Meeting November 25 1968

Papers

Leukoplakia and Oral Cancer

by Professor R A Cawson MB FDS RCS MCPath
(*Department of Oral Medicine and Pathology, Guy's Hospital, London*)

The incidence of oral cancer in Britain appears to be more than 1,850 cases per annum according to the National Cancer Registration Scheme for 1963–64. The incidence rises sharply with age. The Registrar General (1967) records a mortality for oral cancer of approximately 900 a year, i.e. the death rate is very close to 50%.

Little is known of the etiology of oral cancer but leukoplakia is regarded as a precancerous disease. If so, its proper management might be expected to make some contribution to reducing the high mortality of oral cancer.

Chronic white lesions of the mouth include a variety of conditions, but the relationship of any of these individual types to oral cancer is not clear. The following comments can, however, be made.

Developmental leukoplakia: There are two main types. In one there is widespread, irregular, œdematous thickening of the superficial epithelium and there may be a family history suggesting inheritance as a simple dominant. The other variety classically forms a butterfly pattern under the tongue with sharply-defined margins and wrinkled surface, soft to the touch and without inflammation.

Though these plaques are sometimes called congenital they are not seen in children except on very rare occasions and are often not found until middle age. This does not exclude their developmental nature but the term 'developmental' should not be taken necessarily to mean 'benign' (Fig 1). There are well-recognized developmental or hereditary diseases which are precancerous, e.g. xeroderma pigmentosum.

Frictional keratosis: The mucosa abraded by a broken tooth, for instance, may become keratinized. Though this is traditionally regarded as a cause of cancer, experimental evidence suggests that mechanical injury alone is not carcinogenic. In any case the condition is readily dealt with and the mucosa will rapidly revert to normal if trauma is the sole cause.

Smokers' keratosis: In the usual form there is keratosis of the palate with inflammation and swelling of mucous glands. Leukoplakia is sometimes severe but seems in most cases to be reversible if the patient will stop smoking. Heavy smoking has a close association with carcinoma of the bronchus and several epidemiological studies in America (e.g. Keller 1967) have shown a significant relationship between oral and pharyngeal cancer and heavy smoking. Contrary evidence has been presented by Einhorn & Wersäll (1967) and it should also be noted that the commonest site of leukoplakia due to smoking is around the centre of the palate, a site rarely affected by cancer.

Moore & Catlin (1967) showed that the main sites of oral cancer are in the 'drainage area' of the mouth, that is in the crescentic zone between the lingual aspect of the jaw and the sides of the tongue extending into the pharynx. Over 75% of oral cancers develop in a region which forms only 20% of the whole mouth area. This suggests that if there is a relation between oral cancer and smoking, direct physical injury affects the palate but it is possible that carcinogenic products dissolved in the saliva could leak down and affect the drainage areas.

Syphilitic leukoplakia: This is usually regarded as especially prone to malignant change. Weisberger (1957), for instance, noted that of 14 patients with leukoplakia and serological evidence of syphilis, carcinoma developed in all of them. The mechanism and present incidence is, however, unknown. The decline in incidence of oral cancer may be at least partly due to the decline in tertiary syphilis. The characteristic site, i.e. the dorsum of the tongue, is an uncommon one for cancer. There are other noteworthy features of this disease: first, it is an infective cause of leukoplakia and, secondly, it appears to set up a sequence of events which, beyond a certain stage, are irreversible. A patient who has syphilitic leukoplakia has a strong chance of developing cancer even though the infection has been treated and the Wassermann reaction made negative.

Lichen planus: This condition is usually differentiated from 'leukoplakia' because its clinical appearance is usually quite characteristic and because it is often regarded as benign. Even less is known of the pathogenesis of lichen planus than of other white lesions and various observers have suggested that carcinoma may develop in a small but appreciable number of cases, i.e. from 10% (Wärin 1960) to less than 1% (Altman & Perry 1961). Andreasen & Pindborg (1963) reviewed 46 cases of cancer developing in patients with oral lichen planus reported between 1910 and 1961. Single cases have been reported since then but there are few large series giving any realistic

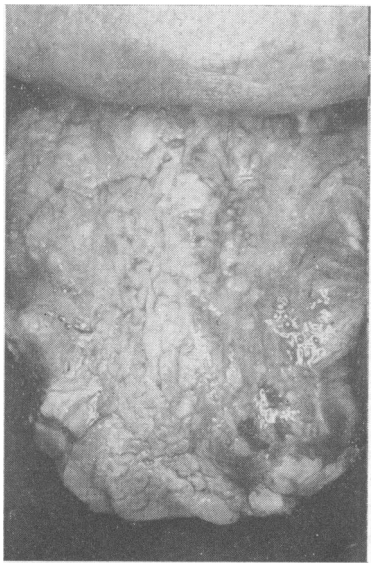

Fig 1 *A gross white lesion of the tongue known to have been present since childhood. Although labelled a 'developmental' lesion, multiple oral carcinomas developed*

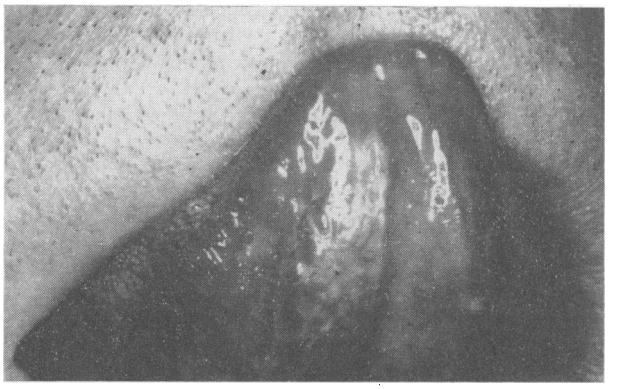

Fig 2 *This inconspicuous, soft, lacy lesion on the right underside of the tongue is dyskeratotic histologically and progressed to invasive carcinoma within two years*

indication of incidence. Andreasen & Pindborg found that cancer developed in relation to erosive lesions in 16 cases and in relation to plaques in 11 cases. Possible additional predisposing factors, including syphilis, were recorded in 24 of the 46; no information was available for the remainder and the importance of lichen planus itself in the development of cancer seems somewhat uncertain. The incidence of carcinoma in association with lichen planus is probably less than 1%, to judge from the larger series, and this is in agreement with our own findings where there appears to be a single case among 150 patients. Now that lichen planus appears in most cases to be a treatable condition it may be that this factor can be eliminated (Cawson 1968).

Leukoplakia of unknown cause and dyskeratotic lesions: Many leukoplakias have no recognizable cause; a minority of these are dyskeratotic. In theory the lesions already discussed can also progress to dyskeratosis but it is exceedingly rare to see unequivocal clinical or histological evidence of this transition.

Dyskeratotic lesions cannot be recognized clinically though Pindborg *et al.* (1963) found that the speckled leukoplakias were frequently dyskeratotic or were carcinomas. This is sometimes a useful clinical guide but must not be entirely relied upon (Fig 2).

Carcinoma-in-situ, that is the presence of frankly malignant cells within an epithelium showing no deep invasion, is a rare finding in the mouth; it should not be assumed that leukoplakia, dyskeratosis and carcinoma-in-situ are the usual or inevitable preliminary stages of invasive carcinoma. In the uterine cervix, carcinoma-in-situ is common but is found at an age when invasive carcinoma is rare. Ashley (1966) has suggested that they are two separate forms of the disease and that the in-situ variety is followed only after an interval of many years by a slowly growing invasive carcinoma with little tendency to metastasize.

Verrucous carcinoma, of which a series of 105 cases was recently reviewed by Kraus & Perez-Mesa (1966) forms a warty plaque which though grossly proliferative may be regarded as another variant of conditions intermediate between leukoplakia and carcinoma. It has little tendency to invade deeply or to metastasize.

One aspect of leukoplakia and oral cancer that should perhaps be reconsidered is that of hæmatological disease; patients with Paterson-Kelly syndrome (PKS) have a high incidence of oral cancer. Suzman (1933) reported the histology and autopsy findings in PKS and noted that the lesions were essentially hyperkeratotic with areas of desquamation. Ahlbom (1936) reported two women with PKS, both of whom had multiple oral cancers; he also noted that in Sweden, at that time, about (*sic*) 40% of oral cancer affected women, and suggested that this high incidence was related to PKS since about half these women were so affected but that only about 15% used tobacco.

Savilahti (1946) described the histology of leukoplakia of the mouth and larynx of women with PKS coming to autopsy and quotes Rosenquist (1944) as also finding leukoplakia in this disease. Wynder & Fryer (1958) found that of 114 women with PKS and cancer the oral cavity was affected in 18%. Shamma'a & Benedict (1958), reporting 58 patients with PKS, noted that 6

developed oral carcinoma but only 3 developed œsophageal cancer. Similarly Watts (1961) described 5 patients with PKS developing cancer and this was in the mouth in 3 cases.

PKS should not be regarded merely as a clinical syndrome with dysphagia as the main symptom, but as a major disorder of hæmopoiesis and of the epithelia of the upper gastrointestinal tract with varying clinical manifestations. The hæmatological changes of PKS are variable: hypochromic anæmia is present in approximately 50% (Elwood *et al.* 1964), a minority have macrocytic anæmia, while the rest have changes probably only detectable by marrow biopsy. This strong association between anæmia and oral cancer in PKS suggests that careful hæmatological investigation is essential, especially in women. If a defect of hæmopoiesis is present it may affect the prognosis of a leukoplakia. It is noteworthy that in two of the most recent surveys of leukoplakia (Pindborg *et al.* 1968, Silverman & Rozen 1968) the normal sex incidence is reversed and women form the majority of those developing carcinoma.

Keratinizing squamous cell carcinoma: Early cancer can form a white lesion, clinically indistinguishable from any other, and has caused confusion concerning the incidence of carcinoma in leukoplakia. Many cancers of this appearance have been labelled as malignant change in leukoplakia when in fact they were neoplasms from the start. Some of these lesions appear remarkably innocent but inevitably have a different course from leukoplakia proper. The white lesion is bound to be small but advances rapidly; progressive growth and tissue destruction soon lead to obvious ulceration.

Candidosis as a form of leukoplakia: Histological evidence of candidal invasion in leukoplakias is regarded by Jepsen & Winther (1965) as 'superimposed' infection. This presumably may happen, of course, but no evidence has been produced to show that pre-existing leukoplakias do in fact become so infected. The reasons for suggesting that candidal infection itself is a cause of leukoplakia are these:

(1) Invasion of epithelium by candidas is a potent cause of hyperplasia; the striking feature of the tissue response in thrush is the gross epithelial proliferation which indeed forms the clinical plaque of thrush (Cawson 1965).

(2) The plaques of chronic hyperplastic candidosis show similar epithelial hyperplasia and other histological features in common with those of thrush (Cawson 1966, Cawson & Lehner 1968).

(3) The progressive development of plaques in patients known to have had long-standing candidal infections can occasionally be seen.

(4) Intermediate forms between thrush and chronic hyperplastic candidosis exist.

(5) Leukoplakia is virtually unknown in childhood except as part of the uncommon but well-recognized syndromes of mucocutaneous candidosis such as that associated with endocrine disorders, notably hypoparathyroidism. Candidal 'granuloma' is unassociated with endocrine disease but, as pointed out by Lehner (1964), shows much more gross superficial lesions and, in very striking degree, the epithelial proliferation which this infection can cause. *Candida albicans* is unusual in that it appears able directly to attack and invade the oral mucosa causing stomatitis. The main skin pathogens by contrast appear not to have this power. Montes & Wilborn (1968) have shown by electron microscopy that *C. albicans* can attach itself to epithelial cells by means of a thick floccular material and can invade the cell: bacteria by contrast remained in an extracellular position (Fig 3).

Analogies may be drawn between chronic candidosis as a cause of leukoplakia and late syphilis. Both are infective. Both seem to be capable of provoking epithelial proliferation which, beyond a certain point, appears to be irreversible even after the precipitating infection is removed.

Follow-up Studies of Leukoplakia and Oral Cancer

Many studies consist of the purely histological finding of the number of carcinomas found in specimens clinically labelled 'leukoplakia'; Renstrup (1958) and Shafer & Waldron (1961), for instance, showed an incidence of carcinoma of 9% and 17·7% respectively. More informative studies have been carried out by Cooke (1964), for example, who followed 50 patients with leukoplakias for periods of up to ten years and found the incidence of carcinoma to be 12% overall. More recently Einhorn & Wersäll (1967) followed 782 patients with clinical leukoplakia for periods of one to forty-four years, with a mean period of observation of twelve years. This study is important not merely for the very great extent and duration of the survey but for the finding that, while the great majority of the leukoplakias developed in tobacco-users, the incidence of carcinoma in non-smokers with leukoplakia was nearly 8 times greater in a five-year period. Overall, carcinoma developed in 2·4% within ten years and in 4% in twenty years. The incidence of carcinoma in this very extensive study is low in comparison with other series. It may be argued that the clinical diagnosis of leukoplakia was loosely used and conditions such as lichen planus included. On the other hand, since all these patients had been referred to a cancer hospital, it seems possible that most of them were severely affected or had advanced lesions.

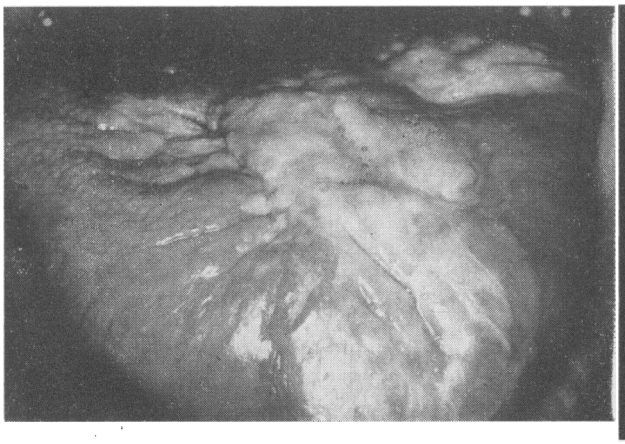

Fig 3 *Candidal leukoplakia. This is a recurrence of the plaque after wide excision and grafting. The patient was not given antimycotic treatment after the operation*

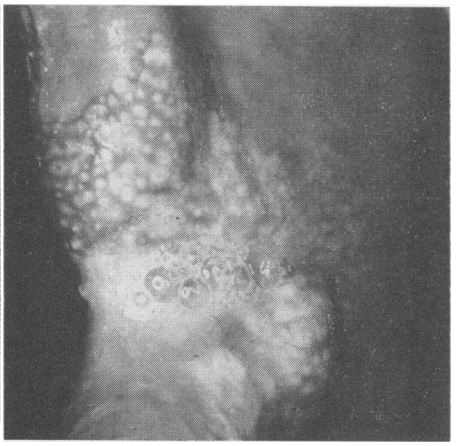

Fig 4 *A speckled lesion of the commissure and buccal mucosa due to chronic candidosis. A small carcinoma has developed within the plaque*

More recently Pindborg *et al.* (1968) followed 214 patients and found malignant transformation in 4·4% in a period of 3·7 years. Even at the lowest of the published figures, this represents an incidence of cancer 50–100 times greater than that in the normal population but the findings of Einhorn & Wersäll (1967) emphasize the important principle that the causes of leukoplakia are not necessarily the same as those causing cancer.

In none of these studies has the relationship of oral candidosis to carcinoma been looked into. There have been virtually no long-term studies of mucocutaneous candidosis in children, but Kugelman *et al.* (1963) reported a patient who first developed candidosis at the age of 4; he had persistent candidosis of the mouth, skin and œsophagus, developed œsophageal carcinoma at the early age of 38 and died from secondary spread of this neoplasm. Jansen *et al.* (1963) reported 15 patients with persistent candidal infection of the lips, one of whom subsequently developed carcinoma.

A retrospective histological study (Cawson 1966) of lesions regarded as leukoplakia on clinical grounds revealed that among 138 specimens, 15 showed the changes of chronic hyperplastic candidosis. Subsequent examination of the records of these patients showed that of 10 who were followed up no fewer than 6 developed carcinoma. In contrast, the cases reported by Cawson & Lehner (1968) were generally much less severe, since a deliberate attempt was made to detect cases of chronic hyperplastic candidosis; these were then treated. In view of the very small number of cases no undue weight is put upon these findings but they are sufficient to suggest that the association between advanced candidal leukoplakia and cancer may be strong (Figs 4, 5 and 6).

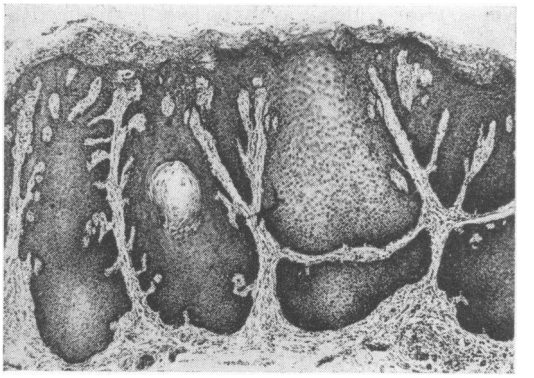

Fig 5 *A section from the lesion in Fig 4 shows early malignant change, thin parakeratotic plaque and extensive superficial inflammatory exudate is just visible. H & E.* × *25*

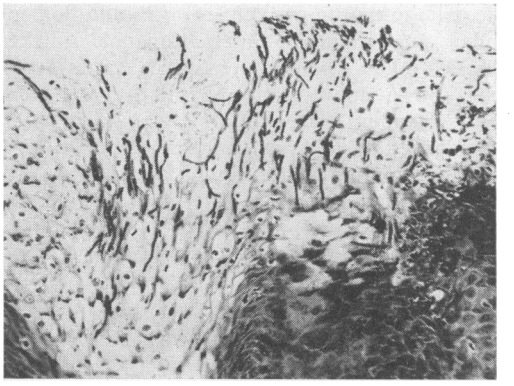

Fig 6 *A higher power view of the same specimen showing hyphæ and parakeratotic plaque with inflammatory exudate at its base. PAS* × *120*

Management and Prognosis

The main problem is whether to excise areas of persistent leukoplakia. Clearly, small lesions (i.e. of about 2 cm across) should be removed entirely. This is a minor operation, well tolerated by the patient and provides an adequate specimen for histological examination. To remove only part of a small lesion for biopsy is pointless. Other indications for excision suggested by Hodson & Crawford (1966) are plaques involving the denture-bearing areas, painful leukoplakias and those affecting the lips or cheek because, it is suggested, of the greater risk of malignant change.

The justification for excision depends first on the acceptance that leukoplakia is a precancerous disease in a high proportion of cases, and secondly that excision will cure the disease, i.e. will not be followed by recurrence of the plaque and will prevent malignant change. These assumptions are open to question. Where a cause cannot be eliminated it seems at least possible that the epithelial abnormality will recur. There is also as yet no clear evidence as to the long-term effectiveness of excision. Einhorn & Wersäll (1967) found that in a period of fifteen years the incidence of carcinoma was twice as high in those cases where excision had been attempted as in those where there had been no surgical intervention. Selection presumably affected these figures and it seems likely that excision was attempted mainly in advanced or dyskeratotic lesions. Even so the figures can hardly be said to favour surgery.

Another factor to be considered is the level of risk of malignant change. If a figure between the extremes of incidence of malignant change reported, i.e. of about 5% in a five-year period, can be accepted then it follows that 95% of leukoplakias will remain benign for such a period. There is also no certain means of detecting those with a high risk until there is histological evidence of dyskeratosis. A conservative approach therefore seems appropriate in most cases. After adequate initial biopsy the lesion should be kept under three-monthly observation and further biopsies taken when any change becomes apparent. The patient must also be told to report back if he becomes aware of any change between attendances. Should malignant change develop, it must be treated immediately and vigorously. Radiotherapy is probably the preferred method today.

Superficial irradiation is also a possible method of treatment of leukoplakias. Excessive epithelial activity can be reduced and some plaques made to disappear in this way. But there is insufficient information as to the ultimate prognosis.

The main facts concerning leukoplakia may be summarized in trying to assess the prognosis of the disease in individual cases as follows:

(1) The incidence of cancer in leukoplakia is probably 50–100 times greater than in the normal mouth.

(2) The great majority of leukoplakias, 90–95%, are benign or will not develop cancer within a five-year period.

(3) The incidence of cancer rises sharply with age.

(4) The 'drainage area' of the oral cavity is the most frequent site of cancer and leukoplakias within this area must be expected to have a higher chance of malignant change.

(5) The carcinogenicity of different etiological factors has not yet been firmly established: the role of smoking is controversial but infective types of leukoplakia, i.e. syphilis or severe candidosis, may be more dangerous.

(6) Disorders of hæmopoiesis should be looked for, especially in women; if present they may affect the prognosis adversely.

(7) The clinical appearance of leukoplakias provides little assistance in assessing the prognosis. All lesions should be biopsied and biopsy should be repeated if there is the slightest doubt as to the progress of the lesion.

(8) There is as yet no convincing evidence that excision of leukoplakias is curative or will prevent malignant change, and in most cases the management should be essentially conservative as long as there is no histological evidence of dyskeratosis.

REFERENCES

Ahlbom H E (1936) *Brit. med. J.* ii, 331
Altman J & Perry H O (1961) *Arch. Derm.* **84**, 179
Andreasen J O & Pindborg J J (1963) *Nord. Med.* **70**, 861
Ashley D J B (1966) *J. Obstet. Gynæc. Brit. Cwlth* **73**, 382
Cawson R A (1965) *Dent. Pract it. dent. Rec.* **15**, 10
(1966) *Oral Surg.* **22**, 582
(1968) *Brit. med. J.* i, 86
Cawson R A & Lehner T (1968) *Brit. J. Derm.* **80**, 9
Cooke B E D (1964) *Ann. roy. Coll. Surg. Engl.* **34**, 370
Einhorn J & Wersäll J (1967) *Cancer (Philad.)* **20**, 2189
Elwood P C, Jacobs A, Pitman R G & Entwistle C C (1964) *Lancet* ii, 716
Hodson J J & Crawford B S (1966) *Brit. J. Surg.* **53**, 321
Jansen G T, Dillaha C J & Honeycutt W M (1963) *Arch. Derm.* **88**, 325
Jepsen A & Winther J E (1965) *Acta odont. scand.* **23**, 239
Keller A Z (1967) *Cancer (Philad.)* **20**, 1015
Kraus F T & Perez-Mesa C (1966) *Cancer (Philad.)* **19**, 26
Kugelman T P, Cripps D J & Harrell E R jr (1963) *Arch. Derm.* **88**, 150
Lehner T (1964) *Brit. dent. J.* **116**, 539
Montes L F & Wilborn W H (1968) *J. Bact.* **96**, 1349
Moore C & Catlin D (1967) *Amer. J. Surg.* **114**, 510
Pindborg J J, Renstrup G, Jølst O & Roed-Petersen B (1968) *J. Amer. dent. Ass.* **76**, 767
Pindborg J J, Renstrup G, Poulsen H E & Silverman S jr (1963) *Acta odont. scand.* **21**, 407
Registrar General (1967) Statistical Review of England and Wales for 1966. HMSO, London
(1968) Statistical Review of England and Wales, Supplement on Cancer for 1962–1964. HMSO, London

Renstrup C (1958) *Acta odont. scand.* **16**, 99
Rosenquist K (1944) *Nord. Med.* **24**, 1891
Savilahti M (1946) *Acta med. scand.* **125**, 40
Shafer W F & Waldron C A (1961) *Surg. Gynec. Obstet.* **112**, 411
Shamma'a M H & Benedict E B (1958) *New Engl. J. Med.* **259**, 378
Silverman S jr & Rozen R D (1968) *J. Amer. dent. Ass.* **76**, 772
Suzman M M (1933) *Arch. intern. Med.* **51**, 1
Warin R P (1960) *Brit. J. Derm.* **72**, 288
Watts J McK (1961) *Postgrad. med. J.* **37**, 523
Weisberger D (1957) *J. Amer. dent. Ass.* **54**, 507
Wynder E L & Fryer J H (1958) *Ann. intern. Med.* **49**, 1106

The Side-effects of Carbamazepine

by J J Gayford MB FDS RCS[1]
and T H Redpath FDS MRCS LRCP[2]
(Department of Oral Medicine, Institute of Dental Surgery, London)

Schindler of the Geigy Laboratories showed in 1953 that carbamazepine had anticonvulsant properties, but it was not until 1962 that Blom saw its potential in the treatment of paroxysmal trigeminal neuralgia. Chemically it is a tricyclic compound consisting of two benzine rings linked by an azepine with a short side chain from the nitrogen atom (Fig 1). It differs only slightly from the anti-depressant imipramine (Fig 2) and amitriptyline, where the azepine ring is replaced by a cycloheptone ring (Fig 3).

Carbamazepine has revolutionized the treatment of paroxysmal trigeminal neuralgia. Although it may not effect a permanent cure in all cases, it is the only effective medical treatment and thus has widened the circle of those able to treat this condition. Therefore the potential dangers of carbamazepine must be stressed.

The initial trial in cases of paroxysmal trigeminal neuralgia (Blom 1962) proved highly successful. This led to further series being reported by Blom (1963), Taylor (1963), Spillane (1964), Vanderfield (1964), Burke & Selby (1965), Campbell *et al.* (1966), Dalessio & Abbott (1966), Rockcliffe & Davies (1966), Walsh & Smith (1966) and Redpath & Gayford (1968). Although most authors are primarily concerned with the effectiveness of the drug, they do mention the side-effects encountered. Some of the more serious side-effects are recorded separately, such as aplastic anæmia (Donaldson & Graham 1965, Dyer *et al.* 1966); jaundice (Ramsey 1967); Stevens-Johnson syndrome (Coombes 1965); and chronic discoid lupus erythematosus (Simpson 1966). These side-effects are summarized in Table 1; they occurred in 309 out of 510 patients taking carbamazepine.

[1]Present address: Royal West Sussex Hospital, Chichester

[2]Present address: Department of Oral Surgery, Guy's Hospital, London

Discussion

It could be argued that the cases presented do not represent a fair sample of patients taking carbamazepine, in that both series of cases and individual reports are included together. As the individual cases not included in the series amount to only 7, this is insignificant and does not grossly distort the frequency of side-effects. Rare side-effects need to be stressed because of their severity. A number of these have been observed by only one author and many have been recorded only in individual cases.

The majority of the side-effects are seen in the nervous system, occurring in 34·5% of patients.

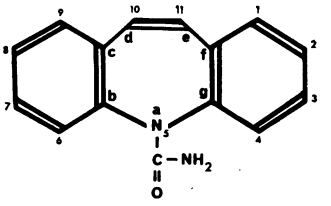

Fig 1 *Carbamazepine*

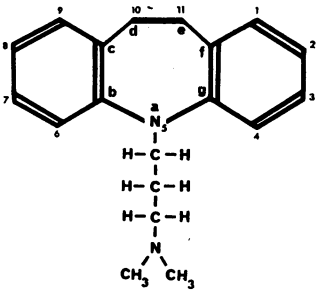

Fig 2 *Imipramine*

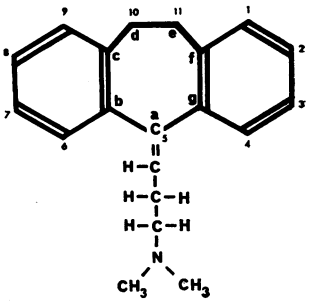

Fig 3 *Amitriptyline*