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The role of drugs in the pathogenesis of gingival overgrowth

A collective review of current concepts

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The gingiva and associated soft tissues of the periodontium may be enlarged in response to various interactions between the host and the environment. Although such enlargement usually represents an inflammatory response to bacterial plaque (91), increased susceptibility as a result of systemic factors or conditions should always be considered during the course of patient evaluation (139). Systemically related gingival enlargements include, but are not limited to, scurvy, leukemia, puberty, pregnancy, multi-system syndromes and selected drugs and/or agents (139, 182). In addition, fibrotic gingival enlargement has been reported and is believed to be the result of a genetic predisposition (such as hereditary or familial gingival enlargement); however, an idiopathic variant that has not been associated with genetic linkage or cause has also been described. Since the fibrotic gingival enlargements occur infrequently, minimal interest has been shown in the recent scientific literature, except for case reports and associated histological observations (138, 139, 182).

Of the predisposing factors associated with disproportionate, disfiguring and functionally compromising overgrowth of gingival tissues, selected anticonvulsant drugs, calcium channel blockers and a potent immunosuppressant (cyclosporin A) have generated the most investigative attention in the scientific community. Unfortunately, the underlying pathogenic mechanism that mediates gingival overgrowth in affected individuals remains undefined despite intense clinical and laboratory investigation.

The purpose of this chapter is to review gingival overgrowth and its association with anticonvulsant agents, calcium channel blockers and cyclosporin A. Discussion of the respective drugs and their association with gingival overgrowth will include pharmacokinetics, clinical manifestations, pathogenesis, histological characteristics and approaches to prevention and treatment based on current knowledge and investigative observations.

Anticonvulsants

Phenytoin (5-diphenylphenytoin) has been used to control seizure disorders in patients with epilepsy since its clinical introduction by Merritt & Putnam in 1938 (102). Within a year of its initial clinical use, reports linking phenytoin to gingival overgrowth appeared in the literature (81). Due to the effectiveness of this medication in controlling convulsive seizure disorders and its low cost and availability, phenytoin has entertained sustained and extensive use for this purpose over the last 60 years, and as a result of the frequent occurrence of gingival overgrowth associated with its use, numerous investigations and case reports related to this side effect have appeared in the medical and dental literature (5, 6, 24, 67, 149). Seizure disorders may be broadly categorized as partial (focal) or generalized (widespread), and other anticonvulsant medications besides phenytoin are also effective in controlling the various types of seizures (86, 139). The primary drugs recommended for controlling partial seizure disorders include phenytoin (Dilantin®), carbamazepine (Tegretol®), primidone (Mysoline®) or phenobarbital (Luminal®). Generalized seizure disorders are managed primarily with phenytoin, carbamazepine, phenobarbital or valproic acid (Depakene®, Depakote®), while the

recommended agents for controlling generalized absence seizures (petit mal) are ethosuxamide (Zarontin®) and valproic acid (Table 1) (86, 139). Despite the widespread availability of anticonvulsant drugs, phenytoin and phenobarbital remain the most commonly prescribed antiepileptic medications (64, 86). Although capable of inducing gingival overgrowth, the anticonvulsant agents (except for phenytoin) are infrequently associated with this clinical side effect (Table 1) (41, 108, 165).

Table 1. Drugs associated with gingival overgrowth

	Agent	Trade name
Anticonvulsants		
Hydantoins	Ethotoin	Paganone®[1]
	Mephenytoin	Mesantoin®[2]
	Phenytoin	Dilantin®[3]
Succinimides	Ethosuximide	Zerontin®[3]
	Methsuximide	Celontin®[3]
	Phensuximide	Not reported*
Valproic acid	Valproic acid	Depakene®[1]
Immunosuppressant	Cyclosporine A	Sandimmune®[2]
		Neoral®[2]
Calcium channel blockers		
Dihydropyridine derivatives	Amlodipine	Lotrel®[4]
		Norvasc®[5]
	Felodipine	Plendil®[6]
	Nicardipine	Cardene®[7,8]
	Nifedipine	Adalat®[9]
		Procardia®[5]
		Other
	Nimodipine	Nimotop®[9]
	Nisoldipine	Sular®[10]
	Nitrendipine	Not reported*
Benzothiazine derivatives	Diltiazem	Cardizem®[11]
		Dilacor XR®[12]
		Tiazac®[13]
		Others
Phenylalkylamine derivatives	Verapamil HCl	Calan®[14]
		Isoptin®[15]
		Verelan®[16]
		Covera HS®[14]
		Others

[1]Abbott Laboratories, North Chicago, IL; [2]Sandoz Pharmaceuticals Corp., Hanover, NH; [3]Parke-Davis, Morris Plains, NJ; [4]CIBA Geneva Pharmaceuticals, Summit, NJ; [5]Pfizer, New York, NY; [6]Astra Merck, Wayne, PA; [7]Roche Laboratories, Nutley, NJ; [8]Wyeth-Ayerst Laboratories, Philadelphia, PA; [9]Bayer Corporation, Pharmaceutical Division, West Haven, CT; [10]Zeneca Pharmaceuticals, Wilmington, DE; [11]Hoeschst-Marion Roussel, Kansas City, MO; [12]Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA; [13]Forest Pharmaceuticals, New York, NY; [14]G.D. Searle & Co., Chicago, IL; [15]Knoll Pharmaceutical Co., Mount Olive, NJ; [16]Lederle Laboratories, Carolina, Puerto Rico.
*Product information obtained from the 1997 *Physician's desk reference* (126).

Pharmacokinetics

Phenytoin selectively depresses the motor cortex of the central nervous system and is believed to mediate this action by stabilizing neuronal discharge and limiting the progression of neuronal excitation by blocking or interfering with calcium influx across cell membranes (86, 138, 150, 182)

Reports of the incidence of phenytoin-associated gingival overgrowth range from 0% to 84.5%, with an average effect approximating 50% (5–6, 121). An increased prevalence of gingival overgrowth has been observed in children and institutionalized people (34, 164). In a 2-year longitudinal study, Dahllöf & Modéer (34) observed the clinical onset of gingival overgrowth after 1 month of phenytoin use. Although overgrowth occurred progressively over the study period, it continued at a decreased rate during the second year. Associated gingival overgrowth appears to reach maximum severity 12–18 months after initiating phenytoin treatment (1, 19, 90).

Although the daily dose, duration of use and blood or salivary levels of phenytoin have been related to the presence and degree of overgrowth (3, 80), several studies have failed to detect any correlation among these factors (34, 67, 172). Nevertheless, there is probably a trough or minimal threshold dose below which gingival overgrowth does not occur. The usual therapeutic plasma level of phenytoin necessary to maintain effective seizure control is 10–20 μg/ml. Patient compliance, metabolism and other medications are among the factors that may affect plasma levels and, thus, seizure control (34). By all indications, the plasma level of phenytoin necessary to ensure seizure control exceeds the suspected trough or minimal threshold dose necessary to induce gingival overgrowth (138).

Clinical manifestations

Phenytoin-induced gingival overgrowth is characterized by initial enlargement of the interdental papillae, and is less frequently accompanied by increased thickening of the marginal tissue (6). Affected tissues typically present a granular or pebbly surface, with the enlarged papillae extending facially and/or lingually, obscuring the adjacent tissue and tooth surfaces. Affected papillae may become enlarged to the point that they contact, resulting in the clinical presence of pseudoclefts (Fig. 1). Although florid tissue overgrowth usually diminishes as it approaches the mucogingival junction, coronal progression may partially or totally obscure the crowns of the teeth (6). The facial gingiva of the anterior sextants is more commonly affected and often results in aesthetic disfigurement (24, 89). There is no evidence suggesting that sex or race affects the occurrence of phenytoin-associated gingival overgrowth (67). Enlargement of the gingival tissues may result in malpositioning of teeth and interference with normal masticatory function, speech and oral hygiene (127). There are

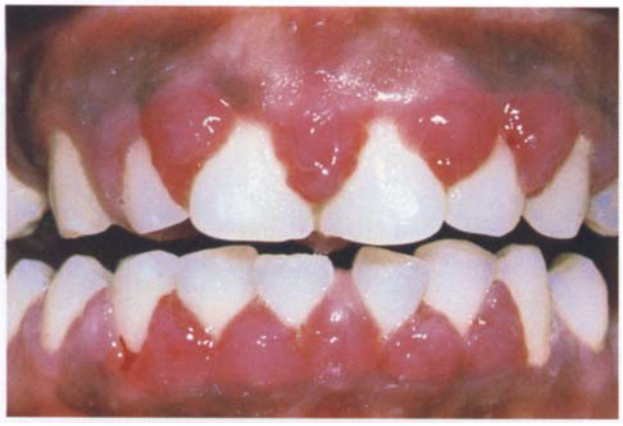

Fig. 1. Note the florid overgrowth of affected papillae and presence of pseudoclefts resulting from overlapping of adjacent marginal gingiva and papillary confluence. The patient had been on long-term phenytoin therapy for seizure disorder control. Photo courtesy of Lloyd K. Thomas.

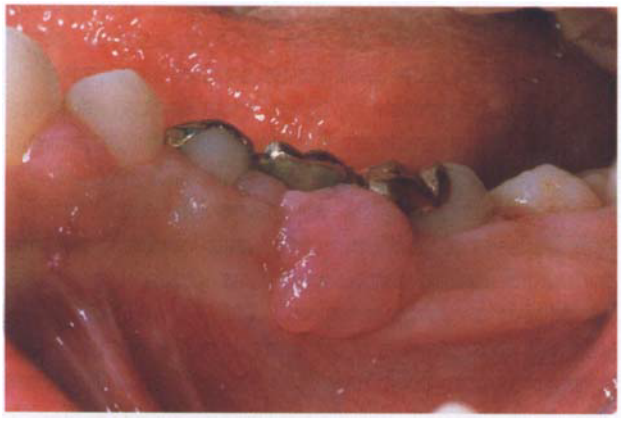

Fig. 2. Patient on long-term phenytoin therapy presenting with exaggerated gingival overgrowth occurring in association with the fixed partial denture pontic replacing the lower left first molar.

also reports of phenytoin-induced gingival overgrowth prior to the eruption of the primary teeth, which resulted in delayed eruption (28, 144).

Although considered rare, phenytoin gingival overgrowth has also been observed in edentulous patients and beneath pontics of fixed partial dentures (18, 43) (Fig. 2). In one edentulous case report, four dental implants were placed in an area devoid of any tissue enlargement. Eighteen months later, gingival overgrowth was recorded around each implant abutment, and corresponded to an increase in the patient's phenytoin dosage 3 months earlier (18). This finding may be an important consideration when evaluating prospective dental implant patients who take phenytoin or in the supportive treatment phase of patients who have dental implants and are subsequently placed on this anticonvulsant.

Dahllöf et al. (33) studied the effect of phenytoin withdrawal in 10 children with previously developed phenytoin gingival overgrowth. Significant regression of the condition was observed at 1 month, and the buccal-lingual gingival dimensions were comparable to a control group of children taking other anti-epileptic drugs when evaluated at 6 months post-phenytoin withdrawal. These observations were made without patients receiving professional prophylaxis (33), and the regression interval coincided with the 1-month period generally required for gingival overgrowth to appear after initiating phenytoin therapy (34).

Pathogenesis

The pathogenic mechanisms responsible for phenytoin-associated gingival overgrowth remain undisclosed. *In vitro* studies have investigated the effect of phenytoin on human gingival fibroblasts in tissue culture (155, 178, 179). Shafer (155) reported that the optimal rate of cell growth (2×) occurred at a phenytoin concentration of 5 μg/ml, compared to non-phenytoin controls. The major metabolite of phenytoin is 5-parahydroxyphenyl-5-phenylhydantoin and accounts for 50–75% of the daily dose (155). Hassell & Page (69) demonstrated gingival overgrowth in response to 5-parahydroxyphenyl-5-phenylhydantoin in an animal model. In a separate study, Cockey et al. (30) found that minor metabolites of phenytoin, notably 3-0-methyl-catecol, modified the behavior of cells *in vitro* but did not affect cellular proliferation.

Johnson et al. (77) studied the effect of donor age on the synthetic properties of fibroblasts obtained from phenytoin-induced gingival hyperplasia and reported significantly greater collagen and protein production by these cells when compared with normal gingival controls. While an age-dependent decrease in synthesis was observed in fibroblasts from normal gingiva, such changes were not observed in the phenytoin-cells, suggesting that they may represent a unique phenotype. Vijayasingham et al. (179) failed to detect any fibroblast cell growth occurring in response to phenytoin *in vitro*. An important variable to consider may be the existence of functionally heterogeneous subpopulations of connective tissue cells in the gingiva (39, 60, 70, 110). These collective observations led Hassell & Hefti (67) to propose "(1) that normal human gingiva contains several or many phenotypically distinct and different subpopulations

of fibroblasts; (2) that phenytoin reacts with some but not all such cells; and (3) that the clinical appearance and histologic features of gingiva are, at least in part, a reflection of such populations". During a cell culture study by Hassell & Gilbert (65) in which strains of human fibroblasts derived from 17 individuals with normal gingiva were exposed to phenytoin, only 41% were responders, demonstrating the influence of phenytoin on protein synthesis. These and other observations support the concept of genetically-predetermined phenytoin-sensitive subpopulations of gingival fibroblasts and suggest an increased host susceptibility to phenytoin-associated gingival overgrowth (64–67).

It has been shown that tissue from phenytoin-induced gingival overgrowth has an increased glycosaminoglycan content compared with normal gingival controls (9, 33, 36). This led to further investigation in an attempt to define the mechanism of action. Pagliarini et al. (120) studied the effect of phenytoin on glycosaminoglycan synthesis in fibroblasts derived from human free and attached gingiva. The proportion of intracellular sulfated glycosaminoglycan was increased in attached gingival fibroblasts, whereas extracellular sulfated glycosaminoglycan was increased in free gingival fibroblasts (120). Phenytoin influences intracellular calcium metabolism in normal fibroblasts, resulting in significant increases *in vitro*. No such influence was observed in cells derived from phenytoin-associated gingival overgrowth (17).

Further investigation has been directed toward the potential role of growth factors in influencing, and possibly regulating, gingival overgrowth. Modéer et al. (105) studied the interactive effect of phenytoin and epidermal growth factor, a polypeptide in saliva that is known to promote glycosaminoglycan synthesis and stimulate influx of calcium ions into mammalian fibroblasts *in vitro*. In phenytoin patients with and without associated overgrowth, epidermal growth factor receptor metabolism was downregulated in responder fibroblasts and upregulated in nonresponder fibroblasts. Since epidermal growth factor has been recognized as a facilitator of extracellular matrix deposition in connective tissue, the authors felt that these findings were significant and warranted further study (105). Dill et al. (40) have proposed that phenytoin increases the production of platelet-derived growth factor, a dynamic cytokine involved in the process of connective tissue growth and repair, and that excessive platelet-derived growth factor production would mediate gingival overgrowth. Using *in situ* hybridization, the authors demonstrated that phenytoin facilitated the expression of the gene for platelet-derived growth factor-B expression (*c-sis*), thereby offering an explanation for the occurrence of gingival overgrowth. In a subsequent *in vitro* and *in vivo* study, Iacopino et al. (74) examined the effect of phenytoin on macrophage phenotype regulation and expression of platelet-derived growth factor and interleukin. Gingival tissue from normal (minimally inflamed), severely inflamed (non-phenytoin) and phenytoin-induced gingival overgrowth patients were evaluated. No significant differences in the number of the different macrophage phenotypes were observed in the minimally inflamed (normal) gingival normal specimens. However, in severely inflamed tissue, the inflammatory macrophage phenotype was significantly increased, and the reparative/proliferative macrophage phenotype increased significantly in overgrowth tissue. Phenytoin-induced platelet-derived growth factor-B upregulation was six times greater than that produced by inflammation alone. Interleukin-1β messenger RNA levels showed no significant increase in phenytoin-treated patients but increased in severely inflamed gingival samples. The authors concluded that the clinical appearance of inflammation and phenytoin-induced gingival overgrowth is associated with specific macrophage phenotypes that express platelet-derived growth factor-β in the overgrowth tissue, and the pro-inflammatory cytokine interleukin-1β in inflamed tissue (74).

Other mechanisms by which phenytoin may influence gingival overgrowth have been proposed. It is well established that phenytoin may interfere with folic acid absorption and metabolism. Resulting folic acid deficiency primarily affects the epithelium, gonads and bone marrow. As a result of its role in DNA synthesis, tissues with higher turnover rates (such as epithelium) are often affected first (95). Compromise of the oral epithelium may potentiate inflammatory alterations of the underlying lamina propria in the presence of bacterial plaque (20, 42, 131). Only a single human study has shown an association between topical folic acid and reduction of gingival overgrowth (42). At this time, available evidence does not appear to support the use of folic acid as an effective means of preventing or treating phenytoin-induced gingival overgrowth.

A strong correlation has also been observed between production of inactive collagenase and phenytoin exposure of responder fibroblasts. These cells produced and secreted more collagenase (active and inactive) than human gingival fibroblasts from nonresponders (60). Phenytoin may also inter-

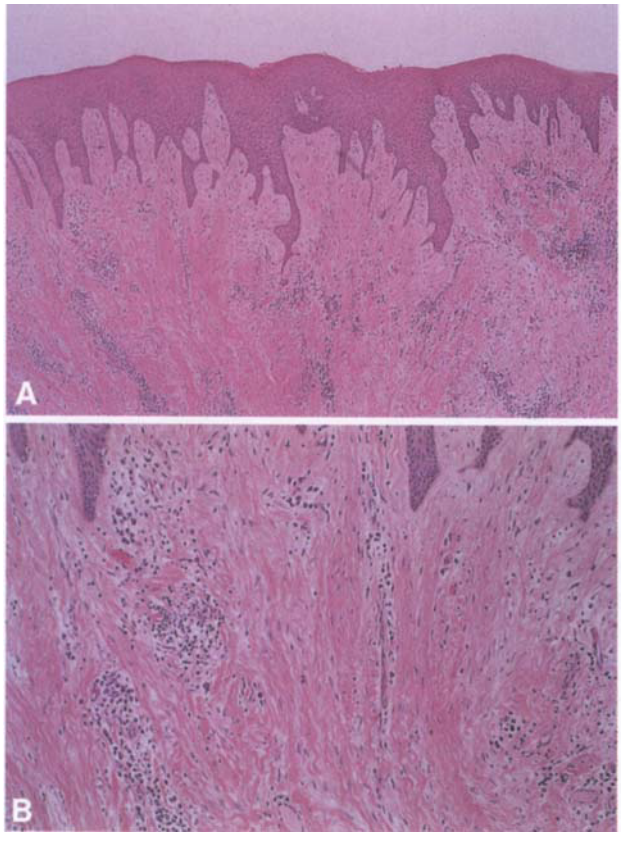

Fig. 3. A. Hematoxylin and eosin stained section from a phenytoin-associated gingival overgrowth specimen. Long thin rete pegs of epithelium extend deep into the lamina propria. B. The lamina propria of this section is characterized by presence of increased collagenous and non-collagenous components. Note the presence of the inflammatory cell infiltrate, occasional vessels and numerous fibroblasts in this specimen.

fere with and reduce prolyhydroxylase production, an enzyme responsible for post-translational hydroxylation of prolyl residues during collagen synthesis. In addition, phenytoin can also decrease the activity of collagenase (88, 106).

In summary, while the pathogenesis of phenytoin-induced gingival overgrowth has not been determined, evidence suggests a direct effect on specific subpopulations of fibroblasts, genetic predisposition, intracellular calcium metabolism exchange, molecular mechanisms (cytokines such as epidermal growth factor, platelet-derived growth factor-β), inactivation of collagenase and inflammation induced by bacterial plaque (9, 17, 35, 36, 40, 42, 53, 59–61, 64, 66, 74, 77, 88, 95, 105, 106, 155, 178). These dynamic variables may act on the gingival milieu individually or collectively to alter the homeostatic steady state present in health.

Histological characteristics

Histologically, tissues from gingival overgrowth biopsies present a thick stratified squamous epithelium with long thin rete pegs, often acanthotic, that extend deep into the lamina propria. The lamina propria is characterized by proliferation of fibroblasts and increased collagen formation, accompanied by an increase in non-collagenous proteins (5, 24, 41) (Fig. 3). More recently, Bonnaure-Mallett et al. (15) compared fractional area occupied by total collagen, types 3 and 4 collagen, fibroblasts, vessels, and elastic fibers from gingival overgrowth specimens obtained from patients taking phenytoin, nifedipine and cyclosporine. The overall histological features were similar, but the extracellular matrixes differed. The area of fibroblasts in the nifedipine and cyclosporine tissue specimens was not significantly greater than that observed in tissues from healthy controls. However, collagen occupied a significantly greater area in the nifedipine tissue than that observed in either phenytoin or cyclosporine specimens (15).

Based on current histological and ultrastructural observations, drug-associated gingival changes are more accurately referred to as gingival overgrowth or enlargement, rather than hypertrophy or hyperplasia (15, 35, 36, 111).

Prevention and treatment

Significant correlations between the occurrence and/or severity of phenytoin-induced gingival overgrowth and the presence of plaque and calculus accumulation have been reported in numerous studies (41, 68, 121, 138, 168). Bacterial plaque has been causally linked to gingival and periodontal disease and has provided a logical focus for efforts directed at preventing or containing the process of gingival overgrowth. Oral hygiene represents the risk factor most likely to be controlled by the patient, dental hygienist and dentist (128). With proper instruction, motivation, assessment and reinforcement, oral hygiene may be effectively addressed by the patient during the course of a systematic approach to periodic and recurring supportive treatment. For institutionalized and/or physically and mentally impaired patients, such care is sporadic and dependent on others, and consequently often deficient (162). The general consensus is that zealous oral hygiene efforts are extremely important to the preventive and therapeutic management of drug-induced gingival overgrowth (29, 59, 162) and should be instituted

prior to starting such therapy whenever possible (56, 104). In a 15-month longitudinal study, Pihlstrom et al. (128) studied the effectiveness of a preventive dental program in 13 outpatients who were taking phenytoin for seizure control. All patients received professional preventive care consisting of supragingival and subgingival scaling, polishing and oral hygiene instruction (brushing, flossing, disclosants) within 30 days of initiating phenytoin therapy. Dental prophylaxis and gingival assessment was repeated at 3-month intervals until completion of the study. Although a small increase in gingival enlargement was observed anteriorly during the first 6 months, no further enlargement occurred. The authors concluded that a preventive dental program consisting of frequent prophylaxis and oral hygiene reinforcement could effectively minimize phenytoin-associated gingival enlargement (128). Hall (56) observed patients who had gingival inflammation eliminated prior to initiating phenytoin therapy. In 20 patients who received preventive dental treatment within 10 days of phenytoin administration and were examined for at least 160 days, none developed gingival enlargement. Preventive treatment improved but failed to eliminate pre-existing conditions in two individuals who had gingival enlargement prior to entering the study.

In a 2-year longitudinal study, Dahllöf & Modéer (34) initiated a preventive dental program (oral hygiene instruction and regular dental prophylaxis) for 16 children scheduled to begin phenytoin treatment for seizure control. Gingival enlargement was evident after 1 month and was not prevented by the program. However, none of the patients developed pseudopocketing or showed significant enlargement after the first year, leading the authors to conclude that the plaque control program may be beneficial in phenytoin patients. Modéer & Dahllöf (104) studied development of phenytoin-induced overgrowth in 59 non-institutionalized epileptic patients subjected to different plaque control programs over 2 years. The authors reported a significant positive correlation between the amount of time without plaque control and development of gingival overgrowth. The more intense preventive program resulted in no pseudopocketing. It was recommended that, in order to minimize gingival enlargement in phenytoin patients, a preventive dental program should be initiated prior to starting the medication.

Since phenytoin patients often experience difficulty with effective oral hygiene maintenance, approaches may need to be modified in a effort to meet patient needs. This may include the use of an electric toothbrush and adjunctive antimicrobial sprays or mouthrinses (118). Shibley et al. (156) prescribed 0.12% chlorhexidine gluconate rinses twice a day in 30 patients exhibiting drug-associated overgrowth. Compared with gingival overgrowth patients using a placebo rinse, the chlorhexidine group had a significant reduction in plaque accumulation, gingival inflammation and gingival overgrowth. Although chlorhexidine use should be considered for patients who are otherwise unable to effectively implement personal oral hygiene procedures (127), the effectiveness of a chlorhexidine-containing toothpaste in reducing gingival overgrowth has been questioned (144).

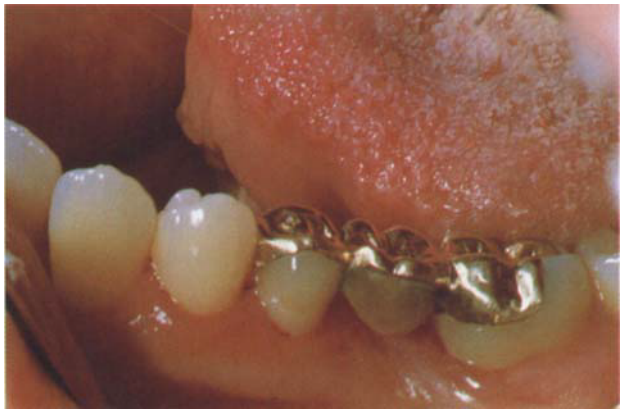

Fig. 4. Patient from Fig. 3, 3 months following gingivectomy to remove gingival overgrowth. Note the high level of plaque control and gingival health.

Predictable prevention and treatment of phenytoin-induced gingival overgrowth continues to defy dental professionals. Although scaling and root planing effectively reduces accompanying inflammation, surgical treatment is often required to manage the consequences of clinically significant gingival overgrowth (79, 127). Consultation with the physician may include consideration of an alternative medication (135, 140, 174) and determination of the patient's risk status relative to proposed surgical procedures. The excessive tissue can be removed using conventional surgical techniques (gingivectomy/flap), laser gingivectomy or a combination approach (141) (Fig. 4). A vacuum-formed surgical stent lined with periodontal dressing or tissue-conditioner may facilitate control of postoperative hemorrhage and protection of the surgical wound (127). Positive pressure appliances have been recommended as a means of preventing or reducing the recurrence of gingival overgrowth (8, 38). A long-term maintenance and recall follow-up program should be instituted consisting of medical history update and re-

view, evaluation, prophylaxis and reassessment and reinforcement of oral hygiene. Oral antimicrobial agents should be considered as a treatment adjunct and may prove beneficial, especially following surgical reduction of gingival overgrowth. A recent study of salivary protein content by Henskens et al. (73) evaluated salivary protein composition in epileptic patients who had taken anticonvulsants over long time periods. Phenytoin resulted in reduced salivary immunoglobulin A levels but similar cystatin C levels compared with controls. The authors suggest that, as a consequence, patients taking this medication may be at greater risk for oral microbial infection (73).

As noted previously, other anticonvulsant agents have been associated with gingival overgrowth, although occurrence of this side effect is considered infrequent compared with phenytoin (87, 139). Other agents include primadone and phenobarbital, mephentoin and ethytoin, ethosuximide, and valproic acid (44, 86, 139). Valproic acid has a broad spectrum of antiepileptic activity compared with other anticonvulsants (44). Seymour et al. (153) compared adult epileptics treated with phenytoin or sodium valproate with healthy controls to determine occurrence of overgrowth. The phenytoin group had significantly greater incidence of tissue enlargement compared to either the sodium valproate or control groups (153). A similar study in children failed to report gingival overgrowth in association with sodium valproate treatment (45). These findings lead one to conclude that sodium valproate carries a relatively low risk for development of gingival enlargement and may be a reasonable treatment alternative to phenytoin.

Cyclosporin-induced gingival overgrowth

Cyclosporin A was first isolated in Switzerland in 1970 as a metabolite of the fungus species *Tolypocladium inflatum Gams* but proved to have little value as an antifungal antibiotic. However, as a cyclic polypeptide with potent immunosuppressive action, cyclosporin A prolongs survival of allogeneic transplants involving skin, heart, kidney, liver, pancreas, bone marrow, small intestine and lung. Cyclosporin A (Sandimmune™; Neoral™) has been demonstrated to suppress some humoral immunity (B lymphocytes); and to a much greater extent, cell-mediated immunity (T lymphocytes) such as allograft rejection, delayed hypersensitivity, graft-versus-host disease and autoimmune diseases.

Pharmacokinetics

The discovery of cyclosporin A is attributed to Jean Borel, and its first reported use (in renal transplantation procedures) was by Calne et al. (26). The exact mechanism of action of cyclosporin A is not known, but its effectiveness is due to a specific and reversible inhibition of immunocompetent lymphocytes. T lymphocytes are preferentially inhibited, with T-helper cells as the main target, although T-suppressor cells also may be suppressed. Specifically, cyclosporin A inhibits interleukin-2 (IL-2) synthesis and release at oral dosages of 10–20 mg/kg body weight per day (serum concentrations of 100–400 ng/ml). At these therapeutic levels, cyclosporin A also inhibits the ability of cytotoxic T lymphocytes to respond to IL-2 while it has a sparing effect on T-suppressor cells. In addition, cyclosporin A produces immunosuppression by inhibiting the activation of macrophages and preventing the production of IL-1 receptors on the surface of T-helper cells. Therefore, cyclosporin A appears to be selective in its action on T lymphocytes (39, 151).

Cyclosporin A is water insoluble and absorption depends on the presence of bile salts. The drug is extensively metabolized in the liver and mediated through the cytochrome P450 monooxygenase enzyme system. Most of the metabolites are excreted via the bile through feces, with only 10% excreted through the kidneys. Impairment of liver or renal function may alter adequate absorption and excretion, leading to high blood levels of the drug. Peak plasma concentrations of cyclosporin A occur 3–4 hours after administration, and the drug has a serum half-life of 17–40 hours (13).

Cyclosporin A is widely used for prevention of organ transplant rejection, either as the primary immunosuppressant or in combination with steroid therapy (25, 160). It has also been shown to reduce morbidity from graft-versus-host disease in bone marrow transplants (132). The drug has also been effective in disorders of the immune system, including insulin-dependent diabetes, Behçet's disease, rheumatoid and psoriatic arthritis, bullous pemphigoid and pemphigus, Crohn's disease, ulcerative colitis and pulmonary sarcoidosis (4, 55, 98, 107, 116, 137, 163, 170).

The adverse side effects of cyclosporin A include gingival overgrowth and multiple systemic effects. Most of these effects are dose-dependent and are frequently reversible without sequelae upon decrease or discontinuance of the drug. Nephrotoxicity is well documented and reversible, showing oliguria

and weight gain related to high serum trough levels. It has been noted in 25% of renal transplant cases, 38% of cardiac transplants and 37% of liver transplant cases (83). Hepatotoxicity occurs less frequently than nephrotoxicity and is characterized by elevated serum bilirubin, transaminase and alkaline phosphatase levels, all of which are reversible via dose reduction. Hypertension is a common finding, with an incidence ranging from 38.5% to 51.2% in studies of renal transplant cases (57). Other less common side effects include lymphomas, Kaposi's sarcoma, squamous cell carcinoma, hyperuricemia, hyperkalemia, mild anemia, neurotoxicity, visual disturbances, depression, hypertrichosis and a predisposition to bacterial, viral and fungal infections (7, 54, 176).

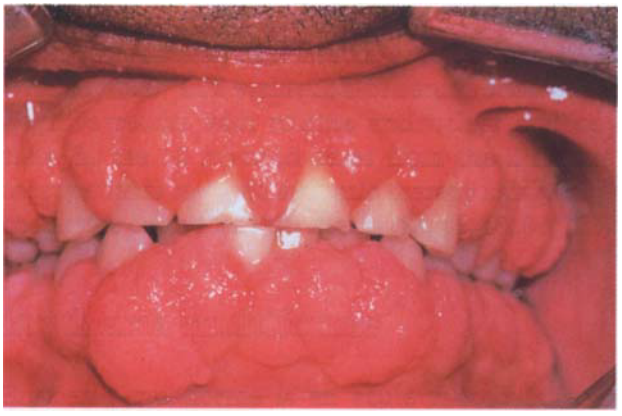

Fig. 5. A 35-year-old man taking cyclosporin A for the past 8 years following a kidney transplant. The presence of generalized gingival overgrowth is seen on both arches obscuring the clinical crowns (photo courtesy of Michael P. Najera).

Clinical manifestations

The first cases of gingival overgrowth caused by cyclosporin A medication in the dental literature were reported by Rateitschak-Plüss et al. (136). They studied 50 kidney transplant patients, most of whom developed gingival enlargement after 4–6 weeks of cyclosporin A treatment. None demonstrated recurrence after the teeth were extracted. Tyldesley & Rotter (176) evaluated 36 renal transplant cases, finding gingival overgrowth in nine patients (25%), with females showing higher incidence than males; 38% to 17% respectively. The cyclosporin A–induced enlargement was more pronounced on the labial aspect of the gingiva and demonstrated considerable bleeding when surgically removed. Friskopp & Klintmalm (49) indicated that the overgrowth was restricted to keratinized gingiva but could extend coronally and interfere with occlusion, mastication and speech. The authors found that 21 of 26 patients (81%) receiving cyclosporin A showed gingival overgrowth, whereas none of the control group receiving azathioprine demonstrated this side effect. They also noted an absence of overgrown tissue in edentulous patients receiving either medication. The enlarged gingival tissues were soft, red or bluish-red, extremely fragile and bled easily upon probing.

These enlarged tissues are generally more hyperemic than the gingival tissues associated with phenytoin-induced overgrowth, which has been reported by several authors (Fig. 5, 6). Rostock et al. (143) reported spontaneous repositioning of migrated teeth after removal of the enlarged tissue, resulting in visible narrowing of diastemata as early as 2 months after surgery, indicating that the tooth migration was a result of cyclosporin A–induced gingival overgrowth. Daley et al. (37) evaluated 100 patients over 2.5 years and reported that 70% exhibited at least mild gingival overgrowth. They suggested that progressive enlargement occurred over several months, often reaching a plateau after 1 year of cyclosporin A therapy. Seymour et al. (152) investigated 24 adult renal transplant patients receiving either azathioprine or cyclosporin A. The cyclosporin A patients seen 3 and 6 months post-transplant had significantly more gingival overgrowth, with probing sites greater than 3 mm. They suggested an incidence of 30% for clinically obvious cyclosporin A-induced overgrowth. In a more recent study, these authors suggested that overgrowth was more likely to develop if the plasma concentration of cyclosporin A exceeded 400 ng/ml (71, 150).

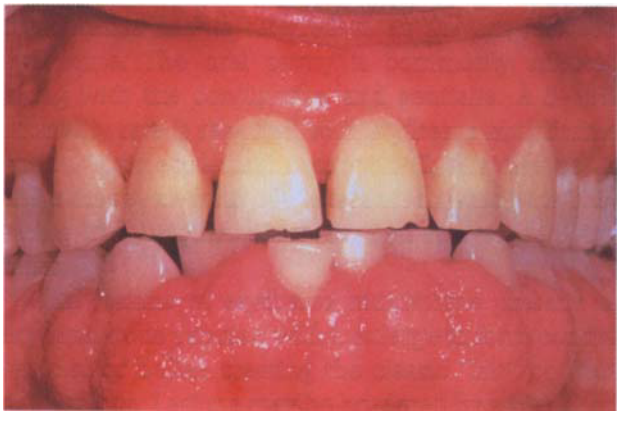

Fig. 6. Same patient 3 months following laser removal of the maxillary gingival overgrowth and prior to removal of the mandibular tissues

The plasma concentration of cyclosporin A re-

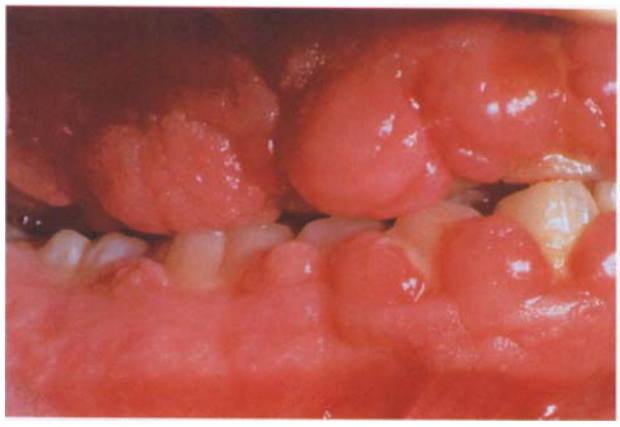

Fig. 7. A 42-year-old man taking cyclosporin A plus nifedipine following a kidney transplant 5 years ago. Note the excessive overgrowth of tissue with an inflammatory component (photo courtesy of Eva Ingles).

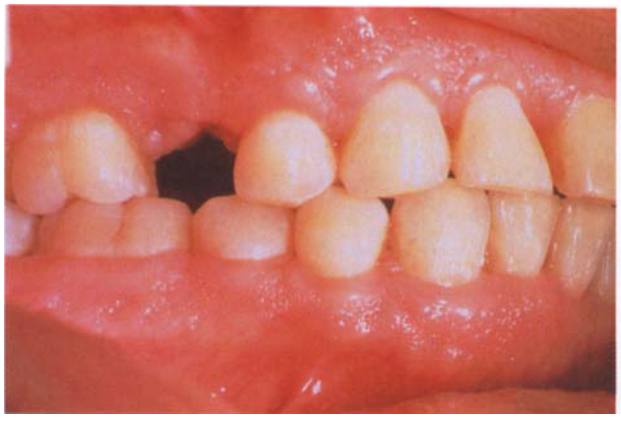

Fig. 8. Same patient 6 months following full mouth gingivectomy and strict supportive periodontal therapy. There has been no recurrence of the gingival overgrowth.

quires a threshold level of the drug for gingival overgrowth to occur, as reported by Hefti et al. (71) in 90 multiple sclerosis patients. In this double-blind study, 40 patients were treated with cyclosporin A and 50 patients with a placebo drug. Seventeen percent of those on cyclosporin A with blood levels below 400 ng/ml developed gingival overgrowth, whereas 59% taking cyclosporin A with blood levels above 400 ng/ml developed enlarged gingiva. This was in agreement with Fuiano et al. (50) and Somacarrera et al. (159), suggesting a positive correlation between cyclosporin A blood concentration and incidence of overgrowth.

Several studies demonstrated a greater risk of developing cyclosporin A–induced gingival enlargement in children, especially adolescents and young females (37, 71, 147, 150). Seymour & Jacobs (151) suggested a possible interaction between cyclosporin A, sex hormones and gingival fibroblasts.

The incidence of cyclosporin A–induced gingival overgrowth varies in each study and generally ranges from 25% to 50%. These differences may relate to drug dosage, plasma concentration, duration of therapy, method of assessing gingival enlargement, underlying periodontal status (especially the inflammatory component), age of the patient, medical status and genetic predisposition to be responders or nonresponders (50, 82, 124, 159).

Synergistic effects have been reported when cyclosporin A is administered concurrently with calcium channel blockers of the dihydropyridine derivatives (such as nifedipine). Slavin & Taylor (158) observed an increased rate of gingival overgrowth in patients taking both drugs compared with those on cyclosporin A alone. Pernu et al. (125) examined 27 renal transplant cases and noted a significantly increased percentage of moderately overgrown gingival units in the patients receiving both cyclosporin A and nifedipine (Fig. 7, 8). O'Valle et al. (119) compared through morphometric analysis patients treated with cyclosporin A alone or cyclosporin A plus nifedipine and found significant differences in their gingival overgrowth. They concluded that combined drug treatment was a significant risk factor for progression or recurrence of gingival overgrowth among susceptible patients. These findings were confirmed in studies by Thomason et al. (171) and Bökenkamp et al. (14) and demonstrated in a case report by Rossmann et al. (142), where substituting another antihypertensive medication for nifedipine allowed successful long-term management of gingival overgrowth in a previously unmanageable renal transplant patient. The recent advent of angiotensin-converting enzyme inhibitors as a preferred antihypertensive drug for renal transplant patients should provide the physician with a viable alternative to nifedipine.

Pathogenesis of gingival overgrowth

Extensive study over several decades has failed to elucidate the pathogenesis of drug-induced gingival overgrowth. Several factors may influence the relationship between the inducing drug and gingival tissues. Since fewer than 50% of patients taking cyclosporin A develop gingival enlargement, the terms "responders" and "nonresponders" have been used in the literature to identify these individual differences and perhaps a genetic predisposition. Wysocki et al. (184) suggested that gingival over-

growth was related to sensitivity of individuals to the drug or it's metabolites. Studies have shown that cyclosporin A and its major metabolite OL-17 could react with a phenotypically distinct subpopulation of gingival fibroblasts, causing an increase in protein synthesis and rate of cell proliferation (63, 76). Coley et al. (31) demonstrated that the effects of cyclosporin A on normal human fibroblast proliferation varied among individual cell strains, where strains were shown to increase, decrease, or remain unchanged. Fibroblast heterogeneity has also been studied, with cyclosporin A affecting the collagenase activity and tissue inhibitor of metalloproteinase activity. There were marked differences among fibroblast strains for collagenase and tissue inhibitor of metalloproteinase production when exposed to cyclosporin A, which may explain in part the variable gingival response in patients taking this drug (175). These studies and others have clearly shown the ability of cyclosporin A to alter the metabolism of human gingival fibroblasts. Another genetic factor that may relate to the expression of drug-induced gingival overgrowth is shown in studies of the human lymphocyte antigen (HLA). Pernu et al. (122) found that patients who expressed HLA-DR1 appeared to have a protective role against gingival overgrowth from cyclosporin A, whereas those expressing HLA-DR2 showed an increased risk for overgrowth. Cebeci et al. (27) later confirmed this in a study of responders versus nonresponders, indicating that an immunogenetic predisposition may have a major role in the pathogenesis of cyclosporin A–induced gingival overgrowth.

Connective tissue homeostasis is a related area of study for the pathogenesis of drug-induced gingival overgrowth, since an essential feature of this tissue is an increase in connective tissue matrix. Collagen production from gingival fibroblasts is controlled by synthesis and release of metalloproteinases and tissue inhibitor of metalloproteinases. *In vitro* studies have shown that cyclosporin A causes a significant increase in collagen synthesis, but not DNA synthesis, with a specific rise in the level of type I procollagen (146). Zebrowski et al. (185) evaluated the role of non-collagenous extracellular matrix glycosaminoglycans in cyclosporin A patients through H^3-glucosamine utilization. They suggested that increased tissue levels of non-sulfated glycosaminoglycans can occur with cyclosporin A exposure, possibly contributing to the occurrence of increased connective tissue matrix.

There is contradictory evidence in the *in vitro* studies. However, many aspects of connective tissue homeostasis may serve as targets for drug-induced gingival overgrowth, and the response of the connective tissue may be the main cause of this diseased condition (99). Growth factors have been studied recently as one obvious target for cyclosporin A-induced gingival overgrowth, and their activation may play an important role in the pathogenesis. Platelet-derived growth factor is a dimeric polypeptide, with the B chain acting as a major mitogen and chemoattractant for fibroblast proliferation and synthesis of glycosaminoglycans, fibronectin, and collagen. Increased gingival levels of platelet-derived growth factor-B may be responsible for promoting fibroblast proliferation and production of extracellular matrix constituents in gingival overgrowth. The macrophage is now recognized as the major mediator of connective tissue turnover, maintenance and repair through release of specialized cytokines (platelet-derived growth factor-B). A recent study by Iacopino et al. (74) revealed that platelet-derived growth factor-B messenger RNA is significantly increased in cyclosporin A gingival overgrowth tissue relative to normal controls and independent of the inflammatory state. This study also suggested that the macrophage plays a primary role in drug-induced gingival overgrowth through changes in phenotype and subsequent upregulation of specific growth factors such as platelet-derived growth factor-B. This was confirmed by Plemons et al. (130) and Nares et al. (109), supporting the theory that cyclosporin A–induced gingival overgrowth is associated with enhanced macrophage platelet-derived growth factor-B gene expression rather than an increase in the number of macrophages producing platelet-derived growth factor-B.

The pathogenesis of cyclosporin A–induced gingival overgrowth is truly mulifactorial and remains uncertain despite numerous investigative studies. Three significant factors appear to be important to the expression of gingival overgrowth: drug variables, plaque-induced inflammatory changes in the gingiva and genetic factors (154).

Histological characteristics

The histological features of all drug-induced gingival overgrowth are comparable, consisting primarily of connective tissue with an overlying irregular, multilayered, parakeratinized epithelium varying in thickness. Epithelial ridges penetrate deep into the connective tissue, creating irregularly arranged collagen fiber bundles. The connective tissue is highly vascularized, and focal accumulations of infiltrating in-

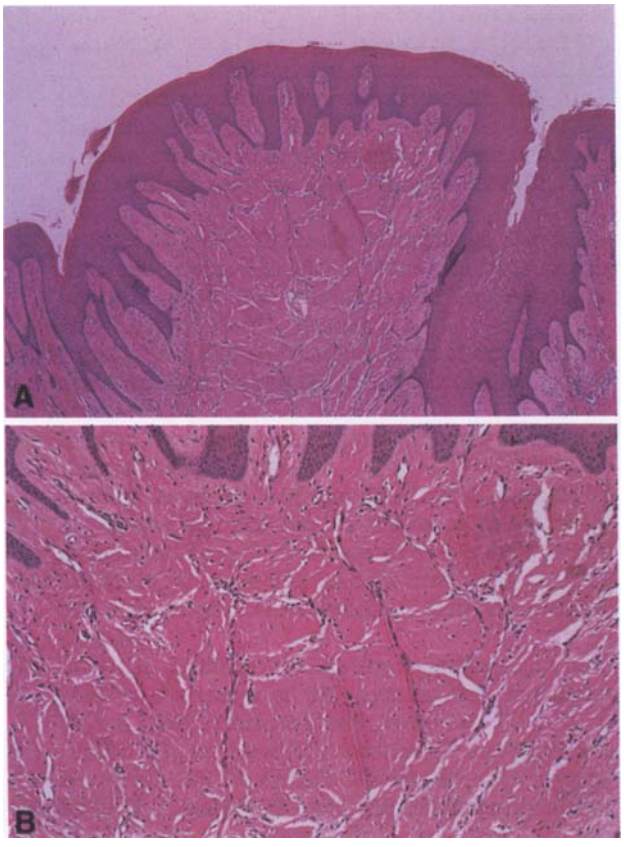

Fig. 9. A. Hematoxylin and eosin–stained section from a cyclosporin-induced gingival specimen. Note the similarity of this specimen to Fig. 3 showing epithelial rete ridges penetrating deep into the connective tissue. B. Higher power of the same specimen showing highly vascularized connective tissue with an inflammatory infiltrate and abundant amorphous ground substance.

flammatory cells have been seen (136). The predominant cell type in the inflammatory infiltrate is the plasma cell, with lymphocytes seen to a lesser degree. The mononuclear cell infiltrate has demonstrated the presence of T lymphocytes and monocytes adjacent to the junctional epithelium, with virtually no B lymphocytes (49). Others have noted acanthosis and parakeratinization of the epithelium with pseudoepitheliomatous proliferation. Focal areas of myxomatous change have been seen more often in the immediate subepithelial tissue than in deeper areas (143). Most histological studies have failed to demonstrate an increase in numerical density of fibroblasts, which has led to the impression that cyclosporin A–induced gingival enlargement is a result of an accumulation of non-collagenous material and a thickening of the epithelium (129). Therefore, the term "gingival hyperplasia" has been replaced by more accurate descriptions such as gingival overgrowth or enlargement (Fig. 9).

Ultrastructural and immunohistochemical examination of cyclosporin A–induced gingival overgrowth shows characteristics of active protein synthesis and secretion, with reduced cytotoxic or degenerative changes. An increased proportion of cells, termed myofibroblasts, have been found which are modified fibroblasts. Additional findings have suggested that cyclosporin A–induced gingival overgrowth is a consequence of individual hypersensitivity to the drug, since abundant amorphous substance has been seen compared with fibrous material, with a marked plasma cell infiltrate in the gingival tissues. As a result, Mariani et al. (96) proposed the term "dimensional increase of gingival tissue" as the most appropriate term for this disease-related change. In a later study, Mariani et al. (97) found that the basal and spinous layers of epithelium show distinct dilatation of the intercellular spaces, characteristic of disease-related overgrowth. The dimensional increase in gingival overgrowth is due to an increased production of amorphous ground substance by the fibroblasts, containing increased numbers of both sulfated and non-sulfated glucosaminoglycans, possibly resulting from an increased release of histamine by mast cells.

Prevention and the role of inflammation

Considerable evidence supports the fact that plaque-induced gingival inflammation exacerbates the expression of drug-induced gingival overgrowth. Most studies suggest that improving plaque control and the resultant reduction in inflammation will inhibit the development and recurrence of gingival overgrowth. Inflammatory changes in the gingiva caused by plaque enhance the interaction between cyclosporin A and fibroblasts. Through selective immunosuppression, cyclosporin A has the ability to inhibit production of interleukins, which are potent stimulators of collagenase. McGaw et al. (99) have shown dental plaque to act as a reservoir for cyclosporin A, which may account for the suppression of immune response in gingival epithelium of cyclosporin A–induced overgrowth patients (112). Bartold (12) has demonstrated the ability of cyclosporin A to inhibit the effects of lipopolysaccharide upon fibroblasts. In concentrations where lipopolysaccharide from dental plaque would normally be cytotoxic for fibroblasts, the presence of cyclosporin A has negated this effect and allowed fibroblastic proliferation. Numerous studies have supported these findings and provide evidence that plaque-induced inflammatory changes have a significant part in the pathogenesis

of cyclosporin A–induced gingival overgrowth (154).

Prevention of cyclosporin A–induced gingival overgrowth has focused on reduction in gingival inflammation. Although studies have disagreed about the presence of plaque as a primary causative agent in cyclosporin A–induced overgrowth, few would dispute the additive effects of gingival inflammation in the development and recurrence of this condition. Rateitschak-Plüss et al. (136) found a significant improvement in gingival enlargement following initial debridement and stated that strict plaque control was of utmost importance in preventing recurrence. Several authors have supported this finding in the literature (2, 49, 71, 99, 124, 143, 159, 176). However, there have also been studies that have found a lack of correlation between plaque, gingival inflammation and cyclosporin A–induced gingival overgrowth. Seymour et al. (152) found no significant correlation between gingival overgrowth and plaque scores in 24 patients. Daley et al. (37) found only a weak correlation existing between plaque and severity of gingival overgrowth, whereas Schulz et al. (147) noted the presence of plaque and gingival inflammation was not found to be related to the incidence of gingival overgrowth in 80 renal transplant cases. Despite these differences, all authors agree that removal of local irritants and reduction of gingival inflammation are important in the management of cyclosporin A–induced gingival enlargement.

Calcium channel blockers

A group of drugs specifically developed to assist in the management of cardiovascular conditions, including hypertension, angina pectoris, coronary artery spasm and cardiac arrhythmia, has been introduced in recent years (168). These drugs, termed calcium channel blockers or calcium antagonists, have proven extremely effective and have entertained extensive and widespread use throughout the world.

Calcium channel blockers may be classified on the basis of their chemical composition as benzothiazepine derivatives (diltiazem), phenylalkylamine derivatives (verapamil) or substituted dihydropyridines (amlopidine, felodipine, isradipine, nicardipine, nifedipine, nitrendipine, oxodipine, nimodipine and nisoldipine) (67, 138, 148).

Pharmacokinetics

Calcium channel blockers act by inhibiting calcium ion influx across the cell membrane of cardiac and smooth muscle cells, thereby interfering or blocking mobilization of calcium intracellularly (115, 138, 148). Depending on the specific agent, this results in dilatation of coronary arteries and arterioles, as well as decreased myocardial contractility and oxygen demand. Since 1978, the substituted dihydropyridines have been used to treat angina pectoris, postmyocardial syndrome and hypertension (67). The primary undesirable side effect of the calcium channel blockers results from excessive vasodilatation, which manifests as facial flushing, dizziness, headache and edema (87, 148). Ramon et al. (134) published the first report in the scientific literature that associated a calcium channel blocker (nifedipine) with the occurrence of gingival overgrowth in 1984. Since that time, human case reports of this associated side effect have been related to five other agents in this class, including amlodipine (149, 168), felodipine (92), diltiazem (16, 23, 32, 52), nitrendipine (21) and verapamil (Table 1) (101, 126). Another agent in this group, oxodipine, has been associated with gingival overgrowth in dogs (180) and rats (118). Publications in the scientific literature have validated the association of gingival overgrowth with calcium channel blockers, significantly increasing awareness of this undesirable side effect in the dental community. Indeed, all dental professionals are encouraged to carefully review the patient's medical history for prescribed calcium channel blockers and to closely examine and monitor gingival tissues for enlargement or dimensional morphological alteration as an integral part of their comprehensive oral examination.

Dihydropyridines

Gingival overgrowth has been reported in 15% to 83% (composite average=42.5%) of patients taking nifedipine (10, 11, 48, 158), approximately 21% of patients taking diltiazem (161) and about 4% of those medicated with verapamil (103). The wide prevalence range reported for nifedipine, the dihydropyridine derivative most often associated with gingival enlargement, may be attributed to variations in population characteristics, sample size and methods of evaluating the gingival enlargement. In a recent study, Nery et al. (111) reported a 43.6% prevalence of gingival hyperplasia among 181 patients taking nifedipine as compared with 4.2% in 71 control patients who were not taking phenytoin, calcium channel blockers or cyclosporin. The 43.6% reported by these investigators compares favorably with the 42.5% (composite average) (10, 11, 48, 156) of the

four referenced studies. Since more patients take nifedipine, accurately determining the true incidence of gingival overgrowth among patients taking various calcium channel blockers is difficult.

Attempts to relate dose or plasma levels of the calcium channel blockers with the occurrence of gingival overgrowth have yielded mixed results. Ishida et al. (75) and Nishikawa et al. (113) reported that a minimum blood level of 800 ng/ml of nifidipine resulted in gingival overgrowth in a rat model and that the degree of overgrowth depended on increased concentrations above this threshold value. Human studies have not supported a relationship between dose or plasma levels of these agents and gingival overgrowth (11, 22, 46, 111, 171). Despite the absence of any evidence corroborating a relationship between nifedipine dose and overgrowth, it is reasonable to suggest that a trough or threshold level must precede the onset of gingival enlargement. This value may differ depending on host (responder) susceptibility and sensitivity.

In a study of nine patients who had taken nifedipine (40 to 80 μg/ml) for at least 6 months, Ellis et al. (47) assayed nifedipine levels in the plasma and gingival crevicular fluid. Five patients (responders) had notable gingival enlargement while four were unaffected (non-responders). Nifedipine concentration in the gingival crevicular fluid was 15 to 316 times greater than plasma levels in seven of nine subjects. Nifedipine could not be detected in the gingival crevicular fluid of two nonresponders. The authors suggest that the very high concentrations of nifedipine that may occur in gingival crevicular fluid favor the likelihood of toxic effects. In a recent human study on cardiac transplant patients medicated with cyclosporine and nifedipine, significant levels of nifedipine were detected in the gingival crevicular fluid. The gingival crevicular fluid levels had no apparent relationship to gingival changes or to plasma nifedipine concentrations (171).

As previously noted, several other substituted dihydropyridine calcium channel blockers are available that exert slightly different cardiovascular effects based primarily on selected sites of action. Amlodipine is an anti-anginal calcium channel blocker that acts by decreasing myocardial contractility and oxygen demand and that dilates coronary arteries and arterioles (115). In a report of three cases of associated gingival overgrowth, Seymour et al. (149) detected amlodipine in the gingival crevicular fluid of each individual, all of whom were long-term recipients of the medication.

In 1990, Brown et al. (21) reported the first case of gingival overgrowth induced by nitrendipine. At that time, this agent was being used in an experimental protocol to treat hypertension and congestive heart failure. Heilj & Sundin (72) previously noted that beagle dogs that were administered nitrendipine over a 20-week period developed marked gingival overgrowth, suggesting this side effect should be expected with this class of medications. A year later, Lombardi et al. (92) reported gingival overgrowth in a patient taking felodipine, a calcium channel blocker that selectively inhibits smooth muscle without directly causing negative cardiac effects and that has proven effective in managing hypertension (67).

Because the case report data on the dihyropyridine agents other than nifedipine are limited the incidence of associated gingival overgrowth remains speculative.

Clinical manifestations

The clinical features of the gingival changes reported in association with calcium channel blockers are similar among all agents of this class (94, 148, 166, 177). The interdental papillae are initially affected, becoming enlarged and resulting in a lobulated or nodular morphology (148). These effects are limited to the attached and marginal gingiva, and are more frequently observed anteriorly, especially on the facial surfaces (84, 148, 177). The enlarged gingival tissues are often accompanied by inflammatory changes associated with poor plaque control (Fig. 10). As the tissues become progressively larger, plaque control becomes more difficult. The enlarged gingiva may extend coronally and partially or completely obscure the teeth, presenting aesthetic and functional difficulties for affected patients (148). Although overgrowth does not appear to affect edentulous areas (93, 182), nifedipine-induced gingival enlargement has been reported around dental implants (157). It should be noted that calcium channel blockers, especially nifedipine, are often used to control hypertension and reduce cyclosporin A toxicity in renal transplant patients. Thomason et al. (171) and Bökenkamp et al. (14) reported increased severity of gingival overgrowth when these two agents were combined, compared with cyclosporin A alone.

Pathogenesis

Despite unrelated pharmaceutical effects, the calcium channel blockers and phenytoin have a common mechanism of action related to the ability of each of these agents to affect calcium metabolism.

Investigations continue to pursue the patho-physiological mechanisms that mediate the gingival overgrowth associated with these agents. The reader is referred to the sections in this chapter on cyclosporin A and anticonvulsants for a review of this subject. Among the factors that may influence the pathogenesis of drug-associated gingival overgrowth are age, genetic predisposition, pharmacokinetic variables, alterations in gingival connective tissue homeostasis and drug effects on growth factors (154).

There does not appear to be a clear relationship between the dose of nifedipine and gingival enlargement. Indeed, the influence of dosage, age, duration of medication, length of time taken, and sequestration of the agent in gingival crevicular fluid warrant further investigation (46, 47, 148). Fujii et al. (51) tested the effect of calcium channel blockers on cell proliferation, DNA synthesis and collagen synthesis on gingival fibroblasts from human nifedipine responders and nonresponders. Cells were tested with nifedipine, diltiazem, verapamil and nicardipine *in vitro*. Responder fibroblasts trended toward greater cellular proliferation rates, DNA synthesis and collagen synthesis compared to the cells from nonresponders or phenytoin positive controls (51). Barclay (11) notes that the collagenolytic effects of inflammatory cells and synthesis of collagenase are calcium-dependent cellular events. Nifedipine, phenytoin and cyclosporin A may interfere with calcium transport and calcium-dependent processes. These agents may reduce cytosolic calcium levels in gingival fibroblasts and T cells, thus interfering with T-cell proliferation or activation and collagen synthesis by gingival fibroblasts (11).

Lucas et al. (93) and Jones et al. (79) suggested that gingival overgrowth results from overproduction of extracellular ground substance characterized by increased presence of sulphated-mucopolysaccharides (glycosaminoglycan) and collagen, and abundant active fibroblasts. McKevitt et al. (100) used fibroblasts from responders and nonresponders to study the effect of phenotypic differences in growth, matrix synthesis and response to nifedipine. The responder cells presented increased growth potential and produced greater levels of protein and collagen than did nonresponder cells. An interesting and unexplained finding was the inhibition of these markers when exogenous nifedipine was added to responder cells and no effect when added to nonresponder cells (100), which suggests the presence of an indirect mechanism or interaction with inflammatory cytokines.

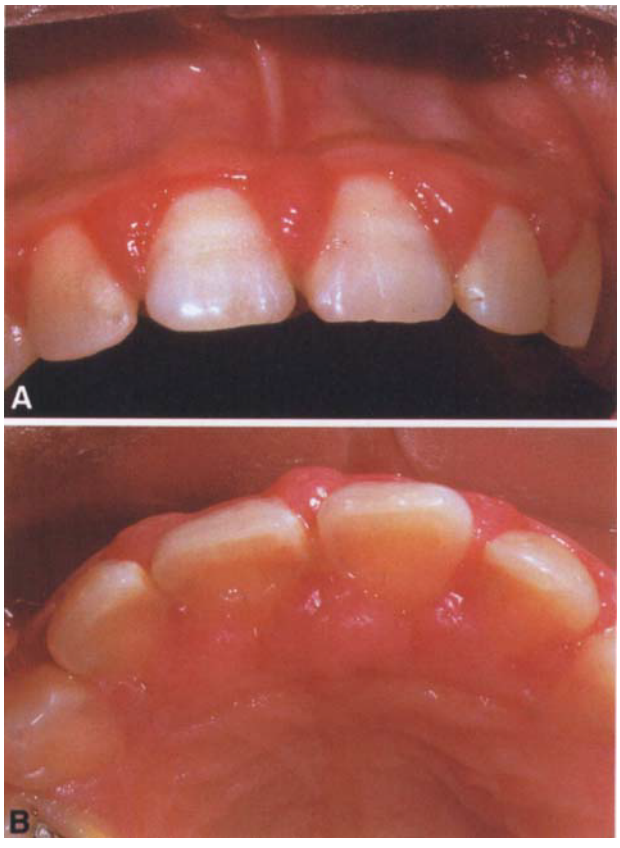

Fig. 10. A. Patient on nifedipine therapy with associated gingival overgrowth. Note enlarged papillae with erythematous margins indicative of inflammation and the pseudoclefts resulting from coverage of adjacent marginal tissues. B. Occlusal view of the patient discloses lateral and coronal extent of the tissue enlargement, which may affect phonetics and function and adversely affect patient oral hygiene and aesthetics.

Investigations related to the pathogenesis of drug-associated gingival overgrowth have been published by Dill et al. (40) and Iacopino et al. (74), and were reviewed in conjunction with the pathogenesis of phenytoin-associated gingival overgrowth section of this chapter.

Histological characteristics

As noted previously, the histological features of all drug-associated gingival overgrowth are comparable (10, 21, 93, 94, 177). Although the connective tissue changes may be predominant, the epithelium exhibits parakeratosis, proliferation and elongation of the rete ridges, which extend some distance into the lamina propria (111, 177). Van der Wall et al. (177) reported a ten-fold increase in epithelial width (normally 0.3 to 0.5 mm), inflammatory changes accompanied by edema, and infiltrates of lymphocytes

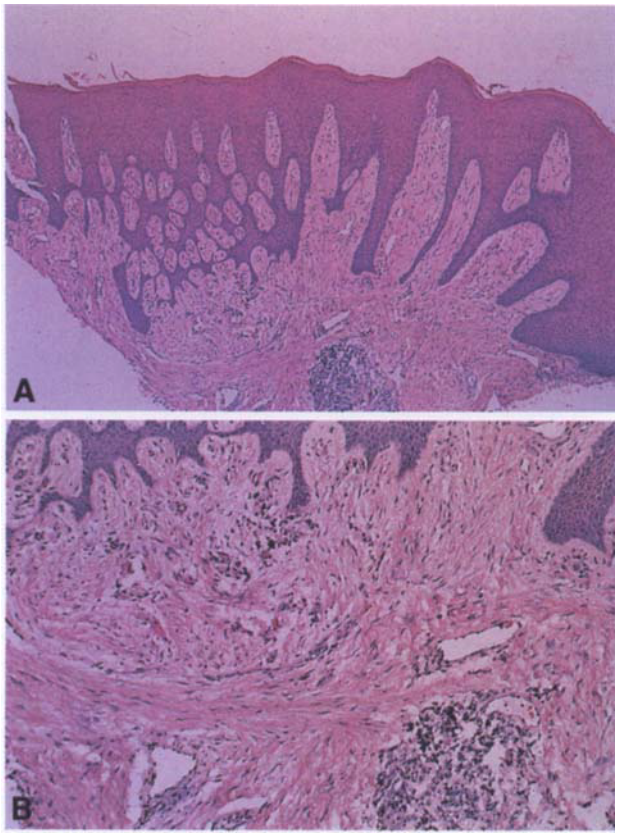

Fig. 11. A. Hematoxylin and eosin–stained specimen from a patient with nifedipine-associated gingival overgrowth, showing hyperkeratotic epithelium that is characterized by long, thin, often interlacing rete pegs. B. The epithelial rete pegs extend deep into the lamina propria, which manifests collagenous and non-collagenous elements, numerous fibroblasts, vessels, and a foci of inflammatory cells deep within the specimen.

and plasma cells. In a study of 34 biopsies of nifedipine gingival overgrowth, Barak et al. (10) described thickening of the spinous cell layer, slight to moderate hyperkeratosis, fibroblastic proliferation and fibrosis of the lamina propria (Fig. 11). These changes were accompanied by increased capillary vascularity and slight perivascular inflammation. Similar to other drug-induced gingival overgrowth histological descriptions, the specimen presented long, tubular rete pegs consisting of layered basal cells that extended deep into the lamina propria (10). The histological changes observed in felodipine-induced gingival enlargement are consistent with those described for nifedipine (92).

Prevention and treatment

Control of gingival inflammation and maintenance of effective oral hygiene are key factors in preventing and managing gingival overgrowth associated with this class of medications (113, 161). The basic approaches to therapy closely parallel those previously discussed for anticonvulsants and cyclosporine-associated gingival enlargement. In an interesting case report, Hancock & Swan (58) successfully achieved significant reduction of nifedipine-induced gingival overgrowth by thorough scaling and root planing and scrupulous plaque control. Surgical reduction of the overgrown tissues is frequently necessary and may consist of conventional gingivectomy and/or laser gingivectomy. Patients must be informed of the tendency for the gingival enlargement to recur as long as the associated medication is continued. In instances where alternate medications can be used, cessation of the associated agent has been shown to result in tissue reduction (85, 113, 161). Regression of nifedipine-induced gingival overgrowth has been reported following a change in medication to isradipine, a companion dihydropyridine calcium channel blocker. Sixty percent of the study patients switched to isradipine experienced a decrease in gingival overgrowth, while comparable patients continuing nifedipine therapy demonstrated a 66% increase (181). When the physician agrees to use an alternative calcium channel blocker in patients with gingival overgrowth, continued monitoring of the gingival tissues is warranted, since most agents in this class may be associated with overgrowth (139). Although discontinuing the use of nifedipine has resulted in gingival improvement within 1 week (85), appreciable response may require much longer (84). Reinstitution of nifedipine therapy following withdrawal has resulted in recurrence of the gingival overgrowth within 4 weeks (85). The use of chlorhexidine mouthrinses and gel has also been suggested as a plaque control adjunct in affected patients (14).

Supportive follow-up care should be recommended for the patient in an effort to monitor the gingival (periodontal) status, to assess and reinforce oral hygiene efforts and to periodically provide professional care.

Other calcium channel blockers

Two other classes of calcium channel blockers have been associated with gingival enlargement. These include diltiazem, a benzothiazepine derivative and verapamil, a phenylakylamine.

Diltiazem is used in the management of angina pectoris and for treatment of hypertension (44). Because only a few cases of gingival overgrowth associated with diltiazem have been reported, it has been

difficult to accurately assess incidence of this side effect (16, 32, 52, 148). Steele et al. (161) compared 115 patients taking calcium antagonists with 27 unmedicated controls and reported a gingival enlargement prevalence of 21% with diltiazem, 19% with verapamil and 4% in controls. The clinical and histological features of diltiazem-associated overgrowth are similar to those observed with phenytoin and other calcium channel blockers that present this side effect (16, 148, 161, 183). Although the pathogenic mechanism is not well understood, a common factor among the anticonvulsants (phenytoin) and calcium channel blockers relates to cellular calcium interaction. The medication may act directly or indirectly on calcium dependent mechanisms to alter collagen homeostasis and adversely affect the gingival tissues (148). In a heart patient who developed gingival overgrowth as a result of verapamil therapy, discontinuance of the drug resulted in resolution. However, the overgrowth recurred when an alternate medication, diltiazem, was administered, suggesting a similar mode of action at the gingival level (52). Close cooperation and communication with the patient and physician are key factors for effective management.

Verapamil is used to treat angina pectoris, essential hypertension and supra-ventricular arrhythmias (103). Although Steele et al. (161) reported a 19% prevalence rate of gingival enlargement among verapamil patients, Miller & Damm 103) found this side effect in only 4% of verapamil subjects examined. The clinical features of this lesion parallel those previously described for other drugs associated with gingival overgrowth (103, 148, 182). Prevention and treatment are directed at meticulous plaque control, scaling and root planing, antiseptic rinses and surgical approaches described elsewhere in this chapter (101, 103). Discontinuance of the medication is the only absolute treatment for associated gingival symptoms, which may resolve within 15 days (52). Because of the relatively low apparent risk of gingival overgrowth with this agent, it has been used as a treatment alternative to other calcium channel blockers (134).

Conclusion

Three very different groups of pharmaceutical agents have been associated with the occurrence of gingival overgrowth in susceptible individuals. These agents are anticonvulsants, cyclosporin and calcium channel blockers. Despite their pharmacological diversity, all three types of drugs have a similar mechanism of action at the cellular level, where they inhibit intracellular calcium ion influx. Therefore, the action of these various drugs on calcium and sodium ion flux may prove to be the key to understanding why three dissimilar drugs have a common side effect upon a secondary target tissue, such as gingival connective tissue. The clinical manifestation of gingival overgrowth is similar in all three agents. The enlargement is confined to the gingiva, beginning in the papillary tissues and extending outward. The color and texture is influenced by the presence of plaque-induced inflammation and the underlying periodontal condition.

Histological appearance of gingival overgrowth has common characteristics for all drug-induced enlargement such as an increase in extracellular ground substance and number of fibroblasts. The inflammatory changes within the gingival tissues appear to influence the interaction between the inducing drug and the fibroblastic activity. This relationship between plaque, gingival inflammation and drug-induced gingival overgrowth has been confirmed. Treatment and prevention begins with removal of plaque and calculus, establishing good oral hygiene practices and frequent recalls for supportive therapy. Although many patients respond favorably to nonsurgical treatment of their gingival enlargement, a significant number require surgical removal of the overgrown tissues to accomplish an aesthetic and functional result. Comparable therapeutic outcome by gingivectomy has been reported with knives, lasers or electrosurgery. Since the prescribed drug is a causative agent for gingival overgrowth, recurrence is common and is correlated with control of gingival inflammation, compliance by the patient with regular and frequent supportive periodontal therapy and stability of the medical condition. Until the medical community can provide alternative drug therapy with comparable efficacy that does not induce gingival overgrowth, dental practitioners will be tasked with the labor intensive management of this unwanted side effect. Efforts to increase awareness about this condition within the medical community should continue, and early identification of patients susceptible to drug-induced gingival overgrowth will help minimize the treatment time needed to control this entity.

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