM systems. However, Rich and Radden (1984) were unable to confirm that the STNMP system was of any greater value than TNM in estimating prognosis in a series of 118 patients. They considered that the probable explanation was that the weighting system used in the STNMP system, and indeed in any system where a subjectively measurable variable is given an arbitrary score, is difficult to manipulate statistically to enable valid comparisons to be made.

Evans et al (1982) computed yet another variable - the velocity of growth (V) - by dividing the area of the tumour at presentation by the time elapsed since symptoms were first noted. The area of the tumour was assessed as three-quarters of the length x the breadth of the lesion (a rough estimate of the area of an ellipse). Their analysis showed that this estimate of velocity of growth was even more important than the size of tumour at presentation.

Estimates of the delay between the onset of symptoms and a definitive diagnosis are highly subjective, since they rely on the memory of the patient. Nevertheless, even an estimated velocity of tumour growth appears to have important prognostic significance.

## Conclusions

Staging is clearly important in planning treatment, assessing prognosis and advising patients accordingly. Further, if a valid set of measurable features could be devised, accurate staging would be of immense value in assessing different approaches to treatment. However, it is clear that so many variables are involved that it would require immense numbers of patients, each of whose disease would have to have been equally accurately graded, to provide any useful information. The number of grading systems that have been devised and their

increasing complexity is an indication of the problems involved and it is likely that most surgeons, unless they have unusually small workloads, will continue to rely on simple, essentially traditional, staging systems when deciding on the treatment of any individual patient.

In summary, it is difficult to say more than that the prognosis is poorer for cancer of the tongue, for men, for the elderly, for poorly differentiated tumours, for late (extensive) disease and for those with nodal involvement.

## Management

Overall, cure rates in terms of 5-year survival rates are probably similar for surgery or radiotherapy, and the choice of treatment modality must be made for the individual patient. Combined treatment with radiotherapy before or after surgery is the optimal treatment for most T2/T3 tumours. For some sites - particularly when bone is involved - surgery is normally preferred, whereas for the tongue particularly, where retention of good function is critical, radiotherapy may be preferred. For such reasons, patients with 'head and neck cancer' should be managed in joint clinics with suitable surgical and radiotherapy representation, as well as other specialists such as oral hygienists and speech therapists.

Despite anecdotal reports of cures, there is not as yet any evidence that the use of chemotherapy, either alone or in combination with surgery and/or radiotherapy, confers any benefit. The toxic effects of chemotherapy itself also confer a significant mortality and Stell (1990) has shown that it reduces survival when compared with conventional treatment. It is probably, therefore, at best a treatment of last resort, though clinical trials to evaluate it still continue.

## Surgery

With current surgical techniques it is possible to resect most tumours in the head and neck region. Thus, the vast majority of head and neck cancer patients are potentially treatable by surgery, but many of them should not be because of advanced age, general disability or its mutilating effects. Before the decision to operate is made, four principles must be considered.

1. There must be a reasonable prospect of cure.

2. The entire tumour must be removed.

3. Although normal anatomy and function should be retained or restored whenever possible, this consideration should not compromise the excision.

4. To the patient, the most important consideration will often be whether the final result is cosmetically acceptable. What the patient will tolerate is often very different from what the surgeon may require. The patient should, therefore, be carefully advised of the problems involved and possible complications.

The surgical techniques used today for excision of oral cancer were largely perfected before 1950. The last 30 years have yielded very little improvement in cure rate, but there have been considerable improvements in immediate surgical mortality and reconstruction.

Reil et al (1975) analysed the surgical mortality figures for head and neck resections over a 20-year period, and showed a reduction from 16% to 2.5%. The quality of life following excision has greatly improved, largely due to new techniques for reconstruction. Although in historical terms axial flaps, such as the forehead flap and deltopectoral flap, were great advances, the more recent development of myocutaneous flaps (pectoralis major, latissimus dorsi and trapezius flaps) and microvascular, free flaps (particularly the radial forearm flap and compound groin flap) have revolutionized reconstruction and rendered it a one-stage procedure.

## Spread of carcinoma of the mouth

The critical feature of carcinomas is their capacity to invade local structures and to spread into the neck through the lymphatics and beyond. Control of the disease in the mouth and neck dominates all aspects of management.

Knowledge of patterns of spread of oral cancer is clearly important if excision is to be complete but within practical limits. Nevertheless, there are obvious difficulties in the way of adequately defining such patterns. It must, therefore, be appreciated that, despite all the research so far carried out, the following account should be regarded only as a general guide and that cancers can behave unpredictably. It is essential, as described below, to check that resection margins are clear of tumour.

## Local spread

*Invasion of soft tissues.* Mouth cancers often infiltrate widely into adjacent connective tissues. Particularly in the tongue, extensive infiltration beneath intact mucosa is common and very difficult to detect preoperatively. The risk is, therefore, of encroachment of tumour into resection margins which, of necessity, are often very narrow in the oral cavity. Meticulous frozen section control of all soft tissue margins is, therefore, important during resections and, when radiotherapy is used, any such local extension must be taken into consideration in determining the volume of tissue to be excised.

Carcinomas penetrate deeply between and occasionally within the intrinsic muscle bundles of the tongue, but extension through the mylohyoid and hyoglossus muscles in the floor of the mouth is uncommon. In the tongue, infiltration is usually more extensive posteriorly than anteriorly. Tumours arising more posteriorly in the region of the linguotonsillar groove may, however, spread behind the mylohyoid and enter the submandibular space.

These natural soft tissue barriers and pathways become oblisterated by previous surgery and/or irradiation, by progressive fibrosis. Under such circumstances, the extent and direction of local spread becomes unpredictable.

*Invasion of perineural spaces.* Perineural spread in the head and neck region is particularly characteristic of adenoid cystic carcinoma, but may also be seen with squamous cell carcinomas. Once within perineural spaces, tumour cells can track long distances both distally and proximally. Such centripetal infiltration of tumour along branches of the mandibular nerve (inferior dental, long buccal, lingual) may lead to direct intracranial extension. For this reason, whenever the mandible is resected for control of carcinoma, the inferior dental bundle should be taken as high as possible. Similarly, whenever a rim resection is being considered, the excised portion of the mandible must include the inferior dental canal.

*Invasion of vessels.* Intravascular tumour cells are usually seen as small clumps lying either freely in the vessel lumen or within thrombi. Close et al (1987) demonstrated a significant correlation between vascular invasion and the incidence of nodal metastases, and extended this work (Close et al, 1989) to show a correlation between microvascular invasion and survival from oral and oropharyngeal cancer. The assessment of microvascular invasion in stage determination may, therefore, be important and has been discussed earlier. Paradoxically, no consistent association has been established between penetration of the internal jugular vein and the presence of systemic blood-borne metastases. Invasion of arteries is rare. Infiltrating carcinomas tend to grow around arteries, leaving a distinct peri-adventitial clear zone. Even in patients with carotid rupture, infiltration of the arterial wall is rare. The main predisposing factors are previous irradiation of the neck, necrosis of skin flaps, infection and salivary fistulas.

Thrombi containing tumour cells are rarely seen in lymphatics and evidence of direct permeation along the lumen is uncommon.

*Invasion of bone.* The principal mode of access to the facial bones is by direct extension. Invasion is facilitated by anatomical openings such as the inferior dental canal and incisive and palatine foramina. Access of tumour by periosteal lymphatics is probably not important. Despite its dense cortical plates, mandibular invasion is more common than maxillary invasion. It has been suggested that this is due to the persistence of nutrient vessels running vertically and perforating the crest of the alveolar ridge, even in the edentulous mandible. Reference has already been made to the mylohyoid acting as a barrier to deep invasion. This observation that invasion spreads downwards from the alveolar crest indicates that rim resection of the mandible is a sound procedure in selected cases, provided that the resection includes the inferior dental canal and its contents throughout its length.

The mechanism of bone invasion is mainly by induction of host osteoclasts. Direct erosion of bone by tumour cells is only a very late feature. The osteoclasts are stimulated by a combination of osteolytic factors - such as prostaglandings $E_2$ and $F_2$ - and others such as interleukin 2. These mediators are formed both by the tumour cells and also by host tissues. There is no correlation between the extent of bone destruction or the presence of distant skeletal metastases with hypercalcaemia. There is presumptive evidence that such tumours produce humoral calcium-mobilizing factors.

Preoperative assessment of early bone involvement is difficult. Gilbert et al (1986) have compared the value of clinical assessment, radiography and bone scans, and correlated the frequency of mandibular involvement with spread to lymph nodes. A possible reason for the difficulties in assessing the extent of bone involvement is that it is produced in different

ways. Lukinmaa et al (1992) have shown that oral cancers invade bone either by non-uniform infiltration or on a broad front, and that the extent of infiltration of bone can considerably exceed their superficial dimensions. By contrast, some large tumours with clinical fixation to the mandible may not have invaded bone. There was also no clear correlation between the degree of differentiation and bone invasion.

As to visualizing the extent of bone invasion, Millesi et al (1990) correlated the findings of conventional radiography, sonography, CT and MRI and technetium scintigraphy and concluded that ultrasonography provided the most reliable diagnosis in most areas of the mandible. Bahadur (1984) also compared radiography, CT and isotope scans, found none of them to be completely reliable and recommended resection of the superior margin of the mandible for all carcinomas close to, even when not visibly involving, the bone. By contrast, Ator et al (1990) claim that using $T_1$ and $T_2$ sequences on a small group of patients, MRI was the most reliable method of determining the full extent of mandibular marrow invasion and superior to CT scanning and conventional imaging methods.

## Metastases to regional lymph nodes

Clinical assessment of cervical lymph nodes is unreliable. Crile, as long ago as 1906, observed that 'palpable glands may be inflammatory and impalpable glands may be carcinomatous'. However, the distribution of nodal metastases from cancers of the mouth and jaws is reasonably predictable. Cancers of the tongue, floor of the mouth and alveolar ridges metastasize principally to the ipsilateral submandibular, jugulodigastric and middle deep cervical nodes. Cancers of the retromolar trigone spread to the submandibular, jugulodigastric and upper and middle deep cervical nodes. The parapharyngeal nodes may also be invaded but are not accessible to conventional radical neck dissection. Cancers of the lip and tip of the tongue spread to submental and submandibular nodes. Lesions of the tongue, lip and floor of mouth close to the midline metastasize to nodes on both sides of the neck.

The number of involved nodes is usually small, but extensive involvement of nodes along the entire length of the jugular chain is more frequent with aggressive tongue cancers which also spread to nodes in the posterior triangle.

Important prognostic factors are multiple involved nodes, metastases in the low cervical nodes and extension of carcinoma beyond the node capsule. The degree of histological differentiation in nodal metastases and in the primary tumour is usually similar tand both are equally sensitive, or resistant, to radiotherapy. Extranodal spread results in infiltration of local muscles, the carotid sheath and its contents, bone, salivary glands, skin and prevertebral fascia.

## Distant spread

This is discussed below.

## Radiotherapy

Radical radiotherapy aimed at cure may be used as the sole treatment or combined with surgery. The object is local control, namely complete destruction of the tumour. This

requires the killing of all tumour cells, while at the same time leaving sufficient normal cells in the adjacent tissues to allow repair. In general, radiotherapy is more effective against small tumours, although it is often advocated for the large, so-called inoperable tumour. The larger the tumour, the more likely are tumour cells to survive irradiation and produce a recurrence. Also, as a tumour grows, it tends to outstrip its blood supply, more cells become hypoxic and therefore radioresistant.

Palliative radiotherapy is used to relieve symptoms - such as bleeding, pain and obstruction - without attempting cure. Only a moderate dose is administered (eg, 20 Gy) given over a short period (eg, 5 days) to avoid producing other symptoms due to the acute tissue reaction.

The major argument in favour of radical radiotherapy as primary treatment is that many patients can be cured without surgery, and therefore will be spared the possible hazards of deformity and disability. A few of those in whom radiotherapy fails can be treated successfully by surgery (though surgery is made more difficult), but the converse is not true - radiotherapy rarely cures a patient who develops a recurrence after surgery.

Planned operative radiotherapy aims to improve surgical cure. Its basic assumption is that local recurrence or metastases result from dissemination of tumour cells at operation. Preoperative radiotherapy (40-45 Gy) will kill well-oxygenated peripheral tumour cells without causing surgical complications, but though there is some evidence that it improves local control, it is often difficult to arrange and rarely used.

The purpose of postoperative radiotherapy is to destroy small numbers of malignant cells which may be left behind or implanted into the operative field at the time of radical resection. However, after radical surgery, fibrosis progresses rapidly, resulting in local ischaemia. To be effective, postoperative radiotherapy must be instituted within 6 weeks of surgery and should be given whenever tumour extends beyond resection margins, or there is multiple node involvement or extracapsular spread.

## Interstitial radiotherapy

Interstitial radiotherapy, in which solid sources of radiation, such as iridium wires, are implanted directly into the tumour, produces a high intensity of radiation in the immediate vicinity of the source, while the dose to the surrounding tissues is low because of rapid fall-off. Side effects such as xerostomia, taste loss and bone necrosis are much less than with external radiation. Radiation sources must, however, encompass the whole lesion with a margin of at least 1 cm all round. This technique is, therefore, applicable only to smaller tumours confined to the soft tissues (tongue, cheek, floor of mouth), but gives very good local control rates.

## Fast neutron therapy

After enthusiastic claims for the value of fast neutron therapy based on small numbers of patients with various types of head and neck cancer, it seems that the complications outweigh any suggested benefits. Stafford et al (1992) found that complications were more severe and persisted longer than after conventional radiotherapy. Complications developed,

on average, 5.5 years after fast neutron therapy and included airways obstruction, intractable dysphagia and osteoradionecrosis. Remedial surgery to the irradiated area was compromised by greatly impaired wound healing.

## Salvage surgery

Where radical radiotherapy fails and there is residual or recurrent tumour, salvage surgery may offer hope. Following radical radiotherapy, the tissues tend to have a much reduced blood supply, be fibrotic and heal poorly. Consequently, salvage surgery carries a higher risk of complications such as delayed wound healing, fistula formation, wound breakdown and carotid artery rupture. These hazards increase with time and surgery is best undertaken within 3 months of completion of radiotherapy.

## Management of the neck

*Patients staged N0.* The regional lymph nodes, although clinically impalpable, sometimes contain occult foci of malignant cells. It seems reasonable to expect, therefore, that removal or treatment of regional lymph nodes, even when clinically clear, would improve cure rates. Alternatively, it can be argued that treatment of the regional nodes in all cases is unnecessary, as only a minority have metastases in the nodes.

The arguments expressed in favour of elective bloock dissection are:

- the incidence of histologically involved nodes in N0 neckes varies from 25% to 65%

- survival rates are considerably lower in patients who develop node metastases

- the recurrence rate following block dissection is higher in advanced disease when there is extracapsular spread or multiple nodes

- by waiting for clinically detectable disease to develop, many patients will have a wose prognosis

- some patients fail to attend regular follow-up and may not appear again until nodal metastases are extensive

- block dissection of the neck carries negligible mortality and an acceptable morbidity

- retrospective reviews confirm that patients undergoing elective neck dissection have higher survival rate

- failure to control nodal metastases is a frequent cause of death.

The arguments against elective neck dissection are that:

- it is rare for treatment to fail in the neck when the primary is controlled - only 4.5% in one large series

- the incidence of histologically positive nodes in elective neck dissections exceed the incidence of subsequent clinical nodal metastases, suggesting that some microscopic foci are destroyed by the body's defences

- the primary may recur or a second primary develop and metastasize into the dissected neck, making subsequent management very difficult

- elective neck dissection gives no guarantee against recurrence of the tumour in the neck

- block dissection has a considerable morbidity

- removal of regional lymph nodes may remove a barrier to the further spread of disease

- there is no prospectively controlled trial to support the argument that elective neck dissection does improve the prognosis.

On balance, the weight of these arguments is against prophylactic neck dissection. However, advanced tumours in some sites undoubtedly have a very high incidence of nodal disease, and as the submandibular triangle has to be opened as part of the resection of the primary, function-sparing elective neck dissection is recommended for tumours in the floor of the mouth and lower alveolar ridge with bone involvement. This dissection, in which structures such as the accessory nerve, internal jugular vein and sternocleidomastoid muscle are preserved, can be justified. Further, a survey by Shah (1990) showed that of 501 cancers of the oral cavity, 34% of nodes were found to be positive after elective radical neck dissections. Over 96% of these histologically positive nodes would have been removed by a supra-omohyoid dissection.

The operation should preferably be seen as a staging procedure from which the decision is made to give radical postoperative radiotherapy.

An alternative approach is elective irradiation of the clinically negative neck, and indeed there is some evidence that this is of some benefit in preventing subsequent nodal disease. Certainly, elective irradiation to 40 Gy carries less morbidity than elective neck dissection.

*Patients staged N1/N2a/N2b.* At present, evidence suggests that the treatment of choice is radical neck dissection, either alone or combined with postoperative radiotherapy if multiple nodal involvement or extracapsular extension is found in the resected specimen. In those patients unfit for radical surgery, radical external beam irradiation is indicated.

*Patients staged N2c.* It is uncommon for patients with oral cancer to present with bilateral nodes. When they do so, there is often a large inoperable primary tumour which is best treated by external radiation. It therefore seems logical to treat the neck also by irradiation. Occasionally, particularly in a young patient, bilateral neck dissection can be justified. A full radical neck dissection is undertaken on the ipsilateral side and the internal jugular vein is spared if possible on the contralateral side. Most often, postoperative

radiotherapy will be required for multiple nodal involvement or extracapsular spread. In such situations, severe post-treatment oedema or congestion of the face and tongue may be anticipated.

*Patients staged N3.* N3 inditaces massive involvement, usually with fixation. Large fixed nodes are often associated with advanced primary disease with a poor prognosis. Surgery is not normally advisable: removal of the common or internal carotid artery with replacement, or extensive resection of the base of the skull, although techically feasible, is seldom advisable. Treatment is most often by external radiotherapy. In a few younger patients with resectable primaries, it is worth rendering a fixed mass in the neck operable by preoperative radiotherapy.

## Nodal metastases appearing after primary treatment

Provided that follow-up at regular intervals is rigorously maintained, it should be possible to detect a lymph node metastais while it is still relatively small and therefore operable. Aspiration cytology is particularly useful in this situation to confirm that the palpable node is a carcinoma rather than reactive. Whenever positive, or if there is any doubt, a radical neck dissection is performed, followed by external irradiation if multiple involved nodes or extracapsular spread are found.

## Trends in mortality due to metastatic disease

Crile (1906) reported that 'the collar of lymphatics of the neck forms an extraordinary barrier through which cancer rarely penetrates'. Clinically apparent distant metastases are relatively uncommon, but such deposits are found in about 50% of autopsies of patients dying with cancer of the mouth and jaws. The usual sites are the lungs, liver, bones (vertebrae, skull, ribs) and thoracic nodes. Such skeletal deposits are usually osteolytic. Pulmonary metastases diagnosed on chest X-ray should be carefully evaluated as there is a 15% risk of developing separate primary squamous carcinomas of the lung, pharynx, larynx and oral cavity in these patients.

Since the more widespread introduction of combination therapy, there has been a change in the pattern of failure for oral cancer (Vikram, 1984). The overall survival rate has remained essentially static, but more effective control of the local disease has resulted in greater numbers of deaths from distant metastases and the emergence of second primary tumours. Distant metastases were rarely a problem in the past, as recurrence of locoregional disease was usually responsible for the patient's death. Thus in the past, only 4% died of distant metastases, although autopsy studies showed that up to 50% had metastases present at the time of death (O'Brien et al, 1971). More recently, Luna (1983) has described a rise in deaths due to metastatic disease from 17% fo 32%. Distant metastases have therefore become a major cause of death in oral cancer.

*Multiple primary carcinomas.* The tendency to develop multiple primary carcinomas is a significant problem with oral cancers. In resected specimens of oral cancer, it is possible to find separate islands and foci of carcinoma-in-situ and invasive carcinoma in the adjacent epithelium, thus lending support to the theory of field change in oral cancer. Approximately 10% of patients may have two or more carcinomas in the aerodigestive tract. Many of these

are within the oral cavity. Among 176 oral cancers described by Tytor et al (1990), 21 (8%) developed second primary tumours of the upper aerodigestive tract and other workers have confirmed this high incidence. Indeed, whenever a patient with oral cancer develops an unusual or unexpected metastasis, the possibility of a second primary tumour should be considered. Adequate treatment for such a second primary may occasionally give a prognosis far better than that for an oral cancer with metastases.

## Verrucous carcinoma

This uncommon variant of squamous cell carcinoma characteristically appears as a raised or cauliflower-like, white, warty lesion, and has a more benign course than the more common squamous cell carcinoma. Elderly males are most commonly affected. In the USA, particularly, it is seen as a consequence of prolonged tobacco chewing or snuff dipping.

## Microscopy

Verrucous carcinoma typically has a heavily keratinized or parakeratinized, irregular clefted surface with parakeratin extending deeply into the clefts. The prickle cell layers show bulbous hyperplasia, but for a considerable time at least, the tumour has a well-defined lower border and basal lamina. Atypia is minimal and there is usually a sub-epithelial inflammatory infiltrate.

## Verrucous hyperplasia

A distinction has been made between verrucous hyperplasia and verrucous carcinoma by Shear and Pindborg (1980). Verrucous hyperplasia is said not to extend more deeply than, or is superficial to, the surrounding normal epithelium. Verrucous carcinoma, by contrast, extends more deeply and pulls down the adjacent normal epithelium at its margins. However, verrucous hyperplasia is said to show dysplasia in the majority of cases, and can develop into verrucous carcinoma or squamous cell carcinoma, and it is widely agreed that the two - if they are separate entities - cannot reliably be distinguished and may coexist. The distinction does not seem to be of any great significance, even if it can be made, and in practical terms the management is the same.

## Behaviour and treatment

Verrucous carcinoma grows slowly, becomes invasive only later and metastasizes later still. The regional lymph nodes may be enlarged, but usually as a result of inflammation. Ultimately, if neglected or mismanaged, deeper tissues are invaded and metastases appear.

Wide surgical excision should be curative. Despite earlier claims, there is no evidence that radiotherapy induces dedifferentiation and ivnasive behaviour of verrucous carcinomas. However, any individual palpable lymph nodes should be removed, but block dissection is not justified except on the rare occasions when involvement is confirmed histologically.

## Keratoacanthoma

Keratoacanthoma ('self-healing carcinoma') is a relatively common lesion of the skin and sometimes of the lips, but rarely affects the oral cavity. Clinically, Habel et al (1991), in a review of intraoral keratoacanthomas, found the age of those affected to range from 12 to 80 years and out of 10 reported cases, 6 patients were less than 40 years old. There also appeared to be a strong predilection for males. The lesion appears as a painless cratered nodule. Even more rare is the eruptive variant which lacks the keratin-filled crater and more closely resembles a neoplastic ulcer clinically. Spontaneous regression over a period of 4-6 months, leaving a small scar, is characteristic, but unusual confidence is required to leave such a lesion untreated.

## Microscopy

At low power, keratoacanthoma has a characteristic goblet-shaped form (resembling in some respects an 'invaginated' verrucous carcinoma), with normal mucosa forming the lips of the cup, and showing an abrupt change to the carcinoma-like epithelium. There is typically significant epithelial atypia and despite the absence of deep invasion, there is poor demarcation of the peripheral epithelium from the stroma. Habel et al (1991), in reporting what may be the first case of an intra-oral eruptive keratoacanthoma, confirmed the difficulty of reliably distinguishing the central part of these lesions from a squamous cell carcinoma microscopically. They considered the most distinctive microscopic feature to be the elevation of the normal mucosa at the margin of the lesion and the abrupt change to hyperplasia.

In view of possible difficulties in differentiating keratoacanthoma from squamous cell carcinoma histologically, account should also be taken of the former's clinical features, particularly its more rapid growth, which usually extends over 6-12 weeks and its more frequent appearance in children or young adults.

## Other variants of oral carcinoma

Spindle cell and adenoid squamous carcinomas have been rarely reported in the oral cavity. Too little is known of their behaviour to make any useful practical comments. Basaloid squamous carcinoma is another rare entity showing both basaloid and squamous cells in lobular or trabecular configurations. It appears to behave particularly aggressively.

Epidermoid carcinoma can very occasionally arise from minor oral salivary glands, forming about 1% of tumours there. Unless its origin can be seen to be from salivary tissue rather than from surface epithelium, such tumours are not likely to be distinguishable from the usual type of squamous cell carcinoma, and indeed the distinction is not likely to be of clinical significance.

Basal cell carcinoma is a skin tumour and does not arise in the oral mucosa. However, other tumours such as adenoid cystic carcinomas of salivary glands may have a basaloid appearance.

## Merkel cell carcinoma

Merkel cells are neuroendocrine cells which have synaptic associations with intra-epidermal and dermal nerve endings, but their function is unknown. Merkel cell carcinomas are rare but aggressive tumours which mainly affect sun-damaged skin in elderly patients with a mean age of 75 years. Approximately 40% of these tumours arise in the skin of the head and neck region and most of the remainder in the skin of the limbs. A few examples have been reported in the oral cavity. Vigneswaram et al (1992), in their review, found 12 oral examples of which 11 were in males. Consistent with predilection of these tumours for areas vulnerable to actinic damage, 10 were in the lips while 1 was in the buccal mucosa and the other in the mucobuccal fold. Another example, reported by Hayter et al (1991), arose from just beneath the buccal mucosa in a man of 73.

*Clinically,* oral Merkel cell carcinomas form small, painless nodules which grow rapidly, may ulcerate and may become painful.

## Microscopy

Merkel cell carcinomas usually consist of uniform cells with little cytoplasm, but large round basophilic nuclei with one or two small nucleoli and prominent nuclear membranes. When in sheets, these cells have a lymphoma-like appearance. Otherwise they may form trabeculae, whorls or strands of cells spreading between collagen fibres and do not initially involve the surface epithelium. Intermediate and small cell Merkel cell carcinomas with worse prognoses have also been described.

Differentiation from other small cell tumours, particularly metastases, may be difficult. Immunocytochemistry shows a characteristic staining with the epithelial marker CAM 5.2 and with other low molecular weight, but not high molecular weight keratin antibodies, and Vigneswaram et al (1992) suggest this type of keratin staining together with globular paranuclear staining with antibody to neurofilament proteins, is unique to Merkel cells. Approximately 50% of these tumours are also positive for neuron-specific enolase or chromogranin, but in cases of doubt electron microscopy can be required.

*Ultrastructurally,* Merkel cells contain dense membrane-bound neurosecretory granules and paranuclear whorls of intermediate filaments.

## Behaviour and management

Eight of the 12 oral examples reviewed by Vigneswaram et al (1992) metastasized to lymph nodes or distant sites and 3 patients died from their tumours within 1-11 months. The periods of follow-up of most of the remaining reported cases were short.

The treatment of choice appears to be as wide surgical excision as possible, followed by radiotherapy to which these tumours are sensitive. Prophylactic irradiation of the regional nodes is also advised. Vigneswaram et al (1992) quote a recommended dose of 50 Gy in 25 fractions and with this regimen their patient was disease-free after a year. Complete clinical remission has also been reported with chemotherapy by Wynne and Kearsley (1988). Nevertheless, the aggressiveness of these tumours is shown by the patient reported by Hayter

et al (1991) who, after surgery and radiotherapy (50 Gy), developed a metastasis and pathological fracture in the upper arm. Despite radiotherapy to the humerus and a course of chemotherapy, multiple metastases were found in many sites after the patient died from other causes 8 months after the initial diagnosis.

## Carcinoma of the maxillary antrum

Carcinoma of the antrum is so uncommon as not to have justified an individual entry in national cancer statistics, but is included with nose, nasal cavities, middle ear and other sinuses. Even those together account for only about one-third as many cases as cancer of the mouth. A few (about 15%) of these rare carcinomas spread through the floor of the antrum to appear as oral tumours. They are, with rare exceptions, squamous cell carcinomas, often well differentiated and therefore not distinguishable from carcinomas arising from the oral mucosa. Confirmation of the diagnosis depends on finding the antral mass and destruction of the antral floor. Wide excision and radiotherapy are the usual lines of treatment.