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REVIEW

Medication induced gingival overgrowth

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A number of idiopathic, pathological and pharmacological reactions may result in an overgrowth of the gingiva. This review concentrates on those overgrowths associated with various pharmacological agents. The pharmacokinetics and side effects of each drug associated with gingival overgrowth are discussed along with the clinical and histological features and treatment. By examining the possible pathogeneses for these overgrowths we propose a unifying hypothesis for the causation based around inhibition of apoptosis and decreased collagenase activity modulated by cytoplasmic calcium.

Keywords: Gingival overgrowth; phenytoin; cyclosporin; calcium channel blockers; apoptosis

Introduction

The medication induced overgrowths occur as a side effect following administration of drugs used mainly for non-dental treatment and thus the overgrowth can not be explained as a variation of the intended pharmacological target of the drug. Many terms have been used to describe the phenomenon of gingival overgrowth. The expressions gingival *hyperplasia* ('abnormal increase in the number of normal cells in a normal arrangement in an organ or tissue, which increases in volume' (McCullough, 1982)) and gingival *hypertrophy* ('enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells' (McCullough, 1982)) have previously been used to describe gingival overgrowths. Overgrowth, on the other hand, is a more general term that better describes the lack of understanding of the pathogenesis of these conditions.

This review will examine all known pharmacological agents (broadly categorisd into three major groups (Table 1)) associated with gingival overgrowth. In addition to outlining the usual actions and common side effects of these drugs, the clinical and histological presentations of the overgrowth will be reviewed along with the possible pathogenesis. An attempt will be made to highlight the unifying feature of apoptosis inhibition in the pathogenesis of these unusual drug reactions.

Table 1 Pharmacologic agents associated with gingival overgrowth

Category	*Examples*
Anticonvulsants	Phenytoin
	Sodium valproate
	Phenobarbital
	Vigabatrin
Immunosuppressants	Cyclosporin
Calcium channel blockers	Nifedipine
	Verapamil
	Diltiazem
	Oxodipine
	Amlodipine
Others	Erythromycin

Anticonvulsants

Phenytoin

Phenytoin (PHT, 5,5-diphenylhydantoin) was first introduced as an antiepileptic drug in 1938 (Merritt and Putman, 1938). It remains a drug of first choice for epilepsy, particularly grand mal, temporal lobe and psychomotor seizures (Penry and Newmark, 1979) and may also be useful in the treatment of some forms of cardiac arrhythmia (Badewitz-Dodd, 1997). PHT, frequently marketed under the name Dilantin®, is usually prescribed, for chronic use as capsules and the dosage is individualised.

Pharmacokinetics

PHT is slowly absorbed from the gastrointestinal tract and shows marked inter-individual variation (Gugler *et al*, 1976). Approximately 90% of the serum PHT is bound to serum proteins (mostly albumin) leaving the remaining 10% free and active (Goldberg, 1980). PHT is known to concentrate in the brain (the target organ) at levels 5 to 10 times that found free in the serum (Houghton *et al*, 1975). The drug is extensively metabolised in the liver by microsomal enzymes and the major metabolite (50–75% of the PHT dose) is 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) (Butler, 1957; Dudley, 1980).

PHT has been proposed to act via stabilisation of neuronal cell membranes and suppression of synaptic trans-

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mission (Pincus *et al*, 1980). Depending on the membrane conditions, drug concentration and timing, it appears that PHT acts by affecting the {Na+K} pump, Ca^{++} transport or the sodium influx at the cellular level (Delgado-Escueta and Horan, 1980; Maclean and MacDonald, 1983).

Systemic side effects

PHT may produce toxic side effects, due to variations in absorption and metabolism. Central nervous system (CNS) effects include ataxia, tremor, nystagmus, diplopia and occasionally psychiatric symptoms. Nausea, vomiting, abdominal pain and constipation are gastrointestinal effects that are often minimised by taking the drug during or after meals. Various dermatological complaints (including hirsutism) are seen as well as some variation in haematological parameters (including rare, fatal haematopoietic complications). With respect to pregnancy, PHT is a Category D drug, and is associated with distinctive birth deformities sometimes called foetal hydantoin syndrome (Badewitz-Dodd, 1997).

Gingival overgrowth

Clinical features Since 1939, gingival overgrowth has been observed in patients taking PHT (Kimball, 1939). This reaction usually begins as a diffuse swelling of the interdental papillae, which enlarge and coalesce, (Angelopoulos, 1975a) leaving a nodular appearance (Seymour, 1993). The reported incidence of gingival overgrowth varies widely from 0 to 100% (Thomason *et al*, 1992). This can be attributed, in part, to variations between observers (medically *vs* dentally trained personnel) and differing indices of overgrowth (Aas, 1963; Inoue and Harrison, 1981; Hassell *et al*, 1984; Drew *et al*, 1987). Although clinically significant overgrowth is estimated to occur in half of all patients taking PHT (Angelopoulos and Goaz, 1972; Hassell, 1983), recent evidence suggests this is an overestimate due to previous studies concentrating on institutionalised or hospital neurology out-patient populations (Hassell *et al*, 1984). Clinically significant overgrowth has been reported in only 13% of epileptic patients in general medical practice (Thomason *et al*, 1992). The incidence and severity of overgrowth is greatest on the labial surfaces of the maxillary and mandibular anterior teeth (Angelopoulos and Goaz, 1972). Some case reports have described overgrowth of edentulous ridges (Dallas, 1963; Dreyer and Thomas, 1978; Poppell and Collins, 1987; Darling *et al*, 1988; McCord *et al*, 1992) and it has been suggested that candidal infection may be involved in the aetiology of some of these cases (Darling *et al*, 1988).

The relationship between age of the patient and gingival overgrowth is uncertain. Some authors have indicated more overgrowth in younger patients (Babcock, 1965; Kapur *et al*, 1973) but most recent studies have not found this association to be statistically significant (Klar, 1973; Angelopoulos, 1975b; Addy *et al*, 1983; Peñarrocha-Diago *et al*, 1990). The connection may be clouded by drug dosage, such that a child may receive an *adult* dose. The relationship between severity of overgrowth and daily dose is also unclear. Some authors relate a positive correlation (Panuska *et al*, 1961; Aas, 1963; Klar, 1973; Addy *et al*, 1983) but most have not detected this association (Angelopoulos and Goaz, 1972; Angelopoulos, 1975a; Hassell *et al*, 1984; Peñarrocha-Diago *et al*, 1990). The relationship is a little stronger for serum PHT levels (Kapur *et al*, 1973; Little *et al*, 1975; Addy *et al*, 1983) but again, not all investigators agree (Hassell *et al*, 1984; Maguire *et al*, 1986; Ball *et al*, 1996) and sub-therapeutic serum levels of PHT have been associated with gingival overgrowth (Reynolds, 1975; Peñarrocha-Diago *et al*, 1990). The situation may be further complicated by other anticonvulsant drugs that may alter the pharmacodynamics of PHT (Maguire *et al*, 1986). The salivary concentration of PHT has also been related to overgrowth severity in a pilot study (Babcock and Nelson, 1964) but this finding has not been replicated (Ciancio *et al*, 1972; Hassell *et al*, 1983; Thomason *et al*, 1992; Ball *et al*, 1996). Although duration of drug intake has been associated with a higher frequency and severity of overgrowth (Panuska *et al*, 1961; Aas, 1963; Klar, 1973) this has been questioned in a more recent study (Peñarrocha-Diago *et al*, 1990).

The role of oral hygiene in the pathogenesis is also complex. Obviously any overgrown tissue will aid the accumulation and prevent the removal of plaque. The association between plaque and gingival overgrowth raises the question as to whether the plaque induces the overgrowth, of if the overgrowth helps in the retention of plaque. Cross-sectional studies are unable to investigate this 'chicken or egg first' problem, but longitudinal studies indicate a role for poor oral hygiene in the severity of overgrowth (Steinbuerg and Steinberg, 1982; Addy *et al*, 1983; Hassell *et al*, 1983). Support for these findings comes from studies of plaque control programmes which have prevented or reduced the severity of overgrowth (Pihlstrom *et al*, 1980; O'Neil and Figures, 1982; Modéer and Dahllöf, 1987).

Histological features The histologic appearance of PHT induced overgrowth has been studied using conventional techniques (Glickman and Lewitus, 1941; Dummett, 1954; Radden, 1954) and more recently using histochemical and electron microscopic methods (Hassell *et al*, 1978; Dahllöf *et al*, 1984). The epithelium shows varying degrees of acanthosis and elongated rete ridges which tend to have divided ends. There also appears to be a decreased innervation density in overgrown gingiva (Luthman *et al*, 1988). The most striking feature of the overgrown gingiva is the connective tissue component which shows proliferation of morphologically normal fibroblasts and an increased amount of collagen. A greater understanding of the lamina propria has been gained through the use of tissue cultures and animal models including cats (Hassell and Page, 1978; Hassell *et al*, 1982), monkeys (Staple *et al*, 1977), ferrets (Hall and Squier, 1982), and rats (Nascimento *et al*, 1985; Morisaki *et al*, 1990)).

In a landmark series of studies Hassell and others (Hassell *et al*, 1976, 1978; Narayanan and Hassell, 1985) examined the fibroblasts derived from the lamina propria of overgrown tissues. From these studies it was suggested that PHT selects for a subpopulation of fibroblasts with increased protein synthesis and collagen production as a key feature of their phenotype (Hassell *et al*, 1976). However, it was concluded that the *lesion* 'represents neither

hypertrophy, hyperplasia nor fibrosis,' it is just an overgrowth of apparently normal cell and fibre composition (Hassell *et al*, 1978). This finding was confirmed with respect to the proportion of collagen types and the extent of hydroxylation which were found to be similar between inflamed normal gingiva and overgrown gingiva (Schneir *et al*, 1978). However, later work has suggested that while the amounts of type V collagen are similar, there is less type I and more type III collagen in enlarged gingiva (Narayanan and Hassell, 1985).

Possible pathogenesis Many theories have been proposed to totally or partially explain the gingival overgrowth induced by PHT. Most are centred on the gingival fibroblast and its interaction with PHT and/or its metabolites (Seymour, 1993). Any hypothesis must first deal with the issue of selectivity. Not all patients taking PHT (even those taking high dosages, with and without inflammation), develop gingival overgrowth. Thus, it has been proposed that the response to PHT (and/or *p*-HPPH) is partly determined genetically (Hassell, 1983; Hassell and Gilbert, 1983). Since gingival fibroblasts comprise a heterogeneous mixture of phenotypically distinct subpopulations, some fibroblasts, sensitive to PHT and its metabolite, may produce large amounts of protein (in particular collagen) while others (low-activity fibroblasts) are only capable of synthesising low levels of protein. It may be that PHT is toxic to low activity fibroblasts, thus permitting growth of the more responsive high activity fibroblasts. In this manner, the relative proportions of fibroblast subpopulations could determine the incidence and severity of overgrowth when PHT is administered. Further support for genetic control of the lesion comes from cell cultures of fibroblasts from twins, grown with PHT. Monozygotic twins show more similar protein synthesis thatn dizygotic twins (Cockey *et al*, 1987). This same group have continued to study twins to show that proliferation rates of gingival fibroblasts are under strong genetic control, at least when grown under optimal growth conditions (Cockey *et al*, 1989).

Some investigators have suggested that the overgrowth may, in part, be due to a lack of collagen breakdown (Goultschin and Shoshan, 1980). Thus, PHT has been shown, in human skin explants and fibroblast cultures, to decrease collagenase activity by 50–60% (Baver *et al*, 1980). Furthermore this decreased breakdown may lead to accumulation of collagen and subsequent development of gingival overgrowth (May *et al*, 1985). Indeed fibroblasts from overgrown tissue may produce a collagenase which is partially or totally inactive (Hassell, 1982). Subsequent work investigating collagen mRNA levels suggests that the increased collagen content in overgrown tissues is due to an increased steady state of collagen mRNA but not a decrease in collagen degradation (Narayanan *et al*, 1988). In contrast, Dahllöf and others have claimed that there is a decrease in the volume of the collagenous matrix due to an increase in the non-collagenous (glycosaminoglycan) component (Dahllöf *et al*, 1984). Increased accumulation of sulphated glycosaminoglycans (in particular dermatan sulfate) has been noted in cultures from overgrown gingiva, due to increased synthesis not decreased degradation (Kantor and Hassell, 1983; Dahllöf *et al*, 1986b; Dahllöf and Hjerpe, 1987; Suresh *et al*, 1992). Furthermore, the extracellular matrix produced by fibroblasts from PHT overgrowth may have special properties which regulate cell attachment and spreading (Modéer *et al*, 1988).

Almost half of the patients taking PHT, also have lowered serum folate levels (Jensen and Olesen, 1968) which may be related to the chemical similarity between the molecules in absorption, transport and metabolism (Benn *et al*, 1971; Krumdieck *et al*, 1978; Berg *et al*. 1983). Folic acid is a coenzyme necessary for DNA synthesis, thus tissues with a high turnover rate could be adversely affected. Plaque leads to greater gingival inflammation in cases of folate deficiency, possibly due to the effect on the high turnover sulcular epithelium (Dreizen *et al*, 1970). Folate supplementation in non-PHT treated subjects has been shown to reduce gingival inflammation (Vogel *et al*, 1976; Vogel and Deasy, 1978) and there are some reports of overgrowth reduction (resolution) following folic acid supplementation both systemically (Inoue and Harrison, 1981) and topically (Drew *et al*, 1987). Unfortunately, this effect has not been shown consistently (Mallek and Nakamoto, 1981; Addy *et al*, 1983; Williams *et al*, 1987) or has resulted in only minor improvements (Poppell *et al*, 1991).

Long term use of PHT has been associated with a degree of immunosuppression (Sorrell *et al*, 1971). Therefore a link between gingival overgrowth and a decrease in salivary IgA via a proliferative response to the increased inflammation has been proposed (Aarli, 1976). While this immunosuppression may have a protective role against periodontal diseases in patients taking PHT (Seymour *et al*, 1985), other anticonvulsants such as carbamazepine (Tegretol®, Teril®) are known to cause immunosuppression (Marcoli *et al*, 1985) but do not appear to be associated with gingival overgrowth.

While T lymphocytes have been identified in biopsies from clinically uninflamed PHT overgrowth (Dahllöf *et al*, 1986a) this may reflect the effect of PHT on various effector molecules rather than a cellular immune response *per se*. In culture, PHT and *p*-HPPH induce the release of factors from monocytes which in turn activate quiescent gingival fibroblasts to synthesise DNA (Modéer *et al*, 1989a). For example, monocytes treated with PHT show an increased expression of the gene for the B chain of platelet-derived growth factor (PDGF), an important cytokine for connective tissue growth (Dill *et al*, 1993). In addition, PHT may induce interleukin 1 (IL-1) activity, and potentiates lipopolysaccharide (LPS) induced IL-1 production in subpopulations of monocytes (Modéer *et al*, 1989b). Thus inflammatory mediators may act as cofactors for inducing gingival overgrowth. For example, PHT overgrowth fibroblasts challenged with IL-1 or tumour necrosis factor alpha (TNFα) show an up-regulation of prostaglandin (PGE_2) synthesis (Modéer *et al*, 1992b) which is due to both increased phospholipase A_2 activity and cyclooxygenase activity (Modéer *et al*, 1992a). Furthermore, IL-1 reduces the expression of αI(I) procollagen mRNA and PHT reduces αI(I) procollagen gene expression (Modéer *et al*, 1996). These findings corroborate earlier findings, that PHT reduces total protein and type I collagen synthesis by fibroblasts (Salo *et al*, 1990). IL-1β has also been reported to regulate hyaluronic acid (part of the extracellular ground

substance) synthesis by gingival fibroblasts (Bartold, 1988) which correlates well with the previously reported increased amount of glycosaminoglycans present in PHT induced overgrowth (Dahllöf *et al*, 1986b). On the other hand, others have been unable to show that PHT or its major metabolite, have any effect on the way fibroblasts react to plaque irrespective of their source (normal or overgrown) (Smith and Hinrichs, 1987).

The role of growth factors in the pathogenesis of gingival overgrowth is also likely to be important. Based on a study of two patients, PHT treatment was found to down regulate epidermal growth factor (EGF) receptor metabolism in responding patients (and a corresponding up regulation in non-responders) (Modéer *et al*, 1990). A recent *in vitro* study has shown a six-fold increase in testosterone formation in the presence of EGF and PHT and a corresponding 2.5-fold increase in 5α-dihydrotestosterone (DHT), the biologically active metabolite that stimualtes matrix formation in connective tissue (Soory and Kasasa, 1997).

Transforming growth factor beta (TGFβ) and basic fibroblast growth factor (bFGF) have also been implicated with tissue overgrowth. Overgrown gingival connective tissue has been shown to have a greater number of cells positive for TGFβ and bFGF and their respective receptors. Heparan sulphate glycosaminoglycans, which interact with numerous growth factors have also been identified, in abundance in medication induced gingival overgrowth (Saito *et al*, 1996).

Zhou and others have proposed that reactive metabolites of PHT cause cellular injury which leads to gingival overgrowth. To support this theory, they have described microsomes from the gingiva of patients taking PHT which show significant PHT hydroxylase activity (Zhou *et al*, 1996), but there appears to be little evidence of cellular injury. Nor has the proposal that decreased adrenocorticotropin hormone (ACTH) production leads to increased somatotrophic hormone, promoting fibroblast proliferation received much support (Seymour and Heasman, 1992).

As mentioned above, the therapeutic effects of PHT involve the stabilisation of neuronal cell membranes via sodium, potassium and calcium (Ca^{++}) fluxes. PHT decreases the influx of calcium across the cell membrane by decreasing the membrane's permeability and blocking intracellular uptake of Ca^{++} (Pincus, 1972). Ca^{++} plays a very important role in cell secretion, in addition both EGF and PHT cause an increase in intracellular Ca^{++} in normal gingival fibroblasts but in combination this effect does not occur; similarly fibroblasts from a patient receiving PHT did not respond to EGF (Brunius and Modéer, 1989). Later work by the same group showed that PHT causes a transient increase in the cytoplasmic free Ca^{++} ion concentration in responding gingival fibroblasts. This was in contrast to non-responding gingival fibroblasts that showed no change in Ca^{++} ion concentration. The effect was shown to be dependent on the extracellular Ca^{++} concentration as both fibroblast types showed increased intracellular Ca^{++} concentrations in response to PHT when the cells were serum starved (Modéer *et al*, 1991).

From the above it is apparent that the exact pathogenesis of PHT induced gingival overgrowth is uncertain and may involve a number of differing causalities which result in similar molecular level changes that induce gingival overgrowth.

Treatment Treatment of PHT induced overgrowth has centred on the excision of excess tissue (gingivectomy) by conventional methods and more recently the use of CO_2 lasers (Pick *et al*, 1985; Hylton, 1986; Roed-Peterson, 1993). Submission of tissue for histopathological examination may be prudent following a case report of a fatal squamous cell carcinoma arising in PHT gingival overgrowth (McLoughlin *et al*, 1995). Substitution of PHT with a different antiepileptic drug has long been advocated (Aas, 1963) and is becoming increasingly feasible as new generation drugs become available (Somerville, 1995). Reduction of gingival overgrowth after withdrawal of PHT has been reported (Brunsvold *et al*, 1985) and complete regression, after 6 months has been described in a group of 10 children (Dahllöf *et al*, 1991). Another case report has detailed a significant improvement in gingival overgrowth in a patient also receiving isotretinoin (Roaccutane®) for the treatment of acne (Norris and Cunliffe, 1987). However, the significant adverse effects associated with isotretinoin, would not warrant its long term use in the treatment or prevention of PHT induced overgrowth. Further investigation of the possible mechanism of action via cAMP effecting fibroblast proliferation and collagen formation has been recommended (Seymour, 1993).

Although there are conflicting results regarding the use of folic acid in the treatment/prevention of PHT induced overgrowth, folate enhancement may lead to 'significantly less recurrence of gingival overgrowth ($P \leq 0.05$)' following gingivectomy. However the mean difference between treatment groups was only 6–7% and was not of clinical significance (Poppell *et al*, 1991).

Sodium valproate

Two cases of gingival overgrowth following sodium valproate therapy have been reported. The first involved a 15-month-old child (Syrjanen and Syrjanen, 1979) and the second a 15-year-old child (Behari, 1991). In the latter case, gingival overgrowth was noticed 18 months after starting the drug (600 mg day^{-1}) and regressed within 3 months of stopping the therapy (this individual had never received PHT). The histology has been described for one case as oedematous connective tissue with a dense inflammatory cell infiltrate consisting mainly of mast cells which the authors suggested may be involved in the pathogenesis. These reports are in contrast to others (Seymour *et al*, 1985) who reported no cases of overgrowth in a study of adult patients taking sodium valproate. These reports may represent idiosyncratic hypersensitivities rather than variants of the PHT-like overgrowth.

Phenobarbital

Cases of phenobarbital (Donnatal®, Phenbo®) induced gingival overgrowth have been vague and without strict drug histories (Panuska *et al*, 1961). However a recent report of two cases of monotherapy with phenobarbital is much more precise (Gregoriou *et al*, 1996). Both cases of gingival overgrowth were in profoundly mentally retarded teenage males who had received phenobarbital for most of

their lives. The gingivae were uniformly enlarged without lobulation of the interdental papillae and the overgrowth was more severe in the posterior regions compared to the anterior which is in contrast to most other medication induced overgrowths. Histologically the tissue was predominantly fibrous, myxoid and fibromyxoid with varying degrees of epithelial proliferation, acanthosis, elongated rete pegs and acute and chronic inflammation. The clinical and histological appearance is more like that of familial forms of gingival fibromatosis, and although neither case had positive histories for this condition it can not be ruled out that the gingival signs were part of a syndrome with the phenobarbital just a common thread without being causal. Both cases responded well to surgical excision and good oral hygiene appeared to prevent recurrence at 6 months.

Vigabatrin

Vigabatrin (Sabril®) is a relatively new anticonvulsant drug, which acts as a selective, irreversible inhibitor of the acid transaminase of gamma-aminobuttyric acid (GABA) which is the primary inhibitory neurotransmitter in the brain. Most side effects are related to CNS effects. However, weight gain and oedema have also been reported (Badewitz-Dodd, 1997). Recently a single case report was published of gingival overgrowth attributed to vigabatrin therapy. The overgrowth was first noted 2 months after beginning vigabratin. Histological examination, revealed a widened parakeratinised stratified squamous epithelium with elongated rete pegs, and moderately dense foci of chronic inflammatory cells in the connective tissue. The overgrowth was resistant to conservative periodontal treatment, and recurrence of the lesion was reported even after gingivectomy (Katz *et al*, 1997). There appear to be no other reports of this form of overgrowth, so it is possible that this reaction was an idiosyncratic hypersensitivity.

Immunosuppressants

Cyclosporin

Cyclosporin (Cs) is a lipophilic cyclic endecapeptide (M.W. = 1202.635 (Badewitz-Dodd, 1997)) with unsurpassed immunosuppressive activity (Wenger, 1983). The molecule was isolated as an antifungal, from soil samples containing *Tolypocladium inflatum* GAMS and *Cylindrocarpon lucidum* BOOTH (fungi imperfecti) (Dreyfuss *et al*, 1976). It is a weak antimicrobial, but a good immunosuppressant (Borel *et al*, 1976) due to its selective action on T lymphocytes (Britton and Palacios, 1982). Cs is almost universally used in the prevention of organ transplant rejection. Since its initial use in renal allograft recipients (Calne *et al*, 1978) it has been effectively used alone (Calne *et al*, 1979) and in combination with other immunosuppressant drugs (Starzl *et al*, 1982). It has also been used for hepatic (Starzl *et al*, 1981), pancreatic (McMaster *et al*, 1981), bone marrow (Powles *et al*, 1980), and cardiac (Hardesty *et al*, 1983) transplants, and a number of autoimmune conditions such as rheumatoid arthritis (Seymour and Jacobs, 1992).

Pharmacokinetics

Cs was developed by the Sandoz pharmaceutical company (now Novartis) and first registered in 1983 (Borel, 1993), it is marketed worldwide as Sandimmun® or Sandimmune®. (Approval has recently been gained for a new microemulsion of Cs (Neoral®) designed to give better absorption (Anonymous, 1995). It is expected to supersede the old formulation.)

The molecule's tertiary structure results in the formation of the hydrophilic immunosuppressive binding site and all substitutions to the ring are less immunosuppressive (Wenger, 1988). Cs is variably absorbed in the gut; peak plasma concentration is reached 3–4 h after dosage and it has a variable serum half-life (17–40 h) (Beveridge *et al*, 1981). Bioavailability and time to peak serum concentration varies greatly between individuals (Ptachcinski *et al*, 1986). The drug is mostly bound to both cells (erythrocytes 50%, lymphocytes 5%) and lipoproteins (40%, (Rödl and Khoshsorur, 1990)), with approximately 5% free in the plasma (Hassell and Hefti, 1991). Total blood concentrations may vary according to the assay used, however high-performance liquid chromatography (HPLC) is regarded as the reference method (Kahan *et al*, 1990) and the median therapeutic concentration is reported to be 135 $\mu g\, l^{-1}$ (Bowers, 1990).

Cs accumulates (in decreasing order) in the pancreas, spleen, liver, fat, kidney, lung, bone marrow, heart, and whole blood (Atkinson *et al*, 1982; Kahan *et al*, 1983; Reid *et al*, 1983; Lensmeyer *et al*, 1991). The total amount of drug per weight in tissue can be up to 20-fold greater than in plasma and varies considerably between organs and individuals (Akagi *et al*, 1991). Cs is metabolised in the liver microsomes; in particular by members of the cytochrome P-450-IIIA gene family (Combalbert *et al*, 1989) which is also responsible for the metabolism of hydrophobic compounds such as nifedipine (Yatscoff *et al*, 1991). Another cytochrome, P-450 $hPCN_3$, has also been shown to be involved (Aoyama *et al*, 1989). These monooxygenase enzyme systems produce at least 14 metabolites (Mourer, 1985; Shaw, 1989; Copeland *et al*, 1990) which are not as immunosuppressive as the parent compound. Cs is excreted mainly via the bile, through the faeces (Venkataramanan *et al*, 1985).

Initial *in vitro* and *in vivo* experiments indicated that Cs interferes with T cell activation of B lymphocytes but immunoglobulin secretion which was T cell independent was unaffected (Borel *et al*, 1976). Cs appears to selectively inhibit T helper cells and to have little or no effect on T suppressor cells (Gao *et al*, 1988; Jenkins *et al*, 1988;Thomson and Webster, 1988). Cs acts selectively by inhibiting the T cell response at a number of levels. It inhibits macrophage activation and IL-1 production; and prevents production of IL-1 receptors on T helper cells (Thomson *et al*, 1983). It also inhibits IL-2 synthesis at low concentrations, which limits clonal amplification of cytotoxic T cells; and inhibits their ability to respond to IL-2 (possibly by blocking cell surface receptors) (Hess and Colombani, 1987). Cs can inhibit some *in vitro* B cell responses to T cell independent (type 2) antigens (O'Garra *et al*, 1986) but the clinical significance of this is unclear.

The selectivity of Cs for T cells is enigmatic, as it is

known that Cs passively diffuses through cell membranes of many cells (including all peripheral blood lymphocytes and erythrocytes) and is concentrated in the cytoplasm and nucleus (Hassell and Hefti, 1991). Cs is known to bind both cyclophilin (Handschuhmacher *et al*, 1984) and calmodulin (Colombani *et al*, 1985), but these proteins are found in many cells.

Calmodulin is an intracellular Ca^{++} binding protein which, in the presence of Ca^{++}, binds and activates many important enzymes (eg, adenyl cyclase, guanyl cyclase, phosphodiesterase) (Cheung, 1982). Cyclophylin is a peptidyl-prolyl *cis-trans* isomerase (PPI-ase) (Fischer *et al*, 1989; Takahashi *et al*, 1989) which affects the folding of proteins by catalysing the isomerization of proline (Fairley, 1990). Cyclophilin is a member of a family of PPI-ases called immunophilins that also include the many FK506 binding proteins (FKBPs). The immunophilins act independently of any immunosuppressive effects. The cellular role of the enzymatic activity is poorly understood but there is little doubt that ligand-immunophilin complexes bind to and inhibit calcineurin (a Ca^{++}/calmodulin dependent protein phosphatase) (Marks, 1996).

Effects on non-lymphoid cells have been described. These are mainly inhibitory in action such as growth inhibition of keratinocytes grown in cell culture (in contrast to the stimulating effect on hair follicle keratinocytes) (Nickoloff *et al*, 1988), dermal fibroblasts (Nickoloff *et al*, 1988), and several other epithelial cell types and this effect appears unrelated to the immunosuppressive effect, as other Cs analogues are also cytostatic (Kanitakis and Thivolet, 1990). Rat osteoblasts in culture also show an antiproliferative effect in response to Cs (McCauley *et al*, 1992) and it also inhibits bone resorption by chick osteoclasts (Chowdhury *et al*, 1991). Early work suggested that Cs had no effect on PMN function *in vitro* (Janco and English, 1983). However, impaired neutrophil mobilisation has been shown in *in vivo* models (Ormod *et al*, 1990). Cs has also been shown to inhibit mast cell activation (as measured by histamine release), but only in the presence of extracellular Ca^{++} (Dráberová, 1990).

Side effects

Cs has been commonly associated with a number of unwanted side effects (see Table 2). Assessment of these reactions is complicated by the nature of the disease affecting the patient (ie, conditions existing prior to transplant), concomitant medications and discerning those reactions due to Cs *per se*, rather than immunosuppression. In addition, initial use of the drug involved higher doses of Cs than now currently used, thus some toxic effects are no longer seen. Nephrotoxicity is a common and problematic complication of Cs therapy (Calne *et al*, 1979) of which a number of different forms have been distinguished (Mihatsch *et al*, 1988). Clinically it may be difficult to distinguish between nephrotoxicity and organ rejection in renal transplants. The pathogenesis of the condition is uncertain but it is suggested that Cs alters the balance between prostacyclin and thromboxane A_2 (vascular modulators) in the renal cortex (Coffman *et al*, 1987).

Hypertension has been reported in renal (Hamilton *et al*, 1982; The Canadian Multicentre Transplant Study Group, 1983; Kahan *et al*, 1987), cardiac (Kirk *et al*, 1989), and bone marrow (June *et al*, 1986) transplant recipients and may be associated with nephrotoxicity or renal vasoconstriction (probably due to an effect on other vasodilator systems) (Porter *et al*, 1990). Hepatotoxicity (Calne *et al*, 1981) is often seen early in association with high doses of Cs (Kahan *et al*, 1985). Neurotoxicity is usually manifest as tremors and paraesthesia. However, more serious CNS effects including blindness, seizures and coma have been reported (De Goen *et al*, 1987). Other side effects include diabetes, altered bone metabolism (Rush, 1991) and hirsutism (Laupacis *et al*, 1982). Oral side effects include lingual fungiform papillae hypertrophy (LFPH) (Menni *et al*, 1991; Silverberg *et al*, 1996) and gingival overgrowth (Starzl *et al*, 1980; Rateitschak-Plüss *et al*, 1983).

Table 2 Common side effects of cyclosporin

Selected side effects of cyclosporin	*Reference*
Nephrotoxicity	Calne *et al*, 1979
Hypertension	The Canadian Multicentre Transplant Study Group, 1983
Hepatotoxicity	Calne *et al*, 1981
Biliary calculus disease	Lorber *et al*, 1987
Neurotoxicity	De Goen *et al*, 1987
Diabetes	Rush, 1991
Altered bone metabolism	Rush, 1991
Hirsutism	Laupacis *et al*, 1982
Lingual fungiform papillae hypertrophy (LFPH)	Menni *et al*, 1991
Gingival overgrowth	Starzl *et al*, 1980; Rateitschak-Plüss *et al*, 1983

Gingival overgrowth

Clinical features Gingival overgrowth was first noticed with Cs therapy in the initial human trials of the drug (Starzl *et al*, 1980; Calne *et al*, 1981) but was first described in the dental literature in 1983 by both Rateitschak-Plüss and coworkers in Switzerland (Rateitschak-Plüss *et al*, 1983), and Wysocki and colleagues in Canada (Wysocki *et al*, 1983). The phenomenon was also confirmed in both dog and cat models (Ryffel *et al*, 1983). Cs gingival overgrowth is clinically indistinguishable from that associated with PHT. The overgrowth, which normally begins at the interdental papillae, is more common in the anterior segments of the mouth and on labial surfaces of the teeth (Daley and Wysocki, 1984; Tyldesley and Rotter, 1984). A recent study of 194 organ transplant recipients confirmed this predilection for buccal surfaces and also noted that overgrowth associated with the canine teeth was significantly greater than that around the central incisors (Thomason *et al*, 1996a). Overgrowth is usually confined to the attached gingiva but may extend coronally and interfere with the occlusion, mastication and speech. There are few epidemiological reports for this condition and the reported incidence ranges from 13% (Wondimu *et al*, 1993) to 81% (Friskopp and Klintman, 1986). The reasons for this range are many: the nature of the disease being treated, the age of the patient, the method of assessment, the dosage and duration of Cs and additional medications may all play a part (Seymour and Jacobs, 1992). Cs overgrowth does not

appear to have been described in edentulous patients (Friskopp and Klintman, 1986) or edentulous spaces (Somacarrera *et al*, 1994). A case of severe overgrowth involving all of the edentulous maxillary masticatory mucosa has been described, although this patient was receiving both Cs and nicardipine (a Ca^{++} channel blocker) (Thomason *et al*, 1994). The severity of overgrowth may range from none to marked excess gingiva covering at least three-quarters of the tooth (affecting 17% of patients (Daley *et al*, 1986)).

While some patients are more susceptible to gingival overgrowth, the relationship to drug dosage and serum concentration is contentious and complicated by problems with methodology and an earlier lack of understanding of the temperature dependent blood partitioning of the drug (Akagi *et al*, 1991). Plasma and salivary concentrations, plaque and gingival indices have all been correlated to the severity of overgrowth (McGaw *et al*, 1987) but there was wide individual variation and the authors point out possible problems with the radioimmunoassay used. Whole saliva concentrations of Cs are higher in patients taking the liquid form of the drug compared to the capsule form (Modéer *et al*, 1992c), but salivary concentrations are poorly correlated with trough blood levels. A recent clinical trial with multiple sclerosis patients (which avoids some of the confounding factors associated with organ transplant patients) showed an odds ratio of 17.3 for the association between Cs blood trough level ≥ 400 ng ml^{-1} and the incidence of overgrowth (Hefti *et al*, 1994). A correlation with dosage had already been suggested (Adams and Davies, 1984; Rostock *et al*, 1986) but given the variable absorption of the drug, blood levels would seem to be a more logical methodology. The same study, because it used a randomised placebo controlled method (The Multiple Sclerosis Study Group, 1990), had a better spread of age groups compared to many organ transplant studies, and found that patients with gingival overgrowth were significantly younger than those without overgrowth. This finding was in agreement with others (Daley *et al*, 1986) and was further confirmed by the Newcastle group (Thomason *et al*, 1995).

The role of plaque in Cs induced gingival overgrowth is also uncertain. It has been shown that oral Cs can concentrate locally in plaque (Niimi *et al*, 1990). However, an intensive course of plaque control and removal of gingival irritants has been shown to have little effect on the development of gingival overgrowth (Seymour and Smith, 1991). The distribution of plaque and gingivitis was unable to fully explain the distribution of gingival overgrowth, suggesting a possible role for local anatomical features (fraenal attachments, tongue) in controlling the development of gingival overgrowth (Thomason *et al*, 1996a).

Gingival overgrowth develops within 3 months of taking Cs (Seymour *et al*, 1987). However others have reported overgrowth only in patients taking Cs for more than 3 months (Wysocki *et al*, 1983). The duration of Cs therapy is also reported to increase the chance of gingival overgrowth (odds ratio = 1.38, 95% Confidence Interval = 1.00–1.90) (Thomason *et al*, 1995). A recent report in children indicated a 100% prevalence of overgrowth in subjects taking Cs for longer than 3 months (Karpinia *et al*, 1996).

Histological features Histologically, Cs gingival overgrowth is very similar to PHT induced overgrowth, being described as a 'fibrous hyperplasia' (Wysocki *et al*, 1983). The lesion is primarily connective tissue with a parakeratinised epithelium of variable thickness, and deeply penetrating epithelial ridges. The connective tissue is highly vascularised and there are focal accumulations of inflammatory cells (Rateitschak-Plüss *et al*, 1983). The overgrowth has been attributed to a loss of growth control resulting in a fibrous hyperplasia and also an accumulation of matrix components (McGaw and Porter, 1988). An abundance of amorphous ground substance has been described within the gingival connective tissue when compared to fibrous material (Mariani *et al*, 1993). The fibroblasts of Cs overgrowth show ultrastructural characteristics of protein synthesis and secretion, and resemble myofibroblasts (Yamasaki *et al*. 1987). Inflammatory infiltrates vary, and are dominated by plasma cells suggestive of a neoplastic process; however, no such abnormalities are seen (Deliliers *et al*, 1986). Although rare cases of plasmacytoma (Pan *et al*, 1995), Kaposi's sarcoma (Bencini *et al*, 1988; Qunibi *et al*, 1988), and squamous cell carcinoma (Varga and Tyldesley, 1991) have been reported in Cs induced overgrowth, these most likely result from the immunosuppressive effects of the drug rather than side effects of the drug itself.

The enlargement (at least when used in the treatment of Behcet's disease) may not be due to increased tissue collagen but rather an increased epithelium combined with an accumulation of noncollagenous extracellular matrix (Pisanty *et al*, 1988). Furthermore the gingival overgrowth is associated with an epithelial response and presumptive Cs crystals deposited within the epithelium have been noted (Pisanty *et al*, 1990). Part of the epithelial proliferation has been attributed to the epithelial prickle cells (Belazi *et al*, 1993).

Possible pathogenesis The pathogenesis of gingival overgrowth due to Cs remains enigmatic. However it is most likely to be associated with both direct and indirect effects of Cs on fibroblasts and the extracellular components of the lamina propria. Many studies have examined the effect of Cs on tissue cultures of gingival fibroblasts. Cs can stimulate DNA synthesis and proliferation of gingival fibroblasts and this ability is retained even in the presence of LPS that would normally inhibit these cells, thus suggesting a role for plaque in the pathogenesis of this gingival overgrowth (Bartold, 1989). However, it could not be shown that Cs had any significant effect on protein or proteoglycan production. The effect was more marked in fibroblasts from Cs overgrown gingiva but was also seen in human foreskin fibroblasts. This response has been further studied by others who have shown similar results in normal gingival fibroblasts and fibroblasts from Cs overgrowth (Barber *et al*, 1992).

In situ hybridisation and radioimmune assay (RIA) have shown an increase in IL-6 and IL-6 mRNA (Williamson *et al*, 1994) in overgrown gingiva which is anomalous when compared to the previous understanding that IL-6 downregulated fibroblast proliferation (by inhibiting stimulatory cytokines) (Bartold and Haynes, 1991). Recently it has

been shown that *in vivo* Cs therapy reduces gingival prostacyclin (PGI_2) synthesis. PGI_2 has an antiproliferative effect via increasing cAMP thus gingival overgrowth may result from inhibition of this antiproliferative effect (Nell *et al*, 1996). Cs does not by itself induce prostaglandin E_2 (PGE_2) formation in gingival fibroblasts but potentiates the response to TNFα in a way that is dependent on their concentrations (Wondimu and Modéer, 1997) which the authors suggest may be important in the pathogenesis of the overgrowth.

The variability of gingival fibroblast responses to Cs has also been investigated. A study of 14 gingival fibroblast strains from healthy individuals demonstrated variation in basal collagenase activity in response to Cs. Most strains showed significantly reduced collagenolytic activity but some subpopulations were unaffected and some showed enhanced activity (Tipton *et al*, 1991). This up-regulation of collagenolysis in response to Cs was shown (in two strains) to be due to effects on both collagenase and TIMP (tissue inhibitor of metalloproteinase) levels. Collagenase levels where unchanged or decreased in response to Cs and TIMP levels were either increased or unchanged.

In normal gingival fibroblasts, Cs can directly stimulate collagen synthesis in culture through an increase in type I procollagen mRNA synthesis (Schincaglia *et al*, 1992). Recent work has been unable to show a direct proliferative effect on fibroblasts grown in monolayer or three-dimensional collagen gels but interestingly has failed to show any effect on matrix synthesis either (James *et al*, 1995). This partly agrees with earlier work (Stabellini *et al*, 1991) that showed Cs treated normal gingival fibroblasts in culture showed decreased intra- and extracellular GAGs in both short and long term incubations with Cs (Willershausen-Zönnchen *et al*, 1992).

As for PHT, growth factors may be involved in Cs associated gingival overgrowth. Using a variant of the polymerase chain reaction, up-regulation by Cs of macrophage PDGF-B gene expression *in vitro* has been demonstrated (Plemons *et al*, 1996). *In vivo* the PDGF-B producing cells in overgrown gingiva appear to be macrophages, distributed in a non-uniform manner throughout the tissue (Nares *et al*, 1996).

Fiskopp and coworkers have identified T cells and monocytes adjacent to the junctional epithelium (Friskopp *et al*, 1986) and this was confirmed by others (Savage *et al*, 1987) who characterised the lymphocytes as T helper cells and also described Langerhans cells in the lesion. A recent immunohistochemical study of 30 cases of Cs overgrowth found a greater CD4/CD8 ratio compared to healthy controls (1.82 *vs* 1.35). In addition $CD45^+$, $CD4^+$ and $CD68^+$ cells (markers for pan leucocytes, T helper/inducer cells and monocyte/macrophages respectively) increased with the degree of gingival overgrowth (O'Valle *et al*, 1994). This suggests a possible immunoregulatory mechanism in the pathogenesis of gingival overgrowth.

A marked plasma cell infiltrate, which in the presence of good oral hygiene may be due to individual hypersensitivity to Cs, has been proposed (Deliliers *et al*, 1986; Mariani *et al*, 1993). Thus the Cs overgrowth may be a local manifestation of a wider general phenomenon. Indeed,a dysmorphic syndrome involving coarsening of facial features (thickened nares, lips and ears, puffiness of cheeks, prominent supraorbital ridges and mandibular prognathism) in children has been attributed to Cs therapy (Reznik *et al*, 1987).

In a cohort of 172 transplant recipients, HLA B37 positive patients have been found to be significantly more likely to show severe gingival overgrowth (Thomason *et al*, 1996b). Through tissue typing the issue of susceptibility has been examined and shown that patients taking Cs who do not develop overgrowth are more likely to be HLA DR1 positive, suggesting an immuno-genetic protection (Cebeci *et al*, 1996a).

Animal models for Cs induced gingival overgrowth have been difficult to establish. One group has shown that Cs induces overgrowth in 42% of beagle dogs. They were able to correlate the incidence and severity of overgrowth to the blood concentration of the drug although the concentrations were sometimes very high (25% of the dogs died from infections) (Seibel *et al*, 1989). A rat model has also been developed which indicated that overgrowth may not be plaque-dependent (Kitamura *et al*, 1990) and a different rat model has indicated a dose-dependent effect on severity of overgrowth (Fu *et al*, 1995). Recent histological examinations of Cs treated rats showing the formation of granulation tissue and irregular surfaces on the dental alveoli has lead to the hypothesis that the periodontium is a target tissue for Cs, but whether these results are related to overgrowth in humans is unclear (Nieh *et al*, 1996).

Treatment Treatment is often confined to gingivectomy and occasionally reduction in dose of Cs (Daly, 1992). However, the nature of organ transplants (with the possible exception of bone marrow transplant) often means that alternative therapy or dose reduction is not available. Some patients can use more conventional immunosuppressives such as steroids and azothioprine but survival rates are not as good. New immunosuppressives such as FK506 (tacrolimus, Prograf®:- Fujisawa, Japan), Rapamycin, RS 61443, Mycophenolate mofetil (MMF), may offer some hope, as to date these have not been reported in association with gingival overgrowth (Asantekorang *et al*, 1996; Jain and Fung, 1996). Recent case reports indicate 'improvement' in gingival overgrowth when patients where changed to tacrolimus therapy (Budde *et al*, 1996).

Chlorhexidine (0.12%) mouthrinse has been reported to reverse recurrent overgrowth following gingivectomy (Ciancio *et al*, 1991) and a study in rats indicates it may have a role in limiting but not preventing gingival overgrowth (Pilatti and Sampaio, 1997). As mentioned earlier, a programme of intense oral hygiene failed to prevent the onset of Cs induced gingival overgrowth (Seymour *et al*, 1987) and nor was it particularly effective at reducing existing overgrowth (Friskopp and Klintman, 1986), but was (as expected) of some benefit for general periodontal health. Gingival bleeding and dihydropyridine medication both increase the relative risk of gingival overgrowth in patients taking Cs (Pernu *et al*, 1992, 1993). The use of combined conventional gingivectomy and CO_2 laser has recently been advocated in the treatment of this type of dual drug overgrowth, due to the decreased surgical time and rapid postoperative haemostasis (Darbar *et al*, 1997).

A number of reports have indicated that a short course of azithromycin (an azalide antibiotic) dramatically improved gingival overgrowth (some patients were also receiving Ca^{++} channel blockers) (Wahlstrom *et al*, 1995; Boran *et al*, 1996; Puig *et al*, 1997). This effect may be independent of the antimicrobial action, as similar effects have not been seen with metronidazole (Aufricht *et al*, 1997). This effect is unexplained as azithromycin does not appear to interact with the absorption or metabolism of Cs (Gómez *et al*, 1996; Nahata, 1996).

Recently a significant inverse correlation between periodontal status and duration of therapy has been described and thus the negative effects of the drug could spontaneously decrease over time (Montebugnoli *et al*, 1996). However, this remains to be established clinically.

Calcium channel blockers (CCBs)

Despite the discovery of these compounds in the 1950/1960s, their widespread therapeutic use only began in the 1980s (Fleckenstein, 1983). These are a group of drugs which have different chemical structures and actions, but all are thought to be agonists of the slow Ca^{++} channel into cells (see Table 3). Their different chemical structures would tend to indicate that the effect is not due to a specific receptor, and different CCBs may act in differing manners (Braunwald, 1982). The 1,4-dihydropyridines are generally uncharged at physiologic pH although some are protonated (eg, nicardipine, amlodipine) (Spedding *et al*, 1990).

The CCBs are sometimes classified according to their pharmacological properties (Vanhoutte, 1987): thus Class I drugs (eg, verapamil) mainly affect the heart and have a strong negative inotropic (ie. decrease the contractile force) and chronotropic (decrease the rate of contraction) effect. The Class II drugs (eg. dihydropyridines) have their greatest effect on blood vessels, causing peripheral and coronary vasodilation. Class III drugs (eg, diltiazem) have minimal or slight inotropic effects by acting preferentially on coronary arteries.

CCBs are used for the treatment of many cardiovascular disorders including: vasospastic anginas (Antman *et al*, 1980), stable angina (Stone *et al*, 1982), supraventricular arrhythmias (The Emergency Cardiac Care Committee and Subcommittees American Heart Association, 1992), hypertension (Materson *et al*, 1993), and some forms of acute myocardial infarction (The Multicentre Diltiazim Postinfarction Trial Research Group, 1988; Danish Study Group on Verapamil in Myocardial Infarction, 1990). (The use of short acting CCBs (nifedipine in particular) for hypertension, angina and myocardial infarction has recently been seriously and controversially questioned (Horton, 1995; McCarthy, 1995; Messerli, 1995; Dougall and McLay, 1996; Grossman *et al*, 1996).) The CCBs are very widely prescribed. A recent survey of 1645 elderly patients in Australia (Thomson *et al*, 1995) found almost 18% were taking a CCB (Personal Communication—WM Thomson) and they are considered the antihypertensive of first choice in elderly patients also exhibiting angina or peripheral vascular disease (Beard *et al*, 1992).

Table 3 Chemical classification of CCBs

1,4-Dihydro-pyridines	*Phenylalkyl-amine derivatives*	*Benzo-thiazepine derivatives*	*Diarylamino-propylamine ether*
Nifedipine	Verapamil	Diltiazim	Bepridil
Nicardipine			
Isradipine			
Felodipine			
Nitredipine			
Isradipine			
Lacidipine			
Nimodipine			
Amlodipine			

Pharmacokinetics

The therapeutic effects of CCBs revolve around the essential role of Ca^{++} in contraction of both cardiac and vascular smooth muscle (arteriolar muscle is more sensitive to CCBs than venous smooth muscle). Contraction of muscle cells occurs when increased intracellular Ca^{++} binds to troponin and in the presence of ATP causes the myosin bridge to contract the actin filaments. The process in vascular smooth muscle is a little more complex and results from a cascade reaction involving calmodulin (Adelstein and Eisenberg, 1980).

At least seven different mechanisms regulate the intracellular Ca^{++} concentration in muscle cells (Braunwald, 1982) of which the slow Ca^{++} channels (on which the CCBs act) are but one. The slow Ca^{++} (L-long acting type) channels have various Ca^{++} antagonist receptor domains all located on the $Alpha_1$-subunit. The varying tissue distribution of the L channels partially accounts for the differing selectivities of these drugs (Glossmann, 1990). Because of the marked differences in chemistry, few generalised statements can be made regarding the pharmacodynamics or pharmacokinetics of the CCBs, other than most are highly protein bound, they generally have a short elimination half-life (often metabolised by the cytochrome P_{450} system) and very little of the drug is excreted unchanged in the urine (Yedinak, 1993).

Side effects

The common side effects of CCBs result from excess peripheral vasodilation; they include, headache, dizziness, facial flushing, and oedema (Lewis, 1983). (The sustained release form of some CCBs have a lower incidence of most of these problems due to the more even serum concentrations that result.) Constipation and nausea (McTavish and Sorkin, 1989) are also associated with CCBs along with asthenia (a feeling of weakness) (Buckley *et al*, 1990) probably due to effects on other smooth muscle. Gingival overgrowth was first reported in association with nifedipine in 1984 (Lederman *et al*, 1984; Ramon *et al*, 1984) and was soon also described with verapamil (Cucchi *et al*, 1985) and diltiazem (Colvard *et al*, 1986) usage.

Gingival overgrowth

Nifedipine

Clinical aspects Since its first description, nifedipine induced gingival overgrowth has been described by many authors (Harel-Raviv *et al*, 1995) with the reported prevalence ranging between 14.7% (Barak *et al*, 1987) and 83% (Fattore *et al*, 1991). The real prevalence is not known as only about 100 cases have been reported in the literature and most of these are case reports. It seems probable that the actual prevalence is much less, as the drug is widely prescribed around the world (the annual global revenue from CCBs is approximately US$8 billion). A small controlled (but not randomised) study of 47 patients indicated a prevalence of approximately 20% which the authors considered abnormally high (Barclay *et al*, 1992). The problem relates to the random selection of patients (usually from hospitals or referred), getting large enough numbers of subjects and getting appropriate controls (without confounding factors). A recent large study has attempted to address some of these matters and has reported a prevalence of 43.6% (compared to 4.2% in controls). The use of differing indices of overgrowth, differing populations (their study group was considerably older than others), dosage and duration of medication were cited by the authors as possible explanations for the differences (Nervy *et al*, 1995). They were unable to show any agreement between dose and overgrowth, although an earlier study had shown overgrowth in five cases was associated with higher doses of nifedipine than those patients without overgrowth (Barak *et al*, 1987).

It has been reported that nifedipine concentrates in the gingival crevicular fluid up to 316 times the plasma concentration but the effect was widely variable (15–316 times) and is not entirely correlated to gingival overgrowth (Ellis *et al*, 1992). A subsequent study down-marked the greatest concentration to 90 times that of serum and of the nine patients examined nifedipine could be found in the crevicular fluid of all five of the patients with gingival overgrowth and two of the 'non-responders' (Ellis *et al*, 1993a). Although most studies in this area have not been randomised a male predominance has been described (Harel-Raviv *et al*, 1995). A recent study in rats has suggested that overgrowth is related both to dose and serum levels and that males and younger animals required a lower threshold drug level (Ishida *et al*, 1995).

The role of plaque in nifedipine induced gingival overgrowth is uncertain as no convincing or longitudinal studies have investigated its role. Some role can be inferred from a case study (Hancock and Swan, 1992), where improvement in oral hygiene together with thorough scaling resulted in significant reduction in gingival overgrowth without substitution of the drug. In addition, a separate case has been reported that responded to gingivectomy and thorough oral hygiene with a 4-year follow-up (Nishikawa *et al*, 1991), but this is in contrast to others (Barak and Kaplan, 1988; Zlotogorski *et al*, 1989) who found that conservative scaling and improved oral hygiene was unable to limit the overgrowth. Using a specific pathogen free rat model, both inflammation and plaque have been shown to be unnecessary for the development of gingival overgrowth: however the authors suggest that they may augment the adverse effect of the drug on gingival tissues (Morisaki *et al*, 1993).

Histological features Histologically, the gingival overgrowth noted with nifedipine is similar to that seen with PHT and Cs. There is a varying degree of hyperkeratosis, acanthosis, some fibroblastic proliferation and perivascular chronic inflammation. The striking feature is the elongation of the rete pegs (test-tube shape) which have been used to classify the *hyperplasia* (Barak *et al*, 1987). Within the lamina propria the light inflammatory reaction is composed mostly of plasma cells, while the fibroblasts are prominent with well developed RER and contain membrane lined structures assumed to be secretory granules (Lucus *et al*, 1985).

Cell cultures of fibroblasts from nifedipine induced overgrown gingival tissues exposed to physiological and higher concentrations of nifedipine gave the unexpected result of a down-regulation of total protein and collagen synthesis and inhibited cell proliferation (Nishikawa *et al*, 1991). In contrast, other investigators (Tipton *et al*, 1994) have shown *in vitro* that fibroblasts from gingival overgrowth have enhanced collagen production and decreased collagenase activity. These cells do not proliferate any more rapidly than normal fibroblasts nor do they produce more glycosaminoglycans or fibronectin. More recent *in vitro* studies of normal fibroblasts have shown a short term exposure to nifedipine (up to 1 $\mu g\ ml^{-1}$) causes a significant increase in cell proliferation and after 6 weeks this continues along with a decrease in proteoglycan synthesis (Willershausen-Zönnchen *et al*, 1994). There is an altered pattern of collagen and fibronectin localisation in nifedipine induced overgrowth and it can be distinguished from normal gingivae on this basis. In particular type V and VI collagens were present surrounding blood vessels in a 'crater' and 'honeycomb' appearance respectively (Romanos *et al*, 1993).

Possible pathogenesis Partly because of the evolving understanding of the pharmacology of nifedipine, little is known about the pathogenesis of the gingival overgrowth associated with this medication. It has been speculated that some alteration to Ca^{++} metabolism is involved, as despite divergent pharmacologic actions both nifedipine and PHT interfere with Ca^{++} metabolism and cause gingival overgrowth (Barak *et al*, 1987). Others continued this line of reasoning by highlighting that both drugs prevent or suppress the action of ATPase (Puolijoki *et al*, 1988).

It has also been suggested that an indirect action of nifedipine may also occur by stimulating either production of IL-2 by T cells (Glefand *et al*, 1986) or metabolites of testosterone by gingival fibroblasts (Sooriyamoorthy *et al*, 1990), which in turn stimulates proliferation or increased collagen synthesis (Nishikawa *et al*, 1991). It has recently been proposed that medullasin (a neutrophil elastase-like protease that plays a role in the development of inflammation and enhancement of natural killer cell activity) may have a role in nifedipine induced gingival overgrowth although the mechanism is unknown (Kunimatsu *et al*, 1996). Other work suggests a role for TGFβ, bFGF and heparan sulphate glycosaminoglycan (Saito *et al*, 1996). A

recent *in vitro* study has suggested that nifedipine acts on the metabolism of most fibroblasts (Henderson *et al*, 1997). The site specificity (to gingival tissues) in the accumulation of collagenous proteins in the extracellular matrix may be due to the relatively slow synthesis of these proteins in other tissues or because of altered deposition/resorption in susceptible tissues. The responsiveness of the cells appeared to be inversely proportional to the IL-1β levels in the tissue of origin.

These theories, unfortunately, do not explain why only some patients taking nifedipine develop gingival overgrowth (Seymour, 1991). It seems possible that a number of mechanisms could be acting synergistically to produce clinically significant overgrowth, and it should be noted that many patients taking nifedipine without clinically obvious overgrowth have been rated as having moderate hyperplasia histologically (Barak *et al*, 1987).

Treatment Treatment has centred on withdrawal and substitution of the drug which along with improved oral hygiene has been shown to be successful in many patients (Puolijoki *et al*, 1988; Akimoto *et al*, 1991; Nishikawa *et al*, 1991; James and Linden, 1992; Katz *et al*, 1992; Ramsdale *et al*, 1995; Westbrook *et al*, 1997). However, not all cases respond to this treatment, particularly patients with long standing overgrowth (Harel-Raviv *et al*, 1995). Nor do patients receiving nifedipine respond to conventional treatment as well as patients not taking the drug (Bullon *et al*, 1996). Surgical excision appears to be the second line of treatment (Abitbol and Rosenfeld-Abitbol, 1996) in non-responding cases, and it has been shown to be successful when combined with good oral hygiene (Nishikawa *et al*, 1991). The use of a CO_2 laser may be helpful in these cases which often have medical conditions which are relative contra-indications for conventional surgery (Barak and Kaplan, 1988).

Verapamil

Clinical features Verapamil is a phenylalkylamine derivative CCB. The early reports of gingival overgrowth associated with this drug occurred in the mid-1980s in the non-English literature (Cucchi *et al*, 1985; Smith and Glenert, 1986). These were followed by a case report in English that included a histological description (Pernu *et al*, 1989). The prevalence of verapamil induced overgrowth appears to be very low. Miller and Damm could find only three cases in the literature and their review of 5000 dental patients seen over 3 years found only 24 patients taking verapamil for more than a year. Only one of these patients showed gingival overgrowth (Miller and Damm, 1992). It is interesting to note that patients in all cases presented in the English literature were receiving 480 mg of verapamil per day. This includes the two cases of verapamil overgrowth reported recently in children, who only experienced the overgrowth when their daily dose was increased to this level (Mehta *et al*, 1992).

Histological features The histological picture is similar to other drug induced gingival overgrowths. A thickened acanthotic epithelium with long finger-like rete peges often anastomosing at their ends has been described (Pernu *et al*, 1989; Miller and Damm, 1992). There is a sparse chronic inflammatory infiltrate composed mostly of plasma cells. Paradoxically, cell cultures of overgrown fibroblasts showed a down-regulation of proliferation. Decreased total protein and collagen production were also features of overgrown fibroblasts and these properties were similarly affected when both cell lines were incubated with verapamil (Pernu *et al*, 1989).

Possible pathogenesis Since the mechanism of action of verapamil is more complex than that of nifedipine, this may explain the apparent lack of potency of verapamil in causing gingival overgrowth (Pernu *et al*, 1989). Furthermore the action of verapamil on fibroblasts, combined with inflammation, may select for a subpopulation of fibroblasts, thus altering the balance of regeneration and degradation.

With such small numbers it is difficult to draw conclusions regarding the role of plaque. Two of the reported cases (Pernu *et al*, 1989; Miller and Damm, 1992) had significant levels of plaque but there are no longitudinal data in this area, and indeed, many patients taking verapamil had high levels of plaque but no overgrowth. Good oral hygiene failed to reduce the overgrowth reported in children (Mehta *et al*, 1992). Treatment by substituting the drug has been successful in a number of cases (Cucchi *et al*, 1985; Mehta *et al*, 1992), but gingivectomy with (Mehta *et al*, 1992) and without (Pernu *et al*, 1989) drug substitution has been needed by others to resolve the overgrowth.

Diltiazem

Clinical features Only two cases of overgrowth due to diltiazem appear to have been reported. The first case was of a patient who initially developed overgrowth after 15 days of verapamil therapy (Giustiniani *et al*, 1987). Discontinuation of the verapamil lead to resolution of the gingival overgrowth but when diltiazem (240 mg day^{-1}) was begun as an alternative therapy, the overgrowth returned over a period of 24 days. While not stated, the photograph of the case shows the greatest overgrowth around the labial surfaces of anterior teeth. The other case of gingival overgrowth associated with the use of diltiazem (Bowman *et al*, 1988) was less spectacular, but returned on two occasions following electrosurgery and surgical excision. The diltiazem therapy (540 mg day^{-1}) was not altered. While not stated in either case, plaque may have played a role in the aetiology as it was clearly visible in the photograph of the first case, and developed adjacent to a new crown margin (local predisposing factor) in the second case.

Histological features Both cases of verapamil overgrowth showed a similar histological picture (Giustiniani *et al*, 1987; Bowman *et al*, 1988) that was consistent with other gingival overgrowths. The epithelium was irregularly hyperplastic and showed acanthosis with test-tube-like rete pegs. The connective tissue showed dense collagenous fibres and a moderate increase in fibroblasts.The inflammatory infiltrate consisted largely of lymphocytes and plasma cells. Both reports postulate that the Ca^{++} channel blocking effect of the drug was involved in the pathogenesis of the lesion.

Nitrendipine
Nitrendipine is another, not widely available, CCB. A case report concerning gingival overgrowth due to nitrendipine was published in 1990 (Brown *et al*, 1990). The patient was enrolled on a clinical trial of the drug and had imperfect plaque control. Scaling of the teeth did not resolve the condition and gingivectomy was performed. The histological picture revealed a 'hyperplastic collagenous fibrous connective tissue' with a moderate infiltration of chronic inflammatory cells. The overlying epithelium showed elongated test-tube-like rete peges. The effect was not unexpected as it had already been shown that nitrendipine caused gingival overgrowth in dogs (Heiji and Sundin, 1988). Gingival overgrowth developed in all dogs receiving a high dose of the drug over 10 weeks and continued to further enlarge over the following 10 weeks. The authors describd the overgrown tissue as having a fairly normal appearance with increased vascularity and a looser connective tissue compared to controls.

Oxodipine
Oxodipine is a CCB which causes gingival overgrowth in animals. The overgrowth has been described as weakly dose-related, and only occurred in dogs receiving 23 and 73 times the intended human dose (Waner *et al*, 1988). The authors described the overgrowth as having a similar histological appearance to that described with nifedipine. Later work showed that withdrawal of the drug resulted in regression of the gingival overgrowth (although not complete) after 8 weeks (Laor *et al*, 1989). The overgrowth was seen to develop after 7 weeks in the incisor and canine region and by the 9th week was generalised (Nyska *et al*, 1990b). A similar overgrowth also developed in rats, without the use of ligatures etc, and the histological picture was without an inflammatory infiltrate (Nyska *et al*, 1990a). A recent histological investigation in dogs, using polarised microscopy suggested that the collagen fibres of the overgrown tissue may be less tightly packed than normal and that they may be immature collagen (Dayan *et al*, 1993). A sex difference in the staining properties of overgrown gingiva was also described. The same group have hypothesised a pathogenesis of gingival overgrowth from CCBs. They propose that the gingival overgrowth is due to elevated testosterone levels that could occur after CCBs block aldosterone synthesis. This blockage could lead to a feedback stimulation of ACTH secretion which may, in turn, cause adrenal hypertrophy leading to the accumulation of steroid intermediates that may then be transformed into testosterone (Nyska *et al*, 1994).

Amlodipine
Amlodipine is yet another CCB and has also been reported (in the English literature) to cause gingival overgrowth in three patients (Ellis *et al*, 1993b). Like bepridil (Gill *et al*, 1992) and nitrendipine (but unlike other dihydropyridines) it has a long half-life (35–50 h). The overgrowth began 2–3 months after starting the medication at 5–10 mg day^{-1} and the authors felt these changes were compounded by the patient's existing periodontal condition (Seymour *et al*, 1994). The crevicular fluid concentrations were found to be up to 292 times those found in plasma. Histologically, the authors described an acanthotic epithelium overlying a stroma of loose collagen, enlarged fibroblasts and an abundance of ground substance. Treatment consisted of surgery and in one patient a change of medication lead to complete regression without surgery. The role of amlodipine in gingival overgrowth has recently been questioned in a small observational study which was unable to show an increased prevalence of gingival overgrowth in 150 patients taking amlodipine at 5 mg day^{-1} for at least 6 months (Jorgensen, 1997).

Other drugs

Erythromycin
A single case of gingival overgrowth has been associated with the use of erythromycin in a young boy (Valsecchi and Cainelli, 1992). The condition resolved with withdrawal of the drug and returned upon repeat challenge. The authors were unable to suggest any possible mechanism for the phenomenon.

Combinations of medications associated with gingival overgrowth

Despite their frequent use with other medications there is minimal literature dealing with combinations of these drugs. The most common combination would appear to be Cs and nifedipine. Nifedipine is frequently used to treat hypertension which may be primary or secondary to Cs nephrotoxicity. A significant increase in the incidence of gingival overgrowth has been described in renal transplant patients taking nifedipine as well as Cs compared to those taking Cs alone (51% *vs* 8%) (Slavin and Taylor, 1987).

5α-DHT (a biologically active androgen) is known to stimulate biosynthetic activity in fibroblasts (Southren *et al*, 1978). It has been shown in a single patient receiving both Cs and nifedipine that 5α-DHT was significantly elevated compared to a control, and was also increased slightly compared to a patient receiving only Cs and more so than in a patient receiving only nifedipine (Sooriyamoorthy *et al*, 1990). Further epidemiological study of renal transplant patients receiving Cs or Cs and nifedipine has suggested that while the incidence of clinically significant gingival overgrowth may be similar, the severity of overgrowth appears to be significantly greater in those receiving both drugs (Thomason *et al*, 1993). A larger, more recent study of cardiac transplant patients by the same group has confirmed these findings (Thomason *et al*, 1995). Patients taking both drugs had higher gingival overgrowth scores ($P < 0.0001$), probing depths ($P = 0.001$) and a greater need (a 25-fold increased risk) for surgery ($P = 0.001$). By contrast, other investigators recently reported an increased prevalence and severity in renal patients taking both drugs. They concluded that local factors and pharmacological parameters were unrelated to overgrowth. They indicated a trend for HLA A19 positive patients to show overgrowth, suggesting an underlying susceptibility (Margiotta *et al*, 1996).

Verapamil and Cs interactions have recently been investigated in renal transplant patients. Both presence and severity of overgrowth were greater in patients taking both

drugs but not significantly more than those only taking Cs. Dosage of either drug was unrelated to overgrowth. The authors concluded that verapamil was having no augmenting effect on either the severity or the prevalence of the gingival overgrowth (Cebeci *et al*, 1996b).

Common links?

This review has outlined the remarkable similarity in the clinical and histological appearance of the major medication induced gingival overgrowths. The selectivity of the overgrowth to particular regions of the mouth and only in some patients, suggests a number of factors (including a genetic predisposition) may interact with the local environment resulting in overgrowth. (For an excellent recent review of the possible pathogenesis of gingival overgrowth, see Seymour *et al*, 1996.) With such a broad range of medications it would seem likely that a number of different molecular changes can result in similar cellular and tissue appearances. It should also be remembered that homeostatic processes will also be acting to limit any change. Thus although fibroblasts may be the dominant cell it seems probable that both anabolic and catabolic processes would be affected and other cell types would also be inclined to respond to such changes. This line of reasoning would encompass the diverse range of reported effects such as epithelial alterations and changes to matrix glycoproteins and enzymes.

As to the exact nature of the overgrowth, it seems quite feasible that changes at a molecular level (whatever they may be) may well affect multiple cell types, resulting in alterations to cell growth and/or function. See Table 4. Thus any cell in the correct local environment may well respond. The exact balance of the interaction is likely to be specific for each patient and temporal in nature.

A genetically predisposed individual may have cells that will respond to molecular level changes induced by drugs if positioned in the correct local environment. The cellular response will depend on the cell's normal function and its level of interaction with the local environment. Whether such cellular responses are noticed clinically, may well depend on the number of cells affected, their location, the period and extent to which they are affected (tempered by any homeostatic mechanisms) and the keenness of the observer.

There are a number of features shared by the medications inducing gingival overgrowths including the ability to concentrate in tissues (well in excess of the plasma concentration) (Houghton *et al*, 1975; Akagi *et al*, 1991; Ellis *et al*, 1993a), and the apparent ability to increase 5α-DHT (known to stimulate connective tissue growth) (Sooriyamoorthy *et al*, 1990; Soory and Kasasa, 1997). Thus these drugs are probably present locally (in high concentrations, although with few exceptions (Ellis *et al*, 1993a) this is yet to be proved) and have the potential to increase growth.

The most obvious link between most of the drugs that induce overgrowth is modulation of intracellular Ca^{++}. Calcium is essential to many biologic processes, it is often acting as a cofactor for enzymatic reactions and is involved in normal homeostasis and bone metabolism. PHT suppresses the sodium/potassium ATPase pump (Pincus *et al*, 1970) (Ca^{++} is an essential cofactor for ATPase) and blocks intracellular Ca^{++} uptake (Pincus, 1972), probably via blockage of type I calcium channels which presumably inhibits calcium sensitive intracellular processes (Twombly

Table 4 Factors associated with drug-induced gingival overgrowth (see text for details)

Phenytoin	*Cyclosporin*	*Calcium channel blockers*
Proliferation of fibroblasts	Proliferation of fibroblasts via: • Decreased antiproliferative effect due to decreased PGI_2	
Increased collagen production via: • Selection of fibroblasts	Increased collagen production via: • Increased mRNA of procollagen	Increased collagen production via: • Increased Il-2 or testosterone metabolites
Decreased collagen breakdown	Decreased collagen breakdown	
Increased GAGs via: • Decreased EGF receptor metabolism • Increased PGE_2 leading to increased hyaluronic acid • Increased TGFβ and bFGF		Increased GAGs via: • Increased TGFβ, bFGF and heparan sulphate
Plaque (inflammation) via: • Increased IL-1 • Increased PDGF-B	Plaque (inflammation) via: • Increased PDGF-B	
Decreased intracellular calcium Folate deficiency Cell injury Decreased ACTH Immunosuppression	Immunosuppression Genetic susceptibility	Decreased intracellular calcium Suppression of ATPase

et al, 1988). However PHT causes a transient increase in intracellular Ca^{++} in responding gingival fibroblasts (Modéer *et al*, 1991) thus emphasising the difficulty in interpretation of results from differing *in vitro* studies. Similarly Cs is known to bind calmodulin (Colombani *et al*, 1985) which normally binds intracellular Ca^{++}. Cs also inhibits calcineurin and protein kinase C activity (Fuleihan *et al*, 1994) but increases the Ca^{++} influx in smooth muscle contraction (Lo Russo *et al*, 1996). Obviously CCBs affect intracellular Ca^{++} concentrations (although they decrease rather than increase intracellular Ca^{++}). Alterations to cytoplasmic Ca^{++} (be they increases or decreases) are a likely common feature between the differing drug induced overgrowths. Usually, Ca^{++} influx is associated with cell proliferation, thus any blockage of Ca^{++} would tend to inhibit such a response. However, recently Ca^{++} influx has been associated with apoptosis (programmed cell death): indeed CCBs and Cs have been used to abrogate apoptosis in some model systems (McConkey and Orrenius, 1977).

Gingival overgrowth, conceivably may result from an inhibition of apoptosis and decreased collagenase action, and there is some evidence to suggest this may be the case. There is early evidence to suggest that calcineurin activation is required for some forms of apoptosis. Calcinerin is a Ca^{++}/calmodulin-dependent protein serine/threonine phophatase, which as mentioned previously, is inhibited by Cs/cyclophillin complexes. Recently, calcineurin and the voltage operated calcium channels (types I and II or T and L) have been colocalised, suggesting a direct functional connection (Lukyanetz, 1997). PHT directly blocks Ca^{++} channels (Twombly *et al*, 1988) as obviously do CCBs; thus inhibition of the Ca^{++} influx would inhibit calcineurin which in turn could inhibit apoptosis, which could result in overgrowth. Similar anti-apoptotic processes leading to hyperplasia (Santarosa *et al*, 1994) which are Ca^{++}/calcineurin controlled have been described for other tissues (Ankarcrona *et al*, 1996; Li *et al*, 1997; Su *et al*, 1997). Ca^{++} channels are temperature sensitive (Innocenti *et al*, 1996; Rosen, 1996) so that calcium channels found in anterior labial regions of the mouth are likely to be cooler (eg, 2–4°C) than basal temperatures (Meyerov *et al*, 1991; Perdok *et al*, 1992). It is feasible that blockage of these channels could lead to overgrowth via the above mechanism and this would be in keeping with the distribution of overgrowth that has been described with medication induced overgrowths.

Expression of collegenase RNA from gingival fibroblasts has been linked to increased expression of c-fos (Trabandt and Gay, 1992). This proto-oncogene is expressed in response to intracellular Ca^{++} and this expression is prevented if Ca^{++} sources are eliminated. The Ca^{++} blocking/binding abilities of the drugs associated with gingival overgrowth, could thus decrease collogenase production, also aiding in the formation of gingival overgrowth.

The exact mechanism appears unlikely to be the same in all cases. It has been shown in five different gingival fibroblast strains (all of which were known to respond to PHT) that culturing with Cs and CCBs associated with gingival overgrowth (nifedipine, nitrendipine, feldopine, verapamil and diltiazem) did not necessarily result in increased collagen accumulation or cellular proliferation (Hassell, 1990). For some patients receiving Cs and/or a CCB it has been suggested that those patients exhibiting moderate or severe gingival overgrowth are more likely to be HLA-DR2+ rather than HLA-DR1+ (which others have also suggested marks non-susceptibility to gingival overgrowth (Cebeci *et al*, 1996a)) although how this effects gingival fibroblasts is unclear (Pernu *et al*, 1994).

Table 5 Common commercial names of drugs associated with gingival overgrowth

Generic drug name	*Common commercial names*
Phenytoin	Dilantin
Valproate	Epilim
	Valpro
	Depakene
Phenobarbital	Donnatal
	Phenob
Vigabatrin	Sabril
Cyclosporin	Sandimmune
	Sandimmun
	Neoral
Nifedipine	Adalat
	Procardia
Verapamil	Cordilox
	Isoptin
	Covera
	Calan
Diltiazem	Cardizem
	Tiamate
	Tiazac
	Dilacor
Amlodipine	Norvasc
	Lotrel

Concluding comments

In the future, the numbers of patients taking medications associated with gingival overgrowth is likely to rise. See Table 5 for a list of common commercial names of drugs associated with gingival overgrowth. As our understanding of the pathogenesis of many systemic conditions increases it is likely that many more patients will be receiving some form of pharmacological therapy to control abnormal systemic function. In addition, as life expectancy increases a greater number of patients will be able to live a *normal* ambulatory life for many more years than previously expected albeit with the aid of a variety of medications. It should not be unexpected that dentists will be called upon to treat these patients and need to be aware of the dental implications of these medications.

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