PHENYTOIN-SODIUM INDUCED GINGIVAL OVERGROWTH

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CONTENTS

FIGURES AND TABLES

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SUMMARY

Epilepsy is a fairly common condition and the anti-convulsant drug, phenytoin sodium, has been used in its treatment for over 40 years. Shortly after its introduction, the side-effect of gingival overgrowth was reported and has been the subject of much research. Epidemiological studies showed that gingival overgrowth developed in approximately half the patients treated with this drug, possibly indicating an individual patient susceptibility to this effect of the drug.

One of the aims of this study was to establish an objective method for measuring the amount of gingival overgrowth which occurs in response to the use of phenytoin sodium. The indices used thus far have been too subjective to allow reliable reproducibility. Consequently, it was decided to develop a photometric technique which could be utilized to measure gingival overgrowth. Such methods have been successfully employed to study gingivitis, for the evaluation of colour and morphological changes as well as for epidemiological surveys and a study of mottled enamel.

A standardized technique for taking clinical photographs was devised utilizing a camera supported on a tripod and aligned to each subject in terms of vertical, horizontal and coronal planes. A stainless steel sphere 5 mm in diameter, was attached to the labial surface of the upper left central incisor of each individual to standardize subsequent enlargement. The resultant 35mm colour transparencies were

projected onto a horizontal screen in a custom made viewing box and a standard enlargement of four times actual size was obtained using the image of the 5mm stainless steel sphere. The outlines of the maxillary and mandibular anterior teeth and their interdental papillae and adjacent attached gingiva were traced. A standard technique was used to outline the five upper and lower interdental areas of each subject and these were measured with a compensating polar planimeter. The mean for each of the clockwise and anti-clockwise measurements was then recorded as the overgrowth value for the specific patient. This technique was utilized on 25 epileptic subjects and repeated approximately six weeks later. The resultant sets of data were statistically examined, using the Rank Spearman correlation co-efficient (Rs), in order to establish whether a statistically significant difference could be demonstrated between the two sets of measurements. The results revealed that the data obtained were not different at a probability value of $P<0,01$ for either the maxillary or mandibular surface area measurements. A graphic representation revealed an almost linear relationship between the two (see Figure 5.7). This is particularly significant as the four-fold enlargement used would tend to exaggerate any differences between the two sets of data recorded.

In view of the fact that it was possible to use this procedure to calculate the surface area of the interdental papillae and to successfully repeat the process at a later date, this technique was considered an important addition to the existing methods available for measuring gingival overgrowth.

The same photometric technique was employed to obtain the gingival surface areas of a control group of 25 age and sex matched subjects who had never used phenytoin sodium. These results compared to the mean of the two measurements previously obtained for the 25 epileptics revealed no significant difference at a probability level of $P<0,05$, using the Mann-Whitney U-test. This indicated that the experimental group had a level of gingival overgrowth which was not different from the control group. On the other hand, using a traditional method (Angelopoulos and Goaz, 1972), it was found, however, that the experimental group seemed to have mild overgrowth which indicated the subjective value of the methods used previously. It can thus be concluded that the epileptics studied revealed no noticeable hyperplasia probably because their institution insisted on a good plaque control programme, thus minimizing the risk of gingival overgrowth. In light of the fact that plaque is considered important in the pathogenesis of diphenylhydantoin-induced gingival overgrowth (DGO), the low plaque and gingival indices further support this view.

Several other parameters were investigated using 39 epileptic subjects (the 25 used above plus 14 others) in order to study variations in this sample with regard to age, sex, dosage and duration of drug usage, as well as the plaque, gingival and hyperplasia indices and the volume of gingival crevice fluid. The results obtained from the variables were analysed and no statistically significant differences were found with respect to age, sex or duration of drug usage. However, there was a definite correlation between age and sex with dosage.

The plaque index calculated on a score of 0 - 3 had a mean value of 1,11 while the means for the gingival and hyperplasia indices were 0,28 and 1,10 respectively. These data indicated that only minimal plaque accumulation was present in this sample with at most, a mild gingivitis. These findings concur with the results obtained in respect of gingival overgrowth.

The mean value of 155 Periotron® units recorded, however, indicated a severe gingivitis and was thus not in keeping with the results obtained for the other parameters studied (vide supra). However, it is highly probable that this mean value was erroneous as the Periotron is a very sensitive instrument which has been shown to be accurate but for only small volumes of serum. Furthermore, the old model used in this study was not accurate and produced marked variations which were further aggravated by the presence of moisture and debris on the recording jaws of the instrument. In this respect, the readings were not obtained under ideal conditions with the lack of suction being a major problem in controlling moisture. The generally accepted view, however, is that a definite correlation exists between the volume of gingival crevice fluid (G.C.F.) and inflammation.*

Finally, all variables were cross-correlated and 36 pairs were examined for a significant relationship. Seven of these were found to be statistically significant using the Rank-Spearman correlation coefficient. These were plaque index as related to gingival index, gingival crevice fluid and hyperplasia index while G.C.F. was also

**Harco Electronics, Siemens, Germany.*

found to be significantly related to the hyperplasia index. Furthermore, the correlation between dosage and maxillary gingival overgrowth and dosage and age were both found to be statistically significant at a level of $P < 0,01$ as were the maxillary and mandibular surface area recordings. These results conform with those generally found in the literature and support the view that the prevalence and severity of DGO are affected by many factors with plaque control being the most important.

In conclusion, the results achieved have shown that the photometric technique developed is accurate, objective and reproducible and one which can be used in further research. Furthermore, it was found, in concurrence with most other reports, that an excellent standard of oral hygiene appears to be the most practical method for controlling the degree of phenytoin-induced gingival overgrowth.

OPSOMMING

Epilepsie is 'n redelik-algemene toestand en die antikonvulsiewe middel, fenitoïen-natrium, is alreeds vir die afgelope 40 jaar daarvoor in gebruik. Kort nadat die middel bekend gestel is, is die newe-effek van gingivale oorgroeiing opgemerk en dit was dan ook sedertdien die onderwerp van vele verslae. Epidemiologiese inligting dui daarop dat die gingivale oorgroeiing in ongeveer die helfte van die gebruikers van die middel mag ontstaan. Dit dui waarskynlik op indiwiduele pasiëntvatbaarheid vir hierdie effek van die middel.

Een van die doelwitte van die huidige ondersoek was om 'n betroubare en objektiewe metode te ontwikkel vir die bepaling van die gingivale oorgroeiing wat met die gebruik van fenitoïen-natrium gepaard gaan. Tot op hede is indekse gebruik wat te subjektief van aard was om betroubare herhaalbaarheid te verseker. Gevolglik is besluit om 'n fotometriese tegniek vir die doel te ontwikkel omdat soortgelyke metodes met welslae gebruik is vir gingivitisondersoeke waar kleur en/of morfologiese veranderings as maatstawwe gedien het, asook vir die bepaling van glasuurvlekke.

Kliniese fotos is geneem met gebruik van 'n metode wat 'n vaste vertikale, horisontale en koronale verhouding tussen kamera en onderwerp verseker het. 'n Vlekvrye-staal-sfeer, 5mm in deursnee, is op die labiale vlak van die boonste linker snytand geplak om latere vergrot-

ing te standardiseer. Die 35mm-kleurtranspirante aldus verkry is op 'n horisontale vlak teen 'n vaste vergroting, soos bepaal met behulp van die sfeer, geprojekteer en die buitelyne van die hiperplastiese weefsel in beide mandibulêre en maksilêre gebiede nagetrek. Afgebakende interdentale gebiede is gemeet met behulp van 'n kompenserende planimeter en die gemiddelde van die kloks -en antikloksgewyse metings as die waarde in die betrokke geval geneem. Hierdie tegniek is gebruik op 25 epileptiese persone en na ongeveer 6 weke weer op dieselfde individue herhaal. Die twee stelle metings is statisties vergelyk met gebruik van die Rank-Spearman korrelasie-toets (Rs). Geen statisties-betekenisvolle verskille is egter waargeneem nie, by 'n waarskynlikheidsvlak van $P<0,01$, vir beide maksillêre en mandibulêre oppervlaksmetings. Grafies word hierdie korrelasie in Figuur 5.7 aangedui as 'n reglynige verhouding. Die resultate is veral geldig as in aggeneem word dat die metings teen 'n viervoudige vergroting gemeet is.

Gesien die feit dat die metode van oppervlaksbepaling van die interdentale papille betroubaar herhaal kon word by 'n latere ondersoek, kan die tegniek beskou word as 'n nuttige toevoeging tot die huidige metodiek vir die bepaling van gingivale oorgroeiing.

Hierdie selfde metode is ook gebruik om die gingivale oppervlakte van 'n kontrole-groep van 25 persone te meet wat vergelykbaar was ten opsigte van ouderdom en geslag. Die gemiddelde waardes aldus verkry is met die van die epileptiese groep vergelyk maar geen statisties-

betekenisvolle verskille is bespeur teen 'n waarskynlikheidspeil van 5% nie, soos bepaal met behulp van die Mann-Whitney - U-toets. Dit het dus aangetoon dat die gingivale oorgroeiing van die eksperimentele groep nie verskil het van 'n groep normale persone nie. In teenstelling hiermee is gevind dat, wanneer die kriteria van Angelopoulos en Goaz (1972) toegepas is, daar tog 'n matig-verhoogde oorgroeiing by die eksperimentele groep kon bestaan het wat dus slegs die subjektiewe aard van laasgenoemde metode onderstreep. Indien slegs die meer betroubare fototmetriese waardes geneem word, is egter gevind dat die groep epileptici geen noemenswaardige hiperplasie getoon het nie wat toegeskryf kan word aan die goeie plaakbeheer-program wat deur die betrokke inrigting toegepas is. Hierdie feit onderstreep verder die hipotese dat plaak 'n vername rol speel in die ontwikkeling van gingivale oorgroeiing as gevolg van hidantoïen-inname.

Verskeie ander veranderlikes is in die 39 epileptici (dit wil sê, die 25 oorspronklikes plus nog 14 ander) bepaal om sodoende die variasie van die kenmerke in die groep te ondersoek. Hierdie waarnemings het die volgende omvat: ouderdom, geslag, dosis en duur van middelgebruik, plaak-, gingivale- en hiperplasieindekse en die gingivale vogvloei. Statistiese analise het egter geen betekenisvolle verskille aangedui vir soverre dit ouderdom, geslag of duur van middelgebruik betref het nie. Daar was, egter, 'n duidelike korrelasie tussen ouderdom en geslag aan die een kant en dosering aan die ander. Die plaakindeks, gemeet op 'n skaal van 0 - 3, het in die groep epileptici 'n gemiddelde waarde van 1,11 getoon terwyl die waardes vir die gingi-

vale- en hiperplasie-indekse 0,28 en 1,10 respektiewelik was. Hierdie data dui dus aan dat die gemiddelde proefpersoon slegs 'n geringe plaakneerslag gehad het met gevolglike matige gingivitis. Die resultate sluit aan by die lae waardes wat gevind is vir gingivale oorgroeiing.

Die gemiddelde vogvloei-waardes van 155 Periotron®-eenhede het egter 'n ernstige graad van gingivitis aangedui wat dus teenstrydig was met die vroeere bepalings (sien hierbo). Hierdie verskil kan dalk aan tegniese foute met die gebruik van die Periotron-apparaat* gewyt word omdat dit, alhoewel uiters sensitief, slegs klein volumes vloeistof kan hanteer. Die verouderde model wat vir hierdie studie gebruik is, is ook waarskynlik minder akkuraat as latere modelle wat sedertdien beskikbaar geword het. Die apparaat kan ook maklik beinvloed gewees het deur vog en ander onsuiwerhede op die sensors van die instrument. Dit kan ook aanvaar word dat die omstandighede waaronder die metings gedoen is, minder as ideaal was, soos byvoorbeeld die gebrek aan goeie suiging. Alhoewel dit allerweë aanvaar word dat 'n duidelike verwantskap tussen die sulkulêre vogvloei en die graad van inflammasie bestaan, word die resultate verkry met die Periotron in hierdie studie dus as ongeldig beskou.

Alle veranderlikes was verder met mekaar gekruis-korreleer en sodoende is 36 pare waardes statisties ondersoek vir moontlike tendense. In slegs sewe gevalle is betekenisvolle verwantskappe ontdek soos bepaal

*Harco Electronics, Siemens, Germany.

met behulp van die Rank-Spearman korrelasie-koeffisient. Die plaak-indeks het gekorreleer met die gingivale indeks, met die sulkulêre vogvloei en met die hiperplasie-index terwyl daar ook 'n verwantskap aangetoon is tussen die vogvloei en hiperplasie-indeks. Verder is korrelasies gevind tussen die dosis en maksillêre gingivale oorgroeiings, dosis en ouderdom, en maksillêre en mandibulêre oppervlaksmetings almal teen 'n waarskynlikheid van p = 0,01. Hierdie waarnemings ondersteun dus die gepubliseerde resultate wat aandui dat die voorkoms en graad van gingivale oorgroeiing, as gevolg van difenielhidantoïen, deur verskeie faktore beïnvloed word waarvan plaakvlakke die belangrikste skyn te wees.

Die afleidings wat van die resultate van hierdie studie gemaak kan word toon dat die fotometriese tegniek wat ontwikkel is 'n akkurate, objektiewe en herhaalbare metode is en vir moontlik verdere studies aanbeveel kan word. Dit word ook afgelei dat, in ooreenkoms met heelparty ander verslae, uitstekende plaakbeheer die gingivale oorgroeiing wat gepaard gaan met die gebruik van difenielhidantoïen, kan beheer.

CHAPTER 1

INTRODUCTION AND AIMS OF STUDY

1. EPILEPSY

Epilepsy has been defined in a number of ways but most acceptable would be that of Toman (1970):

> "Epilepsy is a collective term for a class of chronic convulsive disorders which have in common the occurrence of brief episodes (seizures) associated with a disturbance or loss of consciousness. Usually, these episodes are accompanied by characteristic body movements and sometimes by autonomic hyperactivity and are always correlated with abnormal electroencephalographic discharges".

Statistical data show that more than one million persons in the United States of America suffer from recurrent seizures and that ten times that number have a history of seizure at some time in their lives (Hauser and Kurland, 1975). It is, however, not a modern disease but has been known since early times. Epilepsy was described as early as 75 BC by the poet Lucretius who referred to it as "falling sickness". A number of prominent historical personalities have been known to suffer from this disease most notably including Luther, Beethoven, Napoleon and Julius Caesar. The disease itself has fascinated a host of writers

ranging from Hippocrates and Aristotle to modern day researchers. The history of this disease is thoroughly reviewed in a recent monograph by Hassell (1981).

Several types of seizures are recognised and are broadly classified as generalised, localised or somatic (Adams and Victor, 1977). The generalised convulsion is by far the most common. It is characterised by an immediate loss of consciousness followed by stiffening and clonic rhythmic jerking of the limbs. Such seizures tend to commence in one part of the body and progress into a seizure with generalised motor activity. On cessation of the latter, consciousness is regained. The best known form of generalised seizure is the grand mal, a condition in which the generalised convulsions are followed by a state of coma. The comatose state may last up to half an hour leaving the patient drowsy, confused and suffering from severe headache.

Petit mal, or minor epilepsy, tends to occur between the ages of 4 years and adolescence. Motor activity is minimal but multiple episodes of momentary loss of consciousness are characteristic. This condition tends to disappear spontaneously during puberty.

Certain types of seizure such as the psychomotor type are preceded by an unpleasant taste or smell or some other aura, after which the patient enters into a dreamy state lasting from a few seconds up to several hours. Convulsive movements may occur, such as chewing, licking of the lips or turning of the head from side to side. A similar condition is the localised motor seizure which is associated with a frontal lobe lesion, from which dis-

charges may spread very rapidly, resulting in an immediate loss of consciousness. Sometimes the lesion is unilateral and results in the Jacksonian motor seizure, which commences as a clonic rhythmic twitching of the fingers, face or foot on one side and which then spreads to involve the entire ipsilateral side of the body.

Lesions of the parietal lobe may present with a sensation of pins-and-needles of the lips, toes, fingers and may even include hallucinatory reactions. This is known as the somatic sensory seizure and may be focal or become generalised, spreading to other parts of the body on the same side. Occasionally, a patient may have a series of seizures in rapid succession, which can be fatal if treatment is delayed. This condition is known as status epilepticus.

2. DRUG THERAPY FOR EPILEPSY

Over the years a large variety of drugs have been used for the treatment of patients with epilepsy. Merritt and Putnam (1938) were the first to report the use of the drug phenytoin sodium (diphenylhydantoin) and they found the drug effective with minimal side-effects except for a tendency to induce gingival overgrowth (Kimball, 1939). Phenytoin sodium continues to be the drug of choice in the treatment of epilepsy, particular the grand mal variety. Gingival overgrowth due to phenytoin sodium has been extensively documented but in spite of this, much uncertainty remains about its nature.

The literature is replete with reports concerning the relationship between the degree of gingival overgrowth and age, sex, dosage and duration of treatment (for review see Hassell, 1981). Much has also been written about the incidence and prevalence of the condition while several classifications have been offered to record the degree of gingival overgrowth. Attempts have also been made to correlate plaque and gingival indices and crevicular flow with the degree of gingival inflammation and enlargement, in patients on this drug. Although a substantial volume of data has been accumulated on diphenylhydantoin-induced gingival enlargement, most, if not all, is based on indices and classifications that are very subjective.

3. AIMS OF THIS STUDY

The aim of this study was to develop a method of recording the degree of gingival overgrowth in an objective and reproducible manner. Furthermore, it was hoped to apply this method in a survey of epileptics from the Jan Kriel School and on the basis of the accumulated data, to correlate, sex, age, plaque and gingival indices, dosage and duration of dosage with the degree of gingival overgrowth in this sample.

CHAPTER 2

PHARMACOLOGY OF PHENYTOIN SODIUM

1. INTRODUCTION

A large variety of anti-convulsant drugs have been used in the treatment of epilepsy. These include the established compounds belonging to the following chemical groups, e.g. hydantoins, barbiturates, succinimides, oxazolidinediones and benzodiazepines. Relative newcomers to this list include such drugs as sodium valproate and carbamazepine.

It is important to note that none of the currently available anti-epileptic agents actually cures epilepsy. They simply suppress the epileptic process and prevent the spread of the seizure discharge.

Of the currently available anti-epileptic drugs, phenytoin sodium is of special interest in the field of oral medicine due to its extensive usage and ability to cause gingival overgrowth in up to 50% of patients. Phenytoin belongs to the group of drugs known as the hydantoins and is usually used in the form of its sodium salt which is much more soluble than phenytoin itself. It is a powerful anti-convulsant with relatively little hypnotic effect.

The chemical name for phenytoin sodium is 5:5 diphenylimidazolidine - 2,4 dione. The drug is also known as diphenylhydantoin

sodium, phenytoin natricum and soluble phenytoin. In South Africa, the drug is marketed by Parke-Davis under the proprietary name of Epanutin®. However, it is also available combined with phenobarbitone under the trade names Garoin® (Maybaker) and Epanutin with phenobarbitone® (Parke-Davis).

2 FORMULATIONS AND INDICATIONS

Phenytoin sodium is dispensed in capsules containing 50 and 100 mg of the active compound. These capsules should be taken before meals, except in those cases where a gastro-intestinal discomfort ensues in which case the drug may be taken after meals. Phenytoin sodium is furthermore available as a suspension of 125 mg/ml, 50 mg chewable infatabs and in injectable form. Phenytoin sodium should not be given intramuscularly due to precipitation of micro-crystals at the site of injection and the relatively slow absorption from this tissue.

In status epilepticus, patients are treated with a 5ml intravenous injection containing 50 mg of phenytoin sodium per ml. However, intravenous diazepam is currently the drug of choice for this life threatening condition.

3 PHYSICAL PROPERTIES

Phenytoin sodium is an odourless, slightly hygroscopic white crystalline powder which is soluble in water and alcohol but insoluble in ether or chloroform. Its moisture content is less than 2,5 per cent as determined by drying at 105°C.

The drug should be stored in airtight containers as the sodium salt is unstable in air due to its ability to absorb carbon dioxide, a process which results in the release of the relatively insoluble phenytoin.

4 MECHANISM OF ACTION

The exact mode of action of phenytoin in controlling seizures is not understood and the literature abounds with postulates. Various animal studies as well as a human study by Brumlik and Moretti (1966) indicate that phenytoin sodium has a stabilising and protective effect on peripheral nerves by preventing over-reaction and thus controlling seizures while at the same time not interfering with normal physiological impulse conduction. Phenytoin sodium is also thought to act on autonomic ganglia by preventing the transmission of a series of overactive impulses. The action of the drug in the central nervous system is also not understood. Nevertheless, the drug has been associated with decreased synaptic transmission in the motor cortex and is thought to be capable of halting the spread of hyperactivity from the primary focus, thus preventing seizures. Pincus (1972) showed that phenytoin sodium can, like local anaesthetic agents, inhibit movement of sodium and calcium across cell membranes. This inhibitory effect of phenytoin is thought to lower intracellular cyclic nucleotide concentrations, higher values of which may be responsible for the hyperexcitability seen in seizures.

Hopefully, further research will elucidate in more detail the mode of action of phenytoin sodium.

5 PHARMACO-KINETIC PARAMETERS

i) ABSORPTION

As stated previously, phenytoin is more readily absorbed in its sodium salt form, and smaller doses appear to be better absorbed than larger ones (Glazko and Chang, 1972).

Orally administered phenytoin sodium is absorbed slowly, mainly in the duodenum, the amount varying with the particle size and the solubility of the gelatin capsules. Intestinal absorption of phenytoin sodium is improved by mixing the drug with micro-crystalline cellulose. The presence of calcium sulphate, however, reduces phenytoin sodium's absorption by about 70% (Woodbury and Swinyard, 1972).

ii) DISTRIBUTION

Phenytoin sodium is rapidly and widely distributed to all parts of the body and more than 90% is plasma-protein bound. The drug is found in all body fluids including the cerebrospinal fluid. It also crosses the placenta and is found in small quantity in breast milk (Troupin and Friel, 1975).

iii) METABOLISM AND EXCRETION

Approximately 2% of phenytoin is excreted unchanged in the urine. Most of the remainder undergoes aromatic hydroxy-

lation to form 5- p- hydroxyphenyl - 5- phenylhydantoin (P-HPPH). This metabolic process takes place in the liver from where the metabolites are excreted into the bile. A portion of these are re-absorbed and finally excreted in the urine, from where 60 - 70% of the dose can be recovered in the form of HPPH or one of its conjugates.

Excretion is enhanced if the urine is alkaline. About 15% of the total dose of phenytoin is excreted in the faeces.

6 DOSAGE AND BLOOD CONCENTRATION

i) DOSAGE

The dosage of phenytoin sodium varies from 200 - 600 mg per day. On commencing treatment, a patient will be given 100 mg three times a day for a trial period during which the dosage is adjusted until seizure control is achieved. The maximum daily dosage is 600 mg for adults. For children 5 mg/kg per day is used in two or three equally divided doses with a maximum of 300 mg/day, while children over 6 years old may require the minimum adult dosage (300 mg/day).

ii) BLOOD CONCENTRATION

Plasma phenytoin values of 10 - 20 µg/ml appear to be optimal for obtaining seizure control while concentrations of 20 µg/ml are considered to be potentially toxic in both

adults and children. Following an oral dose of 100 mg phenytoin sodium, the plasma level peaks at 1,5 - 3 µg/ml after 3 - 6 hours with a second peak occurring after 10 - 12 hours. The half-life of the drug is dose dependant and varies widely with an approximate range of 7 - 40 hours in both adults and children.

7 DRUG INTERACTIONS

Overdose of phenytoin sodium can cause toxicity while a decrease may result in the recurrence of seizures. Besides actual variation in dosage, effective blood levels can be markedly affected by the administration of other drugs (see Table 2.1)

TABLE 2.1: DRUGS WHICH INCREASE OR DECREASE PHENYTOIN PLASMA LEVELS

Drugs which increase Phenytoin plasma levels	Drugs which decrease Phenytoin plasma levels
Dicoumarol	Phenobarbitone
Disulfiram	Carbamazepine
Sulthiame	Ethanol
Chloramphenicol	Folic Acid
Diazepam	Theophylline
Isoniazid	
Prochlorperazine	
Oestrogens	
Propoxyphene	
Halothane	
Ethosuximide	
Sulphamethizole	

A number of side-effects have been attributed to phenytoin sodium which range from nausea and rashes to nystagmus, leucopenia, purpura, megaloblastic anaemia and even osteomalacia. The main oral side-effect, to be discussed later, is that of gingival overgrowth.

CHAPTER 3

THE CLINICAL AND HISTOLOGICAL FEATURES OF DIPHENYLHYDANTOIN-INDUCED GINGIVAL OVERGROWTH (DGO)

1) INTRODUCTION

One year after diphenylhydantoin was first used as an anticonvulsant drug (Merritt and Putnam, 1938), Kimball (1939) reported the condition of diphenylhydantoin gingival overgrowth (DGO), which had been referred to as 'hypertrophic' gingivitis prior to 1947. In that year, the committee on nomenclature of the American Academy of Periodontology (Orban, 1947) decided to recommend the term gingival hyperplasia because inflammation is not always present and the lesion does not involve an increase in size of individual cells or fibres. It was subsequently pointed out that the condition is not a true hyperplasia either as there is not an increase in the number of cells or fibres per volume. Hassell (1981) subsequently suggested that the term gingival overgrowth be used. The designation diphenylhydantoin-induced gingival overgrowth (DGO) is therefore used in this monograph.

2) CLINICAL FEATURES

The clinical features of DGO are most characteristic and detailed descriptions have been given by Aas (1963) and Angelopoulos (1975a). In most cases, the first change observed is an enlargement of the interdental papillae in both coronal and lateral

directions resulting in the buccal surfaces of the teeth becoming overgrown by gingiva. Sometimes, the enlargement is so pronounced that the lobulated interdental papillae may meet mid-buccally on the teeth. There is, however, always a cleft present and the margins of the cleft are invariably hyperaemic (see Fig. 3.1).

FIGURE 3.1 THE CHARACTERISTIC FEATURES OF GINGIVAL OVERGROWTH ARE THE ENLARGED INTERDENTAL PAPILLAE WHICH MEET MID-BUCCALLY ON THE FACIAL SURFACES OF THE TEETH.

The overgrowth is usually not marked mid-buccally at the gingival margin where there may be only a slight rolling of the tissue. Similarly, the overgrowth becomes reduced as it approaches the muco-gingival junction. Furthermore, the overgrowth occurs most notably about the buccal surfaces of the anterior teeth while lesser changes can be observed posteriorly as well as palatally and lingually. In some cases, the overgrowth is so marked as to cause separation of the teeth and to interfere with the occlu-

sion. Phenytoin gingival overgrowth (DGO) is not usually seen in edentulous persons although such cases have been reported (Dallas, 1963; Dreyer and Thomas, 1978).

With the reduction of overt clinical inflammation, the surface texture of the gingiva becomes stippled and fibrosed. The colour is then pale pink, bleeding is not a prominent feature and the texture of the gingiva is firm and resilient. However, in the presence of persistent plaque-induced inflammation, the tissues adjacent to the gingival margin may appear red, oedematous, spongy and friable and thus tend to bleed easily. Such tissues are easily traumatized, even during mastication. Although first noted by Esterberg and White (1945), the relationship between plaque and DGO was substantiated by Aas (1963) in his sample of 177 patients of whom 45,8% presented with this plaque induced appearance. King, Hawes and Bibby (1976) have shown that excellent plaque control will markedly decrease the degree of inflammation, a tendency also noted by Navarro and Correll (1976) in a case report. Furthermore, post-gingivectomy recurrence of DGO can also be controlled by scrupulous oral hygiene measures (Donnenfeld et al, 1974).

It is known that plaque accumulation in the region of the gingival sulcus will initiate gingivitis (Loë et al, 1965). Furthermore, plaque retentive factors such as faulty restorations, carious teeth, open contacts etc. will aggravate the response of the tissues to phenytoin sodium therapy (Nuki and Cooper, 1972). Thus the elimination of such factors is of the utmost importance. Cunat and Ciancio (1969) have even suggested that ortho-

dontic therapy be carried out where possible to correct imbrication of teeth prior to commencement of phenytoin therapy in order to render plaque control easier.

3 DIFFERENTIAL DIAGNOSIS

While DGO has been shown to be a common side-effect of diphenylhydantoin therapy, gingival overgrowth is also a feature of several other conditions, the commonest being those associated with physiological changes in sex hormone status. Hyperplastic gingivitis is not uncommon in adolescents and during pregnancy a similar condition is seen in some persons with a poor lip seal. It appears that the altered hormonal levels occurring during puberty and pregnancy may elicit an exaggerated response to plaque, a feature that has been shown to be related to the degree of plaque present. It has also been suggested that such hormonal changes in the sulcular fluid tend to select a more pathogenic plaque as found in a longitudinal study in pregnant persons (Kornman and Loesche, 1980).

Both hereditary gingival fibromatosis as well as idiopathic gingival fibromatosis may present with clinical features similar to that of DGO but, unlike the latter, involve the tuberosity regions as well. Both conditions have been thoroughly documented by Savara et al (1954) and Rushton (1957). A history of the absence of phenytoin usage and an hereditary background will provide sufficient evidence to differentiate between these two conditions and DGO. Furthermore, the hereditary type of fibromatosis usually starts early in life when the permanent teeth begin

to erupt and this type of gingival enlargement is less likely to recur after gingivectomy.

While the above conditions are commonly seen, there are several others which, although rare, must be borne in mind when considering the differential diagnosis in cases of DGO. These include leukaemic gingivitis (Winthrop and Kapur, 1965), Hurler's syndrome (Bishton, Norman and Tingley, 1956), acanthosis nigricans, adenocarcinoma and the Sturge-Weber syndrome. The latter three have been described in detail by Gorlin, Pindborg and Cohen (1976).

Recently an interesting type of gingival overgrowth due to another drug has been reported. Rateitschak-Plüss et al (1983) recorded three cases of pronounced gingival overgrowth due to the immuno-suppressive drug Cyclosporin-A which is used in the treatment of kidney and other organ transplant patients. The appearance of the gingival tissues is almost identical to that seen in DGO and similarly, the overgrowth is much more pronounced if plaque control is inadequate or plaque accumulation is enhanced due to local factors such as overhanging margins of restorations. The pathogenesis and aetiology of this newly described form of gingival overgrowth awaits further study but may be of considerable interest due to its similarity to DGO.

4 HISTOPATHOLOGY

Histologically the capillaries in DGO in the area subjacent to the junctional epithelium become dilated and engorged with resultant hyperaemia and oedema (Ishikawa, 1959), a feature seen as

early as seven days after commencement of phenytoin sodium therapy (Glickman and Lewitus, 1941; Staple, 1953). An inflammatory infiltrate consisting mainly of lymphocytes and plasma cells is seen in the lamina propria (Han, Hwang and Lee, 1967). These findings are in fact identical to the initial lesion of periodontal disease (Page and Schroeder, 1976) and represent a typical inflammatory response due to periodontopathic plaque. In later stages it varies from the typical features in that an excessive amount of fibrosis is seen which is the characteristic feature of DGO.

The sulcular epithelium appears as in the "normal" plaque-induced gingivitis. However, the oral epithelium undergoes some hyperplastic change. Shapiro (1959) described this epithelium as acanthotic while hyperkeratosis is infrequently encountered. The rete-pegs are longer, penetrating deeper into the underlying connective tissue and have a rather characteristic forked appearance at the ends (Emslie, 1951). Degeneration of the intercellular bridges of the spinous layer has also been noted (Soni et al, 1967) and although this and the acanthosis are regular features of the condition, it is probably incidental to the changes in the underlying connective tissue. Larmas and Paunio (1976) reported proliferation of the basal cells with increased evidence of mitosis and the presence of mitotic figures in the higher layers (Soni et al, 1967). In the early stage of the lesion, large numbers of fibroblasts have been reported (Aas, 1963; Ishikawa and Glickman, 1961) while Kasai and Tanimoto (1964) demonstrated the accumulation of an amorphous substance considered to be a collagen precursor.

5 AETIOLOGY AND PATHOGENESIS

Kimball (1939) suggested a relationship between vitamin C deficiency and DGO. This he based on a survey of 34 children in a special school for epileptics in Detroit, in whom he found a decreased serum level of ascorbic acid in patients with gingival overgrowth. This study stimulated much interest and further research into the aetiology and pathogenesis of DGO. Although Frankel (1940) and Drake, Gruber and Haury (1941) supported Kimball's hypothesis, the role of vitamin C was questioned by other studies (Milhon and Osterberg, 1942; Emmett, Hartzler and Brown, 1943; Merritt and Foster, 1941), on the basis that the clinical features of the gingiva did not resemble a scorbutic gingivitis nor was the condition improved by increased serum vitamin C levels. In fact, Merritt and Foster (1941) found no differences in the serum ascorbic acid levels measured in patients receiving phenytoin sodium and exhibiting DGO and those of a control group and concluded that vitamin C plays no role in the development of DGO.

The endocrine system as a possible factor in the aetiology of DGO has been suggested and was first postulated by Esterberg and White (1945). They produced clinical evidence of hypertrichosis and increased sexual activity to support their theory and were able to show pathological changes in the adrenal glands. The concluded that hormones may be involved but only as predisposing factors.

Another view was put forward by Noach, Woodbury and Goodman (1958) who found a high concentration of phenytoin sodium in saliva which they considered to be a possible aetological factor in DGO. A similar view has been expressed earlier by Brandon (1948) who had suggested that the metabolites of phenytoin sodium in the saliva were responsible for the DGO. Several workers have subsequently shown a reduced concentration of serum IgA in patients treated with phenytoin sodium (Sorrell et al, 1971; Slavin et al, 1974; Aarli and Tonder, 1975) which is contrary to the normal tendency for elevated IgA levels in inflammatory conditions. Although the exact mechanism for this finding is obscure, it is possible that the reduced salivary IgA levels may increase the susceptibility to gingivitis and consequently DGO, which may well explain the close relationship between the degree of enlargement and the standard of oral hygiene. Van der Kwast (1956) suggested an allergic basis for DGO having observed large numbers of plasma cells as well as increased gamma globulins in the plasma and tissues of many of his patients.

Yet another suggested aetiological factor is the direct irritant effect of phenytoin sodium on the gingival tissues as a result of the release of the drug into the tissues from ruptured blood vessels in the inflamed gingiva (Strean and Leoni, 1959; Babcock, 1965; Millichap, 1972). In support of this view Conard et al (1974) also found that the severity of DGO was associated with the level of phenytoin sodium in the gingival tissues. The local action of phenytoin itself has been indicated by Streiff, Wilder and Hammer (1972) who found the level of phenytoin sodium in the

gingival tissues to be higher than in serum collected by venipuncture at the same time. The local cell types have also been investigated and the degranulation of the mast cells due to the direct action on them by phenytoin sodium has been suggested as an aetiological factor in gingival overgrowth (Angelopoulos, 1975b). The latter author hypothesized that the resultant liberation of histamine, heparin and hyaluronic acid from the mast cells stimulate the fibroblasts to produce the overgrowth of gingival tissue. The fibroblasts have also been shown to exhibit increased protein synthesis activity at about twice the rate at which it occurs in non-epileptic controls not taking phenytoin sodium (Hassell, Page and Narayanan 1976a). In the same study it was shown that such cells produced 9% more collagen when compared to "normal" cells. Experimental work on rabbits by Steinberg, Alvarez and Jeffay, 1972) has also shown the presence of high levels of phenytoin sodium in the tissues apparently unrelated to ruptured blood vessels, as suggested above. Saliva has been identified as a possible source and it was considered highly probable that the small phenytoin sodium molecules could enter the tissues from the saliva via the gingival sulcus and the junctional epithelium. Bacterial plaque, which accumulates at the gingival margin, enters the gingival sulcus and has been related to the chronic inflammation almost always present subjacent to the junctional epethelium. This may well facilitate the passage of phenytoin sodium into the saliva.

In general, the true aetiology and pathogenesis of the condition still remains obscure.

CHAPTER 4

EPIDEMIOLOGY OF PHENYTOIN-INDUCED GINGIVAL OVERGROWTH

1. INTRODUCTION

Since the side-effect of phenytoin-induced gingival overgrowth (DGO) was first described by Kimball (1939), it has been the subject of a considerable number of epidemiological surveys. Although these investigations were primarily undertaken in an effort to establish the prevalance of the condition, it was found that the severity of gingival overgrowth varied widely and several related factors e.g. age, sex, race, dosage of drug, duration of drug therapy, oral hygiene and gingival crevice fluid were involved. The results not only varied greatly but many diverse conclusions were reached. In the following sections these factors will be reviewed in greater depth with particular emphasis on possible reasons for the wide variation.

2. CLASSIFICATION OF PHENYTOIN-INDUCED GINGIVAL OVERGROWTH (DGO)

Numerous classifications of DGO have been offered (see Table 4.1). The most popular index used, even by recent researchers in slightly modified form, is the one originally suggested by Kimball (1939). This index is simply a grading from I to IV employing somewhat vague and subjective criteria. Subjectivity is a problem inherent in most surveys undertaken thus far. For instance Glickman and Lewitus (1941) surveyed DGO in a group of

76 patients but offered no criteria for their differentiation between groups.

An attempt at more objectivity is found in the method used by Gardner, Gross and Wynne, (1962) who related DGO to the degree of gingival coverage of the tooth surface. Their degree I referred to gingival tissues confined to the gingival third of the crown, degree II to the middle third while gingival overgrowth reaching or covering the incisal or occlusal third was designated as degree III. In spite of these criteria, based on the extent of the gingival overgrowth, it too is a very subjective assessment. Later Babcock (1965) used a method which is basically no different from the original classification of Kimball (1939) except in the use of different terms, namely minimal, moderate and severe hyperplasia. Similarly, Angelopoulos and Goaz (1972) used Kimball's classification with the minor modification that they specified anterior teeth only, while Klar (1973) changed the grading to 0 - III using the same vague criteria. Russell and Bay (1978) also used a similar grading but modified their approach by using study models to detect changes in gingival overgrowth. This study was carried out on 30 mentally retarded children over a seven month period. Study model impressions were taken every second month but, although the models offered the potential for accurate measurements from a fixed point(s), the authors assessed the degree of overgrowth in a purely subjective manner. The only advantage of this method was that side by side intrasubject comparison was rendered possible. This is, however, not a method that could be adopted for general use because of the time and cost factors involved.

TABLE 4.1

VARIOUS CLASSIFICATIONS OF PHENYTOIN-INDUCED GINGIVAL OVERGROWTH (DGO)

WITH THE VARIOUS CRITERIA INVOLVED

AUTHOR	YEAR	CRITERIA FOR DGO
KIMBALL	1939	GRADES I - IV I No change II Definite Beginning change III Advanced hyperplasia IV Extreme hyperplasia
GLICKMAN & LEWITUS	1941	Degree of hyperplasia varies related to local factors
GARDNER et al	1962	DEGREES I - III I Enlargement 1/3 crown II Enlargement 1/3 - 2/3 III Enlargement 2/3
BABCOCK	1965	MIN - SEVERE I Minimal II Moderate III Severe
ANGELOPOULOS & GOAZ	1972	GRADES 0 - III Grade 0 - no hyperplasia Grade I - 1/3 crown covered Grade II - 1/3 - 2/3 Grade III - 2/3
KLAR	1973	0 - III 0 = None I = Slight II = Moderate III = Severe
RUSSELL AND BAY	1978	SCORE 0 - III 0 = No G.H I = 1/3 II = Up to 2/3 III = 2/3
W.H.O.	1978	Blunted interdental papillae Gingival coverage 1/3 crown History of phenytoin sodium intake

The W.H.O. (1978) suggested somewhat different criteria for hyperplastic changes of the gingival margin. These included blunting of the interdental papillae; gingival coverage of the anatomical crown of at least one-third of a single tooth; surface appearance (smooth, stippled and of normal colour); and a history of the patient receiving a daily dose of phenytoin sodium. Whilst these criteria, collectively, may accurately reflect the presence of overgrowth, they cannot be used to indicate the degree of overgrowth.

Clearly, none of the classifications discussed above provide a reproducible method for assessing the degree of DGO and consequently the available data on prevalence, and particularly the degree of DGO, is at best, purely descriptive. More accurate, objective and reproducible methods of recording DGO must be employed for the purpose of analytical epidemiology.

3. PREVALENCE

The prevalence of phenytoin-induced gingival overgrowth (DGO) has been reviewed by Angelopoulos and Goaz (1972) and Hassell (1981). Using the data reported by these authors, the references cited by them (omitted in some instances from the present reference lists) have been divided into two separate tables relative to the period 1939 to 1950 (see Table 4.2) and the post-1950 period (see Table 4.3). This approach revealed a considerable difference between the two time periods in that the earlier period had a prevalence range of 0 - 76.0% (mean 32.15%) and the latter a range of 1-100% (mean 54.92%). These variations can

TABLE 4.2

THE PREVALENCE OF DIPHENYLHYDANTOIN GINGIVAL OVERGROWTH COMPILED FROM REPORTS PUBLISHED PRE-1950, ACCORDING TO DATA AS PUBLISHED BY ANGELOPOULOS AND GOAZ (1972) AND HASSELL (1981). (NOT ALL REFERENCES ARE CITED IN THE PRESENT LIST OF REFERENCES)

AUTHOR	YEAR	N	PREVALENCE %
*Merritt & Putnam	1938	142	NR
Merritt & Putnam	1939	350	6
Kimball	1939	152	57
Kimball & Horn	1939	220	57
Hodgson & Reese	1939	88	3
*Frost	1939	9	NR
Blair et al	1939	58	1
McCartan & Carson	1939	20	5
*Phillips	1939	12	NR
Pratt	1939	52	50
Steel & Smith	1939	20	69
*Weaver et al	1939	14	NR
Williams	1939	91	0
*Allen	1940	65	NR
Berg & Pearlman	1940	57	14
Butter	1940	43	2
Fetterman	1940	28	25
Frankel	1940	48	62
*Johnson	1940	20	NR
Merritt & Foster	1940	182	22
*Morgan	1940	8	NR
*Robinson & Osgood	1940	100	NR
*Ross & Jackson	1940	73	NR
Schlotthauer	1940	32	12
Weinberg & Goldstein	1940	32	12
Glickman & Lewitus	1941	76	26
Lowry	1941	34	29
*Mallet & Foley	1941	NR	50
Ziskin et al	1941	18	56
Finkelman & Arieff	1942	44	39
*Harris & Ewalt	1942	NR	20-30
Mcfarlane et al	1942	78	55
Milhon & Osterberg	1942	17	32
Milhon & Osterberg	1942	13	46
Polk	1942	20	50
Prudhomme	1942	57	30
Robinson	1942	143	19
Bindslev, Stubbe and Teglbjaerg	1943	130	42
McLendon	1943	67	0
Pinsky	1943	29	3
Stern et al	1943	50	52
Esterberg & White	1945	244	54
Bergman	1946	86	55
*Bashinski	1946	30	NR
*Swinehart	1947	NR	50
Scarzella & Berlatti	1947	38	76

* = Incomplete Data
Range = 0 - 76%
Mean prevalence for the 33 with complete data = 32.15%

TABLE 4.3

THE PREVALENCE OF DIPHENYLHYDANTOIN GINGIVAL OVERGROWTH COMPILED FROM REPORTS PUBLISHED POST-1950, ACCORDING TO DATA AS PUBLISHED BY ANGELOPOULOS AND GOAZ (1972) AND HASSELL (1981). (NOT ALL REFERENCES ARE CITED IN THE PRESENT LIST OF REFERENCES)

AUTHOR	YEAR	N	PREVALENCE %
Janz	1950	85	1
Arnold & Ulrich	1951	45	35
*Kröber	1951	NR	33
*Hine	1952	NR	40
Dummett	1954	123	38
King	1954	312	72
Port	1954	38	68
Giancotti	1955	92	10
Spira	1955	52	69
Ishikawa	1956	887	56
Collins & Fry	1960	50	64
Panuska et al	1960	546	32
Apostolou	1961	85	58
Panuska et al	1961	69	42
Gardner et al	1962	77	78
Rusu et al	1962	80	26
Aas	1963	80	25.0
Mutschelknauss	1964	31	35
Babcock	1965	369	36

AUTHOR	YEAR	N	PREVALENCE %
*Bergman	1965	NR	40
Winthrop & Kapur	1965	137	72
Wolf	1966	100	36
*Bergman	1967	NR	40
Tollaro	1968	71	85
Al-Safi	1968	129	58
Livingston & Livingston	1969	15000	40
Love	1969	61	65
*Chechel	1970	74	"Most"
*Kötzchke	1970	NR	72
Angelopoulos & Goaz	1972	173	53
Grob & Herold	1972	20	100
Lefebre et al	1972	29	69
Kapur et al	1973	227	67
Klar	1973	312	45
Londberg	1973	52	85
*Baine et al	1973	NR	25
Matsumoto et al	1975	215	30

* = Incomplete Data
Range = 1 - 100%
Mean prevalence = for the 30 with complete data = 50.83%

possibly be explained by the fact that most of the earlier investigators were neurologists or physicians whilst the more recent researchers have been dentists who, by virtue of their training, were possibly better able to detect minor gingival changes. On the other hand some variations may be due to bias introduced by the differing populations studied. Angelopoulos and Goaz (1972), for example, studied 173 hospitalized patients who were all middle-aged or over, while Kimball's study (1939) involved 119 patients of unspecified age. As will be discussed later, age appears to have a significant influence on the prevalence of DGO (vide infra).

4 AGE SPECIFIC DATA

The data obtained from a large number of patients with DGO revealed correlations between age and prevalence (Aas, 1963; Babcock, 1965; Angelopoulos and Goaz, 1972; Klar, 1973 and Matsumoto, Nakaguwa and Kaneko, 1975).

TABLE 4.4 THE PREVALENCE OF DIPHENYLHYDANTOIN GINGIVAL OVERGROWTH RELATED TO VARYING AGE GROUPS IN SAMPLES FROM SEVERAL INSTITUTIONS

AUTHOR	YEAR	N	PREVALENCE %	AGE RANGE	PATIENT POPULATION
Aas	1963	177	25.0	0 - 30	Department of Dental and Oral Surgery of Rikshospitalet, Oslo
Babcock	1965	369	36.0	5 - 25	Newcastle State Hospital
Angelopoulos & Goaz	1972	173	53.0	30 - 39	Central & Eastern State Hospitals, Oklahoma
Klar	1973	312	45.0	1 - 10	Seizure Clinics in Virginia
Matsumoto et al	1975	219	2.85 14.70 12.76	0 - 15 15 - 35 35 - 55	Dept. of Neuro-Psychiatry - Osaka University Hospital

Aas (1963) found that children and adults up to about age 30 had a greater tendency to develop DGO than older individuals who commenced phenytoin sodium therapy later in life. This view was supported by the data from surveys of Babcock (1965) who examined patients at the Newcastle State Hospital and found an overall prevalence of DGO of 36% with higher rates for the 5 - 25 age group.

Klar (1973) examined 312 patients from seizure clinics in Virginia and found the greatest degree of gingival overgrowth in the groups aged 11, and older. There were 71 out of a total of 137 patients (45 %) with DGO in the 1 - 10 year old group while out of the 175 patients examined in the 11 - 20 year age group, 131 patients or 74.4% exhibited gingival overgrowth. This was in contrast to the study of Angelopoulos and Goaz (1972) whose sample of 173 patients revealed a 45.0% prevalence rate in the 30 - 39 age group. This study did not support a significant correlation between age and the degree of DGO.

In only one study was DGO more common in older age groups. A survey of 219 patients in the department of neuro-psychiatry at Osaka University Hospital, revealed an age range of 2.5 - 55 years with a mean of 22.8 years (Matsumoto et al, 1975). Seventy of these patients fell in the under 15 age group (±32 %) while the largest number of cases were in the 15 - 35 age group.

5. SEX SPECIFIC DATA

Generally speaking, both sexes seem to have an equal risk of developing DGO which is interesting in the light of the generally

held view that females have a greater tendency to develop hormonal hyperplasia.

Aas (1963) found no significant sex differences in either the prevalence or the severity of DGO, a finding that has been supported by other researchers (Angelopoulos and Goaz, 1972; Kapur et al, 1973). Only one report (Kaemmerer and Elmering, 1965) found DGO to be more common in females.

6. ETHNICITY

No ethnic difference in either the prevalence or severity of DGO has been reported. Dummett (1954) reported that all races appear to be equally susceptible, a view confirmed by Panuska et al (1961) in a survey on 1048 patients who were grouped ethnically as White, Negro and "others". Further confirmation came from Klar (1973) in his study on 312 epileptic patients as well as from Livingston and Livingston (1969) who had examined about 15,000 epileptic patients. The latter reported a prevalence of "about 40 %" for DGO in these patients and stated that there was no ethnic difference although they offered no statistical data to support their statement.

7. ANATOMICAL SITE SPECIFIC DATA

A predilection of DGO for the anterior gingivae, and especially the labial aspects, is found in both maxillary and mandibular arches (Angelopoulos and Goaz, 1972). The degree of gingival overgrowth is however, more marked in the maxilla which may be

related to inadequate lip seal (Glickman and Lewitus, 1941). This view was confirmed by the results of a study by Collins and Fry (1960) who explained that the resultant mouth-breathing had a dehydrating effect on the anterior gingivae. Similarly, both Aas (1963) and Angelopoulos and Goaz (1972) described a greater tendency for DGO on the labial aspect of maxillary and mandibular teeth. Esterberg and White (1945) on the other hand, found no significant difference in the degree of DGO for the mandible and maxilla.

When gingival overgrowth affects the posterior teeth, it is often more marked buccally in cases of DGO whilst in idiopathic fibromatosis, the enlargement presents in a more generalised fashion, a feature of some diagnostic value.

Glickman & Lewitus (1941) suggested that DGO was less marked palatally because of "the cleaning effect of food during mastication". In one study, however, DGO was found to be more prominent palatally (Hänström, Bergenholtz and Gustafson, 1977).

8. DRUG SPECIFIC DATA

8.1 CORRELATION WITH DURATION OF TREATMENT

It would appear that the severity of DGO becomes more marked the longer the patient is on phenytoin sodium therapy. This, of course, will vary greatly with patient susceptibility to develop DGO as well as with the standard of plaque control. Both Dummett (1954) and Orban and

Wentz (1960) suggested an individual susceptibility to DGO and found that gingival overgrowth manifests itself during the first six to nine months of intake of the drug.

The prevalence of DGO in 67 epileptics was found to be 35% at the outset of a survey by McFarlane, Baxter and Mitchell, (1942). They subsequently reported that this figure had increased to 55% one year later in the same group of individuals. Similarly, Love (1969) carried out a controlled study in children from 20 months to 15 years relationship between the severity of the gingival overgrowth and duration of treatment in those subjects who were susceptible to phenytoin sodium.

8.2 CORRELATION WITH DOSAGE

Livingston and Livingston (1969) noted a significant correlation between the daily dosage of phenytoin sodium and the prevalence and severity of DGO. As stated above, their survey refers to the examination of about 15,000 epileptic patients but no specific information is provided. Other researchers such as Angelopoulos and Goaz (1972) reported no correlation. This aspect is further complicated by the fact that several drugs are involved in seizure therapy and during the initial period of treatment, usually lasting several months, a variety of drugs are invoked in differing concentrations until seizure control has been achieved. Because of this daily fluctuation in the dosage of phenytoin sodium, it is very difficult to

correlate dosage with the prevalence of DGO. Therefore, the serum level of phenytoin sodium is a more valid variable to study.

8.3 CORRELATION WITH SERUM LEVELS

Dosage of phenytoin and serum levels are difficult to correlate because so many patients fail to take their medication regularly. However, a direct correlation has been shown between an increased dosage of phenytoin sodium and of age and showed a definite serum levels of phenytoin sodium in a case report by Hassell, (1981). This revealed that doubling the daily dosage of phenytoin from 50mg to 100mg per day resulted in a 400% increase in serum phenytoin. The monitoring of the serum level is thus a useful method of arriving at the correct dosage for a particular patient. It also seems, from the monograph of Hassell (1981) that it would be preferable to relate the prevalence and severity of gingival overgrowth to serum levels of phenytoin rather than to daily dosage, a view which is supported by a study by Kutt (1971).

The direct relationship between dosage and phenytoin sodium serum level has also been shown by Kapur et al (1973). They found that the severity of the condition (DGO) could be increased or decreased after a three to five month latent period, by adjusting the daily dosage of phenytoin sodium. On the other hand, Ciancio, Yaffe and

Catz (1972) found no correlation between gingival overgrowth and serum phenytoin levels.

Naturally, other factors are also involved such as individual variation encountered in absorption, distribution and bio-transformation of phenytoin sodium which dictates that the serum level will vary in different patients. It has also been suggested that variations may occur from time to time in the same patient (Grossman, Journa and Richter, (1974).

Variations may also be due to failure by the patient to take medication on a regular basis. In any event, it is now possible to measure the quantity of one of the major metabolites of phenytoin sodium i.e. 5-(p-hydroxy-phenyl) -5-phenylhydantoin (p-HPPH) in a 24 hour urine specimen in order to assess the amount of absorption of the drug in a patient exhibiting a low serum level.

CHAPTER 5

A PHOTOMETRIC ASSESSMENT OF DIPHENYLHYDANTOIN GINGIVAL OVERGROWTH

1. INTRODUCTION

A review of of the methods of classification of diphenylhydantoin gingival overgrowth, as described in CHAPTER 4, emphasized the need for a more objective and reproducible technique for measuring gingival overgrowth. The use of standardized clinical photographs for measuring the extent of the overgrowth seemed to offer the best solution to this end. Photometric methods have been used to study a number of intra-oral parameters. For instance, Huysen and Boyd (1952) used clinical photographs to study the cleaning effectiveness of various toothpastes, enabling them to make an objective comparison. Clinical photography has also been used by Massler et al (1957) in a study of gingivitis and by Jackson (1962) to record the reduction in gingivitis associated with the use of a toothpaste containing 2% sodium ricinoleate.

Similarly, photometric methods have been employed in epidemiological surveys (James, 1963), to assess morphological changes (Volchansky, 1979/80), to evaluate colour changes in soft tissues (Lees, 1974) and to record mottling of the enamel (Davies, Kruger and Holman, 1967). In most instances, colour transparencies were used and the reproducibility and stability of such transparencies have been shown to be acceptable (Lees 1974, Davies, Kruger and Holman 1967).

It was decided to measure the amount of gingival overgrowth in cases of DGO using a photometric method. A standard technique was developed and subjected to tests for reproducibility. This Chapter describes the apparatus and method used, and the comparative results.

2. THE APPARATUS

A Nikkormat FT2 single lens reflex camera was used with a medical Nikkor F5.6 lens with a fixed focal length of 200mm and fitted with a built-in ring flash.

Cross-hairs, consisting of thin film strips, were glued to the screen as shown in Figure 5.1 below. When looking through the eye-piece, it was possible to align the cross-hairs to coincide with an imaginary vertical line passing between the upper central incisors and a horizontal line coincident with the occlusal plane passing though the incisal margins of the upper central incisors. This allowed for the standardized horizontal and vertical positioning of the patient.

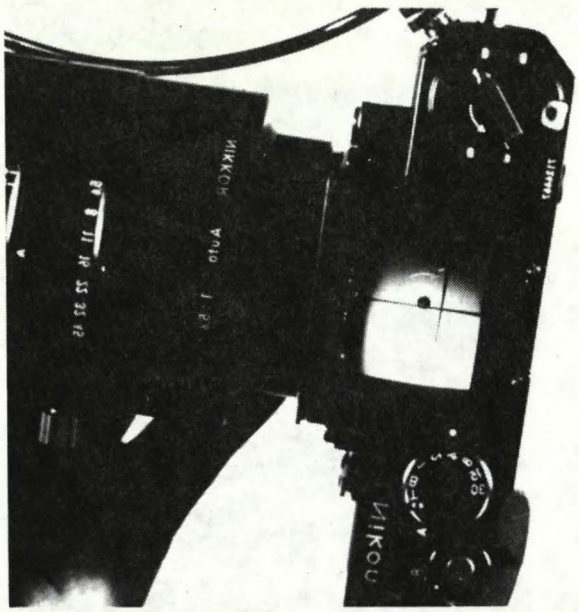

FIGURE 5.1 : THE CAMERA USED SHOWING THE VIEWFINDER WITH CROSS-HAIRS USED TO STANDARDIZE THE POSITIONING OF THE PATIENT

The camera was supported on a Velbon AEF-3 tripod with three separate head-locks on a fully adjustable panhead. The tripod was fitted with a sure-grip handle, an immovable centre column friction lock, quick-action leg lever locks and radial supports. The arrangement allowed a firm basis for camera support, an essential feature for close-up photography.

Having set up the camera, the patient was seated upright in a dental chair with the head supported in a head-rest such that the occlusal plane was parallel to the floor. The positioning was similar to that advocated by Slack (1961) and is demonstrated in Figure 5.2.

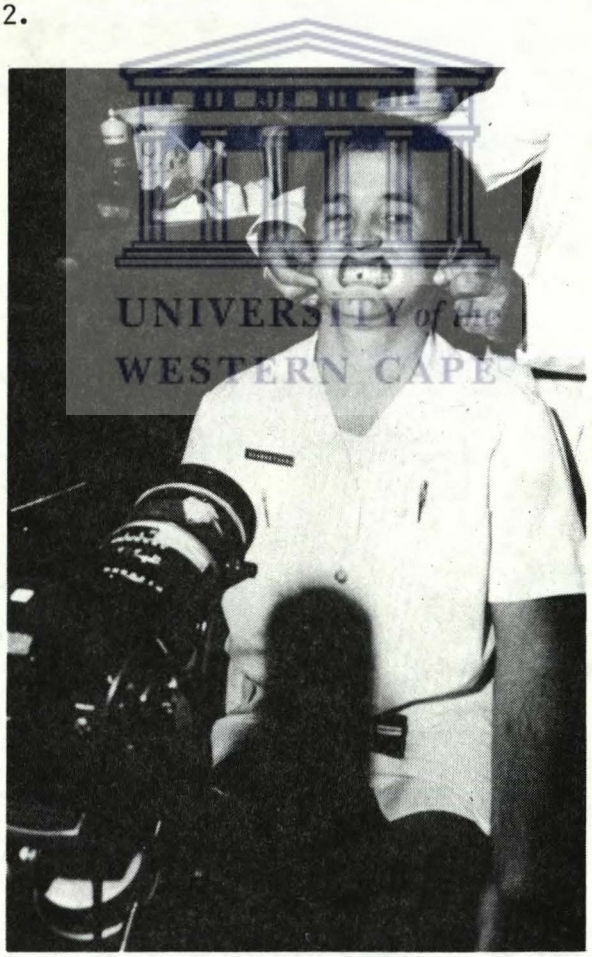

FIGURE 5.2 : THIS ILLUSTRATES THE POSITIONING OF THE PATIENT AND CAMERA USING A VOLUNTEER TO DEMONSTRATE THE CAMERA ON ITS TRIPOD RELATIVE TO THE SEATED PATIENT WITH CHEEK RETRACTORS IN POSITION

The camera, on the tripod, was then adjusted until it was parallel to the floor as indicated by a multi-directional spirit level. Subsequently, the camera tripod setup was moved forwards or backwards until the teeth, exposed by plastic cheek retractors, were in focus.

A stainless steel sphere, 5mm in diameter was attached with adhesive putty to the buccal surface of the upper left central incisor in each case (see Figure 5.3). The fixed diameter of the sphere allowed accurate enlargement of the photographs, thus allowing standardized measurement of the gingival overgrowth (Volchansky, Austin and Cleaton-Jones 1975).

The camera was then finally adjusted to achieve clarity of the picture in the fresnal as well as to ensure that the cross-hairs in the viewfinder were lined up with the midline and the occlusal plane of the teeth. The photograph was then taken.

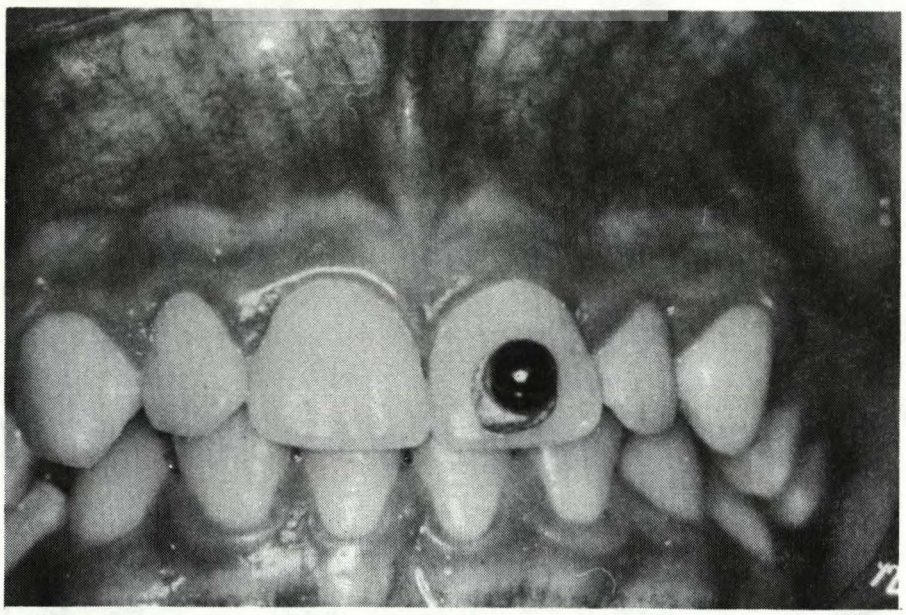

FIGURE 5.3 : A PHOTOGRAPH SHOWING THE 5mm STAINLESS STEEL SPHERE IN POSITION. THE DIAMETER OF THIS SPHERE ALLOWED STANDARDIZED ENLARGEMENT OF THE PHOTOGRAPHS

3. TECHNIQUE FOR MEASURING GINGIVAL OVERGROWTH

A viewing box similar to that described by Volchansky, Austin and Cleaton-Jones, (1975) was constructed. This apparatus (see Figure 5.4 below) consisted of a sheet of glass overlying a three-sided box (30cm x 30cm) supported on a base, on the extension of which a 35mm Kodak Carousel projector was placed. The image from the slide in the projector was then reflected off a front-surfaced mirror set at 45° and projected onto a sheet of tracing paper placed on the glass sheet on top of the box. The position of the projector was adjusted until the diameter of the image of the stainless steel sphere was exactly 20mm or four times its actual size. The tracing of the slide was then completed.

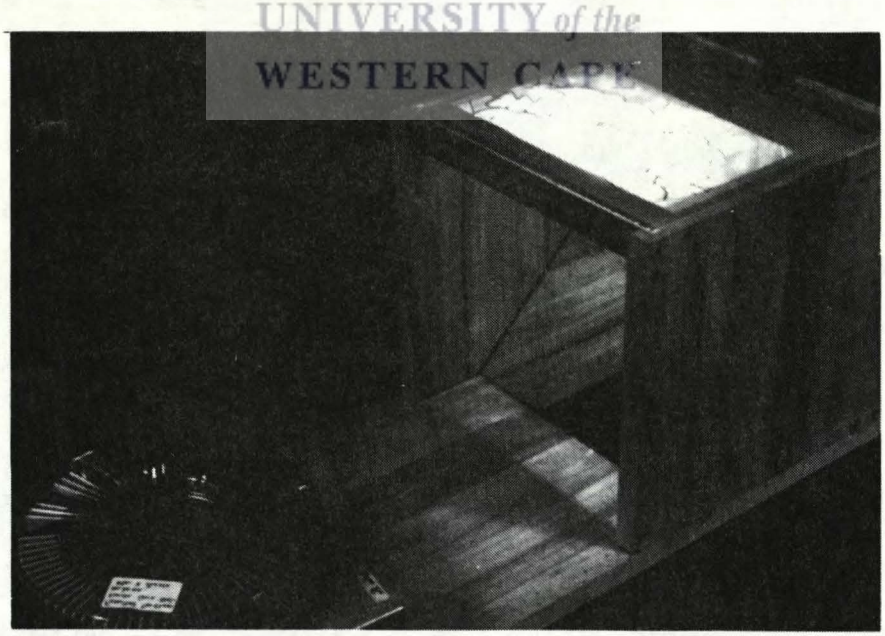

FIGURE 5.4 : THE VIEWING BOX WITH SLIDE PROJECTOR IS SHOWN WITH THE ENLARGED REFLECTION OF THE SLIDE ON THE TRACING PAPER ON TOP OF THE BOX

The tracing of the teeth and gingiva was then modified by drawing horizontal lines through the tips of the upper canines (line AB, see figure 5.5) as well as through the estimated position of the tips of the lower canines (Line CD see Fig 5.5). One side of a T-square was placed on line AB and the most coronal point on the gingival margin of each maxillary tooth was marked along a line at right angles to line AB, (see points GH and E in Figure 5.5). Similarly line CD was used to mark the most coronal point on the gingival arch of the mandibular teeth (see point F in Fig. 5.5). These points were then joined as in GH in Figure 5.5, thus delineating five upper and five lower interdental areas (i.e. GHK, see Figure 5.5).

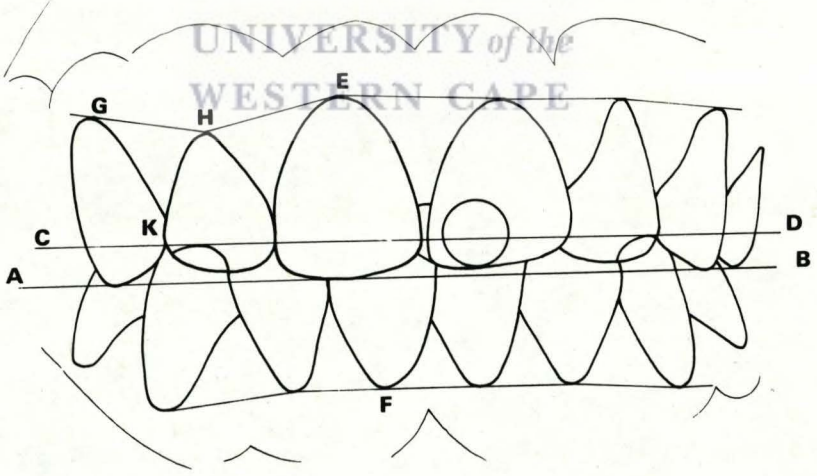

FIGURE 5.5 : THIS ILLUSTRATES THE LINES AB AND CD AS WELL AS THE OUTLINE OF THE INTERDENTAL AREAS MEASURED e.g. GHK.

The outlined areas were then measured with a compensating polar planimeter as illustrated in Figure 5.6. The areas were measured in both a clockwise and anti-clockwise direction and the mean of these measurements taken as the surface area, in mm^2, for the maxillary and mandibular interdental surface areas respectively.

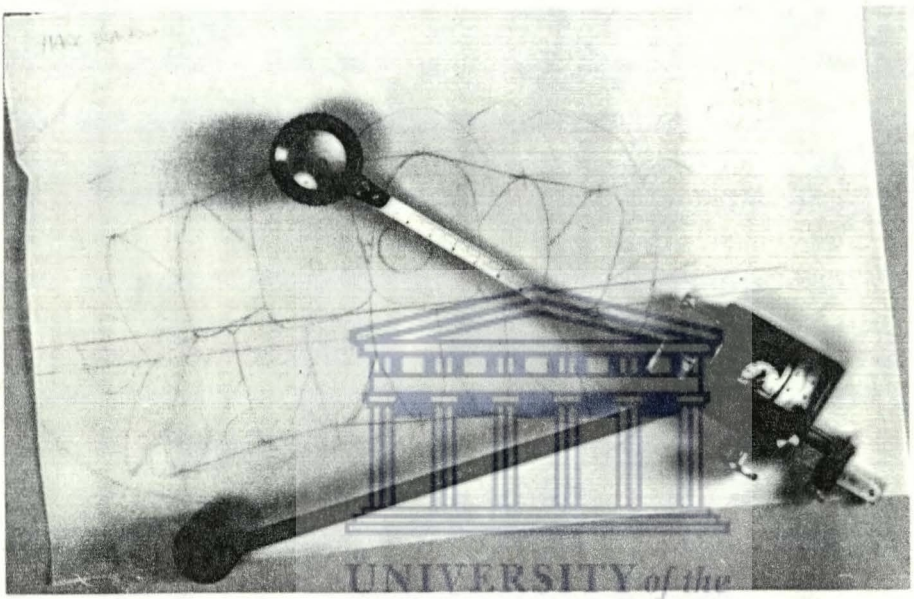

FIGURE 5.6 : THIS SHOWS THE COMPENSATING POLAR PLANIMETER FIXED TO THE TRACING PAPER WITH ITS LOWER ARM, WHILE THE UPPER TRACING ARM IS USED TO MEASURE THE SURFACE AREA OF THE INTERDENTAL PAPILLAE. THE MEASUREMENT WAS PERFORMED IN BOTH CLOCKWISE AND ANTI-CLOCKWISE DIRECTIONS TO OBTAIN A MEAN RECORDING

4. REPRODUCIBILITY OF THE METHOD

In order to test the reproducibility of this method, clinical photographs were taken of the gingivae of 25 pupils from the Jan Kriel School and measurements were made from the resultant tracings as described above. The whole process was repeated blindly

4-5 weeks later on the same subjects and the further set of tracings were measured in the standard way. The results were compared as reflected in Table 5.1. A statistical analysis, using the Spearman Rank Correlation Coefficient Test, gave a result of Rs = 0,99156 for the maxillary and Rs = 0,97786 for the mandible indicating no statistically significant difference (P<0,05). The results are also illustrated graphically (see Figure 5.7) and the linear relationship revealed a slope of virtually one (see Figure 5.7).

TABLE 5.1 : COMPARISON OF THE MEANS IN mm^2 OF THE GINGIVAL OVERGROWTH FOR TWO SETS OF UPPER AND LOWER MEASUREMENTS RECORDED ON THE SAME 25 SUBJECTS AT DIFFERENT TIMES

SUBJECT	UPPER MEASUREMENTS		LOWER MEASUREMENTS	
	1st	2nd	1st	2nd
1	1045	1065	1030	1010
2	1610	1590	1135	1140
3	1235	1235	1300	1290
4.	1610	1670	1275	1290
5	1485	1500	1530	1535
6	1300	1290	1155	1190
7	1300	1300	1190	1225
8	1535	1585	1340	1350
9	1225	1190	1270	1265
10	1510	1490	1390	1395
11	1765	1735	1635	1505
12	1575	1625	1530	1535
13	1585	1615	1185	1190
14	1294	1293	1220	1225
15	1920	1950	1560	1550
16	2290	2325	2685	2705
17	1835	1830	2335	2330
18	1890	1985	1260	1250
19	1450	1444	1350	1360
20	1400	1370	1600	1570
21	2770	2830	2355	2430
22	1440	1470	1190	1300
23	1930	1930	1810	1800
24	2500	2530	2770	2830
25	2300	2280	1940	1970
Means in mm^2 =	1669.96	1679.48	1561.20	1569.60
Rs =	0.99156		0.97786	

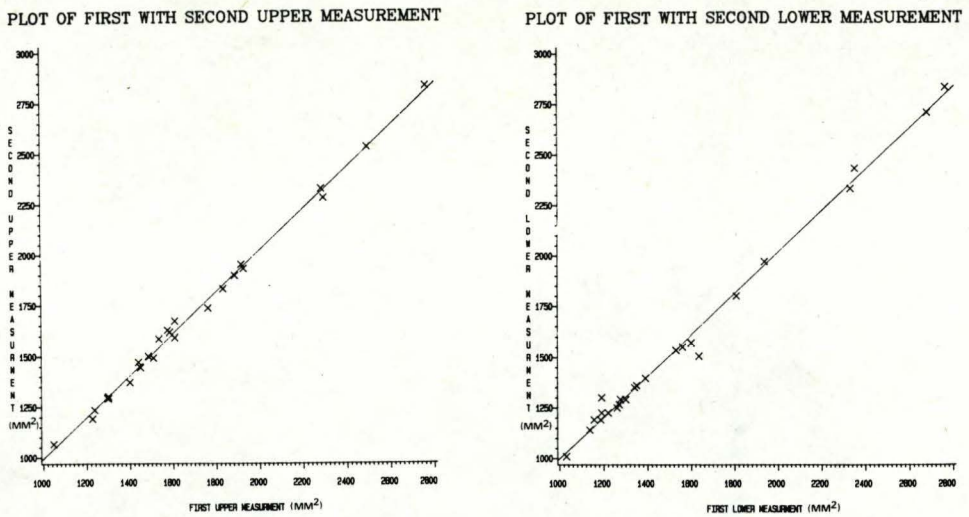

FIGURE 5.7 : GRAPHS FOR THE MAXILLARY AND MANDIBULAR SURFACE MEASUREMENTS IN mm^2 PLOTTED AGAINST THE RESULTS OBTAINED AT THE SECOND OCCASION SHOWING AN ALMOST LINEAR RELATIONSHIP

5. DISCUSSION

The method employed allowed standard alignment of the patient relative to the camera and the use of a stainless steel sphere made it possible to obtain standard tracings. In light of the fact that the enlargement was four times its actual size, the method would tend to exaggerate any latitude in the technique utilized. However the results indicate no statistically significant difference between the two sets of measurements and thus it can be concluded that the technique developed for measuring gingival overgrowth is accurate and avoids the subjectivity inherent in earlier methods (vide supra).

CHAPTER 6

MATERIALS AND METHODS

1. SAMPLE SELECTION

The records of 260 pupils at the Jan Kriel School for Epileptics were examined in order to select a suitable sample for this study. Of the above a group of 39 epileptics were deemed suitable, being the only subjects on a daily intake of phenytoin sodium as their sole medication for a period of 6 months or longer and whose history was not complicated by other illnesses, intake of other drugs or inability to co-operate. The latter was of the utmost importance as several intra-oral investigations were planned which required each subject to sit upright in a dental chair, as described in Chapter 5, and remain still in such position while recordings were made and clinical photographs taken. Of the 39 individuals successful tracings could be obtained of only 25 as the remaining 14 were in the mixed dentition stage. The variation in the gingival margin of the latter individuals made comparative tracings unreliable and furthermore some gingival enlargement was encountered which could possibly have been due to eruption-related inflammatory changes.

Clinical photographs were also taken of 25 age and sex matched control subjects. This group was selected from pupils at the Herzlia High School on the basis of them not having a history of epilepsy nor ever having used phenytoin sodium. Both the experimental and control groups each consisted of 10 females and 15

males with mean ages of 16.35 and 15.47 years for females and males respectively.

In addition to the photographs and tracings, further examinations were conducted on all 39 epileptics from the Jan Kriel School. These investigations, which will be described in later sections of this chapter, were not done for the controls as they were carried out to study their relationship to gingival tissues exhibiting overgrowth associated with the drug phenytoin sodium.

2 THE EXAMINATION

Details of the examination which were recorded on a data sheet (see addendum), included the name of each subject together with a reference code number, age in years and months, sex and plaque, gingival and hyperplasia indices and the volume of the gingival crevice fluid. Furthermore, the use of phenytoin sodium, its dosage and duration of use were recorded together with the area of hyperplasia in mm^2. The method of establishing the area of hyperplasia has already been discussed (see chapter 5) and the other parameters examined are described below.

(i) The Plaque Index was recorded using the modified technique of Silness and Loë (1967). Each of the twelve incisors was scored 0-3 according to specific criteria for each of the buccal, lingual, mesial and distal surfaces (see table 6.1). The scores for all 48 surfaces were totalled and the mean calculated to establish the plaque index for the individual.

TABLE 6.1 : THE CRITERIA FOR THE MODIFIED PLAQUE INDEX (Silness and Loë, 1967)

0	No plaque adjacent to gingival margin
1	Plaque at gingival margin - detectable with a probe
2	Visible plaque at gingival margin
3	Abundance of soft debris at gingival margin

(ii) The Gingival Index was used according to the W.H.O. method of scoring: 1 if bleeding was elicited on gentle probing and 0 if there was no bleeding. Once again the mean value of all 48 surfaces was calculated and noted as the gingival index for the individual.

(iii) The Hyperplasia Index was scored according to the method described by Angelopoulos and Goaz (1972). Because the interproximal tissues were impossible to assess for this parameter, only the visible facial and lingual gingivae were evaluated. A value of 0 was scored if no hyperplasia was present, 1 if the gingival overgrowth covered one-third of the clinical crown of the tooth, 2 if the coverage was between one-third and two-thirds and 3 if more than two-thirds of the tooth surface was covered by gingiva. The mean score for the 24 surfaces was recorded as the hyperplasia index for the individual.

(iv) Gingival Crevice Fluid was measured using a Periotron® instrument according to the directions of the manufacturer (Harco Electronics). The technique required the buccal surfaces of the upper and lower incisors to be cleaned and dried after which the buccal sulci were packed with cotton rolls. Sterile standard size filter strips as supplied with the instrument, were then gently inserted into each gingival crevice until slight resistance was felt. The strips were left in place for 3 seconds to drain the fluid from the gingival crevices and were then removed. After a period of 26 seconds, as indicated by the automatic timer of the unit, a new filter strip was placed into each crevice for a further 3 seconds to collect the accumulated fluid. The strip was then placed between the jaws of the Periotron and a value in Periotron-units was read off the screen of the unit after allowing a stabilizing period of 20 seconds.

The use of phenytoin sodium was noted and records were made of treatment in months and the dosage in mg/day. The use of other medication, such as carbamazepine (Tegretol) and sodium valproate (Epilim) was also recorded but for screening purposes only because such individuals were excluded from the first sample.

Once all the data had been collected, the results were transferred onto magnetic tape and computer-analysed at the Institute of Biostatistics of the South African Medical Research Council. Selected statistical tests were used and are indicated under the relevant headings in the chapter on results. A probability value of at least P 0,05 was selected to express statistical significance in all instances.

CHAPTER 7

RESULTS

1. GINGIVAL OVERGROWTH IN EPILEPTIC AND CONTROL SUBJECTS

As indicated in Chapter 5, the photometric method described was seen to be reproducible at a probability level of less than 1%. This technique was subsequently used to measure the surface area in mm^2 of the gingival tissues in a group of 25 epileptics and 25 controls (see Chapter 6), and the results are summarized in Table 7.1. Each measurement, at four times life size, represents the mean of the clockwise and anti-clockwise tracings obtained with the planimeter. No measurements could be made of the first two maxillary tracings in the control group as the upper canines were only partially erupted.

TABLE 7.1: THE SURFACE AREAS IN mm^2, AT FOUR TIMES ACTUAL SIZE, FOR THE MAXILLARY AND MANDIBULAR GINGIVAE IN 25 EPILEPTIC AND 25 CONTROL SUBJECTS

	EPILEPTICS		CONTROLS	
SUBJECT	MAXILLARY (in mm^2)	MANDIBULAR	MAXILLARY (in mm^2)	MANDIBULAR
1	1750.0	1570.0	NR	1125.0
2	1600.0	1533.0	NR	1050.0
3	1208.0	1268.0	1225.0	990.0
4	1385.0	1585.0	1460.0	1225.0
5	1055.0	1020.0	1457.0	1120.0
6	1235.0	1295.0	1375.0	1425.0
7	2515.0	2800.0	1675.0	1575.0
8	2308.0	2695.0	1165.0	1320.0
9	1935.0	1555.0	1275.0	1175.0
10	1560.0	1345.0	1555.0	1630.0
11	1300.0	1208.0	1425.0	1375.0
12	1295.0	1173.0	1335.0	1220.0
13	1930.0	1805.0	1790.0	1425.0
14	2800.0	2393.0	2410.0	1760.0
15	2290.0	1955.0	1420.0	1140.0
16	1293.0	1223.0	1420.0	1280.0
17	1640.0	1283.0	1200.0	1475.0
18	1500.0	1393.0	1240.0	1425.0
19	1447.0	1355.0	1410.0	1325.0
20	1495.0	1533.0	1575.0	1375.0
21	1893.0	1255.0	1515.0	1350.0
22	1600.0	1108.0	1890.0	1710.0
23	1833.0	2333.0	1400.0	1290.0
24	1455.0	1245.0	1235.0	1170.0
25	1600.0	1138.0	1760.0	1580.0
MEAN =	1677.0	1563.0	1487.5	1341.4

U-VALUES maxillary = 193

U-VALUES mandibular = 249

The mean value for the maxillary gingivae was 1677mm^2 for the epileptics and 1487,5mm^2 for the controls. Likewise, the values for the mandibular tracings were 1563mm^2 and 1341,4mm^2 for the experimental and control groups respectively.

In light of the fact that two separate and independent groups had been investigated and because the number of cases was too small to determine the distribution of the variables, it could not be assumed that the distribution was normal and consequently, the non-parametric Mann-Whitney U-Test was used. The U-value for the maxillary reading was 193 and that for the mandibular 249 which showed no statistically significant difference ($P < 0,05$) in gingival overgrowth between the control and epileptic persons.

2. RESULTS AND ANALYSES OF DATA OF OTHER VARIABLES STUDIED IN 39 EPILEPTICS

Other variables were studied in all 39 epileptic subjects. These included the age, sex and dosage and duration of use of phenytoin sodium. In addition the plaque, gingival and hyperplasia indices were recorded as well as the gingival crevice fluid (see Chapter 6).

The results are reflected in Table 7.2 in the form of the mean, median and standard deviation for each variable. From this table it can be seen that the mean age of the 39 epileptic subjects was 14.09 years with a standard deviation (S.D.) of 3,79. The average duration of phenytoin sodium usage was 40 months (S.D. = 28) while the mean dosage was 227mg per day (S.D. = 90).

The 39 subjects had a mean plaque index of 1,11 indicating a reasonable level of plaque control. The relatively favourable plaque levels are, as could be expected, supported by a mean gingival index of 0,28 indicating little bleeding on probing and only minor gingivitis. The mean for the hyperplasia index was 1,10 which is a low figure and points to slight gingival overgrowth.

On the other hand, the mean for the gingival crevice fluid, measured in Periotron units, was 155 which according to standard values (Garnick, Pearson and Harrell, 1979) indicates a severe degree of inflammation.

TABLE 7.2: THE MEAN, MEDIAN AND STANDARD DEVIATION (S.D.) FOR SEVERAL VARIABLES IN A SAMPLE OF 39 EPILEPTICS

VARIABLE	MEAN	MEDIAN	S.D.
AGE IN YEARS	14.09	15.04	3.79
DURATION IN MONTHS	40.00	36.00	28.00
DOSAGE IN MG/DAY	227.00	250.00	90.00
PLAQUE INDEX	1.11	1.00	0.52
GINGIVAL INDEX	0.28	0.30	0.24
GINGIVAL CREVICE FLUID IN PERIOTRON UNITS	155.00	122.00	116.00
HYPERPLASIA INDEX	1.10	1.30	0.57

3. SEX AND AGE

Further analysis of the data of the 39 epileptics revealed no significant difference between males and females for any of the variables studied, using the Mann-Whitney U-test at a probability level of $P<0,05$ (see Table 7.3.).

TABLE 7.3: INTER-SEX COMPARISON FOR THE SAMPLE OF 39 EPILEPTICS

	MALES				FEMALES				
	N	MEAN	MEDIAN	S.D.	N	MEAN	MEDIAN	S.D.	P-VALUE
AGE IN YEARS	24	14.11	14.58	3.93	15	14.05	15.11	3.68	0.9301
DURATION IN MONTHS	24	41.00	36.00	30.00	15	39.00	36.00	25.00	0.9654
DOSAGE IN MG/DAY	24	204.00	175.00	95.00	15	263.00	300.00	69.00	0.0590
PLAQUE INDEX	24	1.07	0.95	0.58	15	1.17	1.10	0.41	0.3242
GINGIVAL INDEX	24	0.26	0.25	0.26	15	0.32	0.40	0.20	0.1833
GINGIVAL CREVICE FLUID IN PERIOTRON UNITS	24	153.00	105.00	139.00	15	159.00	140.00	72.00	0.1839
HYPERPLASIA INDEX	24	1.03	1.20	0.59	15	1.22	1.30	0.54	0.4007

TEST EMPLOYED : MANN-WHITNEY U-TEST

The data for the 39 epileptics was further grouped into two age groups of equal size, one above and the other below the median of 15.04 years. This approach revealed no significant differences in the data for the two groups except for the dosage of diphenylhydantoin which was found to be greater in the older age group, a feature probably related to a higher mean body weight in this group.

TABLE 7.4 : A COMPARISON OF THE AGE GROUPS ABOVE AND BELOW THE MEDIAN OF 15.04 YEARS

	BELOW 15.04 YEARS				ABOVE 15.04 YEARS				
	N	MEAN	MEDIAN	S.D.	N	MEAN	MEDIAN	S.D.	P-VALUE
DURATION IN MONTHS	20	34.0	35.0	22.0	19	47.0	39.0	32.0	0.2852
DOSAGE IN MG/DAY	20	190.0	150.0	90.0	19	266	300	75	0.0092
PLAQUE INDEX	20	1.13	1.10	0.54	19	0.90	0.50	0.50	0.4893
GINGIVAL INDEX	20	0.24	0.20	0.23	19	0.33	0.30	0.24	0.2210
GINGIVAL CREVICE FLUID IN PERIOTRON UNITS	20	135	116	78	19	177	140	146	0.4562
HYPERPLASIA INDEX	20	1.02	1.20	0.61	19	1.19	1.30	0.53	0.4720
GINGIVAL OVERGROWTH UPPER IN MM^2	9	1570	1455	513	16	1737	1600	383	0.1925
GINGIVAL OVERGROWTH LOWER IN MM^2	9	1466	1295	393	16	1617	1374	552	0.8429

Test = Mann-Whitney U-Test

4. CORRELATION BETWEEN THE VARIABLES STUDIED

All the variables were cross-correlated using the Rank Spearman correlation test (Rs) and the significant correlations are reflected in Table 7.5. The remainder showing no significant correlations are set out in Table 7.6 for the sake of completeness.

Positive and statistically significant correlation between the plaque index on the one hand and the gingival and hyperplasia indices and the gingival crevice fluid on the other, where revealed by this test (see Table 7.5). Likewise, a statistically significant correlation between the gingival crevice fluid and the hyperplasia index was found. The finding that the dosage of the drug was higher in the older age group (see Table 7.4) was further supported by a significant correlation between dosage and age. Dosage also showed a significant relationship to the area of gingival overgrowth in the maxilla although not to that in the mandible (Table 7.6.) The overgrowth values for maxillary and mandibular gingival tissues were also found to be significant at the selected probability level of $P<0,05$.

TABLE 7.5: THE CORRELATION BETWEEN SEVEN PAIRS OF VARIABLES THAT WERE FOUND TO BE SIGNIFICANT AT A LEVEL OF $P<0,05$ USING THE RANK SPEARMAN CORRELATION COEFFICIENT (Rs).

VARIABLES	N	RS	P-VALUE
PLAQUE INDEX & GINGIVAL INDEX	39	0,3690	0,0208
PLAQUE INDEX & GINGIVAL CREVICE FLUID	39	0,4634	0,0030
PLAQUE INDEX & HYPER-PLASIA INDEX	39	0,4796	0,0020
GINGIVAL CREVICE FLUID & HYPERPLASIA INDEX	39	0,3357	0,0367
DOSAGE & AREA MAXILLARY GINGIVAL OVERGROWTH	25	0,5185	0,0079
DOSAGE & AGE	39	0,4265	0,0068
AREA MAXILLARY & AREA MANDIBULAR OVERGROWTH	25	0,6937	0,0001

TABLE 7.6 THE NON-SIGNIFICANT CORRELATIONS OF 29 PAIRS OF VARIABLES ($P \geq 0,05$) USING THE RANK SPEARMAN CORRELATION COEFFICIENT (Rs)

VARIABLES	N	RS	P-VALUE
PI; G.O. UPPER	25	0,2505	0,2271
PI; G.O. LOWER	25	0,3306	0,1065
PI; AGE	39	-0,0582	0,7248
GI; G.C.F.	39	0,2639	0,1045
GI; HYP. INDEX	39	0,1236	0,2508
GI; G.O. UPPER	25	-0,0016	0,9940
GI; G.O. LOWER	25	0,0169	0,9361
GI; AGE	39	0,1632	0,3209
G.C.F.; G.O. UPPER	25	0,1117	0,5950
G.C.F.; G.O. LOWER	25	0,0470	0,8236
G.C.F.; AGE	39	0,1266	0,4425
AGE; G.O. UPPER	25	0,3557	0,0810
AGE; G.O. LOWER	25	0,1762	0,3995
HYP. INDEX; G.O. UPPER	25	-0,1421	0,4979
HYP. INDEX; G.O. LOWER	25	0,0668	0,7512
HYP. INDEX; AGE	39	0,0979	0,5531
DURATION : AGE	39	0,2913	0,0720
DURATION : DOSAGE	39	-0,2062	0,2078
DURATION : PI	39	0,1284	0,4362
DURATION : GI	39	0,1025	0,5348
DURATION : G.C.F.	39	0,1660	0,3125
DURATION : HYP. INDEX	39	0,1239	0,4525
DURATION : G.O. UPPER	25	-0,3692	0,0693
DURATION : G.O. LOWER	25	-0,2469	0,2345
DOSAGE : PI	39	0,0621	0,7072
DOSAGE : GI	39	0,0907	0,5830
DOSAGE : G.C.F.	39	0,2668	0,1006
DOSAGE : HYP. INDEX	39	0,1258	0,4455
DOSAGE : G.O. LOWER	25	0,3049	0,1384

P.I. = plaque index

G.O. = gingival overgrowth

G.I. = gingival index

Hyp. index = hyperplasia index

G.C.F. = gingival crevice fluid

CHAPTER 8

DISCUSSION AND CONCLUSIONS

1. DISCUSSION

Phenytoin sodium has several side-effects of which the unsightly appearance of gingival overgrowth is probably one of the more distressing problems encountered during therapy with this drug. Consequently, it is understandable that the patients in the institution selected for the survey were placed, whenever possible, on alternative drugs. This is probably the reason why only 39 subjects were found out of a possible total of 260 pupils who had used phenytoin sodium as their only medication for at least six months. Furthermore, the vast majority of the pupils at the school suffered from mild epilepsy and could thus be adequately controlled with other drugs such as Tegretol®, Zarontin®, phenobarbitone and Epilim®. The approach at this institution is to treat new pupils with phenytoin sodium initially but to reduce the dosage or eliminate the drug in favour of substitutes as soon as they have been stabilized. Phenytoin sodium is thus mainly prescribed for those individuals who suffer from grand mal seizures.

The mean duration of drug usage of the 39 epileptics selected was 40 months (see Table 7.2). Although minor gingival changes have been reported after only a few weeks of phenytoin sodium therapy (Ziskin et al, 1941; Esterberg and White, 1945; Dolin, 1951), it is generally accepted that gingival overgrowth usually develops several months after the initiation of treatment (Dummett, 1954;

Ishikawa and Glickman, 1961). Consequently, substantial gingival overgrowth could have been expected in this sample but the converse was, in fact, found to be true. This feature of minimal gingival overgrowth may be explained by the excellent standard of oral hygiene practised at the school as well as the possible bias toward selecting mild epileptics for this study. Although the relationship between DGO and plaque is widely accepted, some controversy remains. On the one hand, several authors have reported a positive correlation between the degree of DGO and plaque levels (Collins and Fry, 1960; Panuska, 1961; Navarro and Correll, 1976) while other studies have shown no correlation between these two variables (Milhon and Osterberg, 1942; Esterberg and White, 1945; Dolin 1951). This latter view has also been reported in a more recent study by Klar (1973) who, while showing a positive correlation between inflammatory symptoms and gingival overgrowth, reported that his study did not show oral hygiene to be statistically significant in the formation of gingival hyperplasia. However, the criteria used in this study seemed to be subjective and the conclusions drawn may consequently be erroneous. In general, it is accepted that plaque is the single most aggravating factor in the development of gingival overgrowth associated with the use of phenytoin sodium (Ishikawa and Glickman, 1961; Aas, 1963; Angelopoulos and Goaz, 1972). Nevertheless, in spite of the strong correlation between plaque and DGO, not all persons run the risk of developing gingival overgrowth and it appears that only about 50% of any given epileptic population, treated with phenytoin sodium, will develop this condition (Hassell et al, 1981) while individual patient susceptibility to

the drug seems likely to be a decisive factor (Hassell et al, 1981). In the sample investigated, the degree of gingival overgrowth was found to be small, probably related to excellent plaque control, the latter possibly having a more powerful influence than the genetic background.

In the present study the parameters expressing the standard of plaque control such as the plaque and gingival indices, were found to be quite low at values of 1,11 and 0,28 respectively. In clinical terms this means that patients have relatively little plaque and consequently only exhibited minor bleeding on probing. This association between plaque and gingival inflammation has, of course, been well documented (Loë et al, 1965). Furthermore, the sample showed an hyperplasia index of 1,10 which, applying the criteria used by Angelopoulos and Goaz (1972), indicated minor hyperplastic changes which concur with results reported by Aas (1963) and Angelopoulos Goaz (1972). The criteria used in the present study for establishing the plaque , gingival and hyperplasia indices were based on subjective clinical criteria. Consequently, it was deemed necessary in addition to other more objective methods, to assess the degree of inflammation and gingival overgrowth. This was done by means of the Periotron to measure the volume of gingival crevicular fluid flow (G.C.F.) while a photometric technique was employed to assess the degree of gingival overgrowth.

It has been shown that the amount of G.C.F. has a strong correlation with the degree of inflammation in the tissues (Tsuchida and Hara, 1981). The latter authors reported gingival fluid

measurement to be a useful guide of inflammatory changes in gingivitis and early periodontitis but less suitable for advanced cases as "gingival fluid flow reaches a plateau." In the present sample, the G.C.F. was measured using the Periotron apparatus which has been found to be a sensitive instrument for measuring sulcular fluid (Garnick et al, 1979). The mean value of 166 Periotron units found is, however, an extremely high figure when compared with the values recorded in previous studies (Garnick et al, 1979; Ebersole et al, 1984) and contrary to that expected because of the low plaque and gingival indices recorded for our sample. The reasons for these equivocal results may be due to technical problems rather than biological differences. The values obtained for these persons were much higher than the level of 40 units or more which, according to the manufacturers, indicates severe gingivitis (Garnick et al, 1979). Although the recordings made with the Periotron apparatus are objective, the values obtained in the present survey were beyond the instrument's upper upper limit of 1,4 µl (or 140 Periotron units) as reported by Ebersole et al (1984). In addition Garnick et al (1979) had demonstrated that consecutive readings with this instrument may vary by as much as 11%, an error which may affect reproducibility when using this instrument. In our study use was made of the Periotron HAR 600 , an older model which has recently been superceded by a new model, the HAR 6000 . The latter instrument appears to be more sensitive and reliable than its predecessor (Bickel and Cimansoni, 1984) and its use may well have rendered more reliable information. However, critical assessment of the unit is still required as the accuracy of the Periotron seems to be affected by factors such as humidity, room

temperature, evaporation and contamination of the recording jaws of the instrument. In light of these factors the G.C.F. results obtained in the present study should be viewed with circumspection.

Hitherto, no objective method for assessing the degree of gingival overgrowth has been reported. Consequently, the development of a photometric method of recording this change is a distinct improvement as it reduces subjectivity. This method entailed the use of standardized colour transparencies of each subject which were projected at a standard four-fold enlargement. Tracings were made and measured with a compensating polar planimeter and the resultant values would have, because of the enlargement used, tended to exaggerate any inherent discrepancies. However, the results obtained for two consecutive sets of measurements obtained at different sessions showed an almost linear correlation (see Figure 5.7), which was shown to be statistically significant at a probability value of 0,01 using the Rank Spearman correlation co-efficient (see Table 5.1).

This study thus revealed that the technique developed was reproducible, accurate and sensitive and consequently a more acceptable method than those previously reported. The values recorded in this survey are therefore considered to be valid despite the possible bias in selecting a sample with minor epilepsy involvement. Furthermore, the fact that no difference was found between epileptic and control groups indicated that the hyperplasia index, according to Angelopoulos and Goaz (1972), which was utilized in this instance, gave an erroneously high reading. On the

other hand, the low level of gingival overgrowth, as assessed by the photometric technique, supports the concept that the minimal degree of DGO in this sample is due to the low levels of plaque accumulation (vide supra).

No signficiant difference was found between the degree of gingival overgrowth in the maxilla as compared to the mandible (see Table 7.5), a result which was to be expected as their respective plaque, gingival and hyperplasia indices were all low. Furthermore, while numerous studies have indicated greater gingival enlargement anteriorly than in the posterior segments, no significant difference has been described between the maxillary and mandibular anterior sextants (Aas, 1963; Angelopoulos and Goaz, 1972). However in this study, while dosage was found to have a statistically significant relationship to maxillary gingival overgrowth, no such correlation was found with regard to the mandible (see Tables 7.5 and 7.6). This can possibly be explained by the use of a highly subjective hyperplasia index to record DGO. Furthermore, the median age of the sample was shown to be 15,04 years (see Table 7.4) which age group will tend to show a varying degree of inflammation and gingival overgrowth associated with the hormonal changes of puberty (Sutcliffe, 1972). It is also conceivable that the tissue reaction would be found to be more severe in mouth breathers (Collins and Fry, 1960) due to dehydration of the gingiva. Furthermore, the maxilla may be affected to a greater extent than the mandible by poor lip seal as the lower lip generally covers more gingival tissue than would be the case with a short upper lip.

In the light of the fact that DGO in the epileptics did not differ from the control group, it is not surprising that no statistically significant difference was found between the upper and lower age ranges (see Figure 7.4) in respect of the variables examined. The notable exception was the correlation found between dosage and age at a p-value of 0,0092, which is highly significant. This, however, is probably only a reflection of the higher dosage required for older subjects based on their increased body weight. Similarly, most of the other variables investigated and cross-correlated were also found to be not statistically significant (see Table 7.6).

Because the sample revealed no dramatic changes, it was not found possible to develop a method of classification for gingival overgrowth. It is therefore suggested that the technique described be used on a different epileptic population where marked gingival enlargement has occurred. This should enable the establishment of a specific range of measurements in mm^2 which could be objectively related to a classification on a scale of 0 - 3.

2. CONCLUSIONS

The results achieved have shown that the photometric technique developed is accurate, objective and reproducible. Furthermore, it could be used in further research projects and may possibly be utilized as a means of establishing an objective method for measuring gingival overgrowth, provided that significant enlargement has occurred.

It is also evident that the occurrence of gingival overgrowth is related to individual susceptibility to phenytoin sodium and that the degree of gingival overgrowth, when it occurs, can be well controlled with good oral hygiene measures, which have been further shown to be successful in preventing a recurrence after treatment (Donnenfeld et al, 1974).

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CLINICAL EXAMINATION RECORD SHEET

ADDENDUM

9 = NO DATA

NAME : ..... No. [1 2]

AGE [3 4] [5 6]

SEX (♀ = 1 ♂ = 2) [7]

	FIRST	SECOND	THIRD
PLAQUE INDEX (0-1-2-3)	[8 9 10]	[11 12 13]	[14 15 16]
GINGIVAL INDEX BLEEDING (NO = 0 Yes = 1)	[17 18 19]	[20 21 22]	[23 24 25]
CREVICE FLUID (µl)	[26 27 28]	[29 30 31]	[32 33 34]

FOLLOW CARD [1] 60

DRUG : Epanutin No = 0 Yes = 1	Drug [1]	Duration(mnth) [2 3 4]	Dosage(mg/day) [5 6 7 8]
Tegretol	[9]	[10 11 12]	[13 14 15 16]
Epilim	[17]	[18 19 20]	[21 22 23 24]
Other	[25]	[26 27 28]	[29 30 31 32]

HYPERPLASIA (0-1-2-3) [33 34 35]

AREA HYPERPLASIS (mm^2) [36 37 38 39 40 41 42 43]

CLINICAL PHOTOS no = 0 Yes = 1 [44]

FOLLOW CARD [2] 60

OTHER COMMENTS : .....

- 2 -

NAME : ..... DATE : .....

NO. : .....

	PLAQUE INDEX	GINGIVAL INDEX	HYPERPLASIA (B L L B)	
1.	SCORE	SCORE SCORE		DATE : .....
2.	SCORE	SCORE SCORE		DATE : .....
3.	SCORE	SCORE SCORE		DATE : .....
4.	SCORE	SCORE SCORE		DATE : .....
5.	SCORE	SCORE SCORE		DATE : .....