ORIGINAL RESEARCH

Fibroblasts and Phagocytic Cells in Phenytoin-induced Connective Tissue Proliferation

Rosaiah Kanaparthy, Aruna Kanaparthy, Kamala Devi

ABSTRACT

Objective: To evaluate the relationship of phenytoin-induced gingival enlargement and inflammation to find out if there is any significant correlation between hyperplastic index and periodontal parameters, the number of fibroblasts and phagocytic cells.

Background: The introduction of phenytoin as an anti-epileptic drug in 1938 marked the beginning of a new era in the treatment of grandmal epileptic patients decreasing significantly not only the epileptic attacks but also improving the quality of life. However, there is concern in dentistry regarding gingival overgrowth as a side-effect. A histological study of this tissue can shed some light on the changes taking place.

Materials and methods: Twenty-four epileptic patients on phenytoin therapy were divided into two groups as follows:

- Group I or test group of individuals who had been suffering from gingival enlargement,
- Group II or control patients taking phenytoin without any gingival enlargement.

Plaque, gingival and hyperplastic indices of anterior teeth were determined in all the subjects. Biopsy specimens of all patients were taken and subjected to histopathological examination to determine the number of fibroblasts, macrophages, lymphocytes, and the level of inflammation, capillary proliferation and collagenation.

Results: There is a significant increase in number of fibroblasts, macrophages, lymphocytes,collagenation and capillary proliferation in the enlarged gingiva of test group as compared to the control group.

Conclusion: The degree of inflammation increases with the degree of enlargement. There is an increase in angiogenesis and the number of phagocytic cells thus indicating that phenytoin exerts growth promoting effects on the connective tissues.

Keywords: Phenytoin, Gingival inflammation, Gingival enlargement, Fibroblasts.

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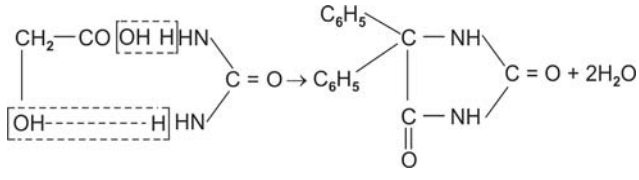
INTRODUCTION

Epilepsy is a collective term for a group of chronic convulsive disorders having in common, sudden transient episodes of loss or disturbance of consciousness, usually but not always with a characteristic body movement (convulsions) and sometimes with autonomic hyperactivity. John Hughlings Jackson postulated about a century ago that epileptic seizures were caused by occasional, sudden, excessive, rapid, local disturbances of gray matter. The normal brain contains billions of neurons which 'fire' asynchronously. Inhibitory feedback loops in the normal brain regulate the frequency of firing of individual neurons and prevent synchronization. When such an inhibitory feedback is defective, a large number of cells in a given area of the brain fire at the same time and produce a self-regenerative electrical impulse. Such an arc constitutes an epileptic focus.

Such foci may be cortical or subcortical. They may discharge intermittently, only to be shown up on the gross surface EEG but not cause symptoms because their spread is blocked by the normal inhibitory mechanisms in the surrounding brain tissue. Factors which themselves cannot initiate seizures may trigger off the abnormal focus as they permit the spread of activity to the normal brain. Such factors include alkalosis, hypoglycemia, overhydration, hypocalcemia, overeating, strong emotional states, such as fright or embarrassment, various stages of sleep, intake of alcohol and rapid blinking of eyes or other rhythmic phonic stimulation. The clinical type of seizure is independent of the brain pathology but is determined by the site of the abnormal focus and by the path taken by the seizure discharge. The response to treatment correlates best with the site of the epileptogenic focus.[1]

Many types of anticonvulsive drugs have been extensively used in the treatment of grand mal and other types of epilepsy. These drugs play a significant role in the control of convulsions and also in their prevention of recurrence, thus relieving the agony of disease. Out of several drugs used, the most commonly used drugs in the treatment of epilepsy are phenytoin and phenobarbitone, a barbiturate. These may be considered as 'life saving group of drugs'.

Apart from producing beneficial effects, these drugs, particularly phenytoin, show certain side effects like gingival enlargement on oral administration. This drug seems to possess a selective stimulating effect on the fibroblasts of the gingival connective tissue causing excessive formation of fibrous tissue.



It has been pointed out in the literature that compounds containing urea radicle have a tendency to produce fibroblastic stimulating effect and cause excessive proliferation of fibrous tissue. Hence, in the light of the above fact that diphenylhydantoin (DPH) contains a urea radicle the cause of gingival enlargement is well-established. The severity of phenytoin (PHT) induced gingival overgrowth and its correlation with dental plaque calculus formation and gingival inflammation has been well documented.[2-5] Inflammation seems to be an important cofactor in PHT-induced gingival overgrowth in both animals and man.

These observations imply some supportive or synergistic role for one or more of the inflammatory cells with the mitogenic effects of PHT on connective tissue fibroblasts.[6] Since, both macrophages and lymphocytes are known to have critical roles in the repair of inflamed connective tissue, these cells were found to be strong candidates for involvement in the PHT-induced growth process.[7]

PHENYTOIN PHARMACOLOGY

The discovery of antiepileptic drugs is a breakthrough in the era of pharmacotherapeutics. Some of these drugs are highly indispensable to the suffering of mankind. One of them being diphenylhydantoin introduced by Merritt and Putnam in 1938 with great success in controlling epileptic seizure particularly the grand mal type. It is the primary drug in the treatment of epileptic seizures with the exception of petit mal. It is otherwise called as dilantin sodium. DPH is obtained by the combination of urea and glycolic acid forming glycolylurea, otherwise called hydantoin. If diphenyl radicals are substituted for hydrogen, then it is called DPH.

MODE OF ACTION

It exerts a selective antiepileptic action without causing drowsiness. The onset of action is slow even on intravenous injection but the action persists for a considerable time after cessation of therapy. This is thought to be due to the light binding of the drug to the nervous tissue. The exact mode of action of this drug is not known, probably, it inhibits the spread of seizure discharges in the brain and shortens the duration after discharge. In patient in whom it is effective, the generalized abnormality in EEG disappears but the abnormal focal electrical activity persists, unlike phenobarbitone, the drug fails to produce a significant alteration in the electroshock seizure threshold in normal animals. The threshold may, however, be elevated to a moderate extent after prolonged therapy. The drug has no protective effect against leptazol-induced convulsions in animals.

The drug is known to decrease the neuronal sodium concentration leading to a reduction in the post-tetanic potentiation (PTP) and to increase the neuronal potassium concentration. The work of Woodbury et al indicates that the stabilizing effect of PHT is closely related to its ability to decrease the intraneuronal sodium concentration. The drug has a stabilizing effect on all neuronal membranes including the peripheral nerve membrane as well as on all nonexcitable and excitable membranes.

Phenytoin also augments brain level gamma amino butyric acid (GABA) as well as 5-HT and homovanillic acid. The restored balance between the excitatory glutamate and inhibitory GABA pathways by PHT might be contributory to its antiepileptic action. PHT is slowly and variably absorbed from the gut and its peak in the plasma occurs 3 to 12 hours after ingestion. It is metabolized mainly by parahydroxylation of one of its phenyl rings in the liver. It is excreted in the urine and in saliva.

ADVERSE REACTIONS

Such reactions are generally mild and only rarely do they enforce a cessation of therapy. Plasma levels of over 20 mg/ml are generally associated with adverse reactions. Introducing of this drug may lead to urticarial, scarlatiniform and measles like skin rashes may occur more frequently in children and in young adults. Hypertrichosis and hirsutism related to increased adrenocortical activity sometimes occurs in females. PHT may lead to vestibulocerebellar syndrome characterized by vertigo, ataxia, nystagmus and dysarthria, others effects like drowsiness, fatigue, headache and confusion are occasionally observed.

Ocular pain with blurring of vision, delusions, hallucinations and other psychotic episodes are sometimes encountered. Peripheral neuropathy has been reported in old people receiving large doses for many years. Gastric irritation, resulting in nausea and vomiting caused by the alkalinity of the drug, can be prevented by taking the total daily dose in individual portions, after meals, with plenty of fluids. Megaloblastic anemia responding to folic acid and rarely, blood dyscrasias including aplastic anemia, pancytopenia, leukopenia, agranulocytosis may appear. PHT has marked enzyme inducing properties and can stimulate the metabolism of many drugs, such as contraceptives, steroids, coumarin anticoagulants, glucocorticoids and vitamin D, thereby reducing their therapeutic efficacy. Dangerous hyperglycemia has been reported in diabetics receiving PHT. This is probably due to inhibition of insulin secretion by PHT.

GINGIVAL ENLARGEMENT

Its reported incidence varies from 3 to 84.5% and it occurs more frequently in younger patients,[2] Babcock JR (1965), Kimbal OP (1939) was the first person to report gingival hyperplasia due to DPH.[8] The primary basic lesion starts as a painless, bead like enlargement on the facial and lingual gingival margins and interdental papillae. When uncomplicated by inflammation, the lesion is mulberry shaped, firm, pale pink and resilient, with a minutely lobulated surface and no tendency to bleed. The enlargement characteristically appears to project from beneath the gingival margin, from which it is separated by a linear groove.[9,10] The hyperplasia is usually generalized throughout the mouth but it is more severe in the maxillary and mandibular anterior regions.

HISTOPATHOLOGY

Most of the histopathological investigations that were carried out on DPH induced gingival hyperplasia are by using conventional staining method (H&E) and the observations are reported by light microscopy. The enlargement entails pronounced hyperplasia of the connective tissue and epithelium. There is acanthosis of epithelium and elongated rete pegs extending deep into the connective tissue, which exhibit densely arranged collagen bundles with an increase in the number of fibroblasts and new blood vessels.[9,10]

MATERIALS AND METHODS

Twenty-four patients were examined to access the periodontal status of their upper and lower anterior teeth. All individuals gave informed consent to participate in the study:

The selection criteria for the patients were as follows:

- The patients taking phenytoin drug.
- Patients who possessed their six upper and six lower anterior teeth were eligible for study.
- None of the patients examined were on antihypertensive therapy or any other medication known to produce gingival enlargement.

STUDY DESIGN

Twenty-four patients, who satisfied above criteria, were selected for study. All examinations were conducted with subject sitting in the dental chair under standardized illumination with a dental mirror and a standardized graduated periodontal probe.

The epileptic patients were divided into a test group of 12 individuals on PHT who had been suffering from gingival hyperplasia and 12 patients taking PHT without enlargement taken as negative control.

Periodontal health of all the patients was assessed by the following parameters.

Parameters of Periodontal Health

Plaque Index

Plaque levels of the labial, lingual and interproximal surfaces of the 12 anterior teeth were scored according to plaque index by Silness and Loe (1964).[11]

Grades	*Criteria*
0	No plaque in the gingival area.
1	A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be recognized only by running a probe across the tooth surface.
2	Moderate accumulation of soft deposits within the gingival pocket and on the gingival margin and or adjacent tooth surface that can be seen by naked eye.
3	Abundance of soft matter within the gingival pocket and on the gingival margin and adjacent tooth surface.

The plaque index for each subject was determined by adding the individual scores and dividing this by the number of surfaces scored. The gingival conditions were assessed using the gingival index (GI) as given by Loe and Silness (1963).[11]

Gingival Index

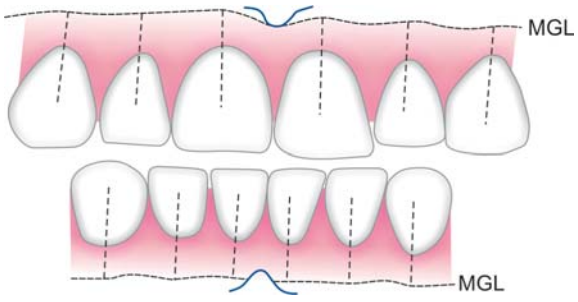
Grades	*Criteria*
0	Normal gingiva
1	Mild inflammation, slight change in color, slight edema, no bleeding on palpation
2	Moderate inflammation, redness, edema and glazing, bleeding on probing
3	Severe inflammation, marked redness and edema, ulceration, tendency to spontaneous bleeding.

The tissues surrounding each tooth are divided into four gingival scoring units.

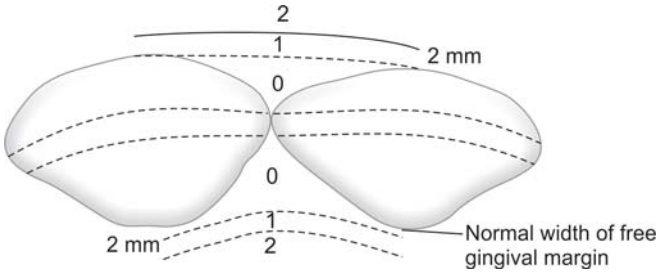
a. Distofacial papilla
b. Facial margin
c. Mesiofacial margin
d. Entire lingual margin

A blunt instrument, such as a periodontal pocket probe, is used to assess the bleeding potentials of the tissues. Totaling the scores around each tooth yields, the gingival index score for the area. If the scores around each tooth are totaled and divided by four, the gingival index scores for the tooth is obtained. Totaling all of the scores per tooth and divided by the number of teeth examined provides the GI score per person. Criteria for assessing gingival thickness in a labiolingual direction for a gingival unit. The numerical score of the GI are associated with varying degrees of clinical gingivitis as follows:

Gingival score	*Degree of gingivitis*
0.1-1.0	Mild
1.1-2.0	Moderate
2.1- 3.0	Severe



Division of upper and lower anterior teeth into gingival units (MGL = mucogingival line)



Assessment of Gingival Hyperplasia

Gingival hyperplasia was assessed for the 12 anterior teeth; using a semiquantitative hyperplastic index (HI). It is comprised of two components that measure independently the vertical and horizontal extension of gingival enlargement. The hyperplasia was measured in the patient's mouth using a calibrated periodontal probe. The upper and lower arches are divided into five gingival units (anteriorly) both buccally and lingually, according to the method developed by Seymour et al 1985.[12] Each unit was from the buccal or lingual midpoint of a tooth, the midpoint of the adjacent tooth, extending from 13 to 23 in the upper arch, and from 33 to 43 in the lower arch.

The vertical component of the HI measured, the degree of gingival enlargement in an apicocoronal direction (vertical) for a gingival unit and was graded by means of a 4-point interval scale (Table 1). This vertical component of the HI has been used as the sole index for assessing gingival enlargement by Hassell TM et al,[13] Conard et al (1947).[14] The horizontal component of the HI developed by Seymous et al (1985) measured the degree of gingival thickening on both the labial and lingual aspect in a labiolingual direction (horizontal) for a gingival unit (Table 2).

Table 1: Vertical hyperplastic index or apicocoronal component

Grade	*Criteria*
0	No gingival hyperplasia
1	Mild hyperplasia (blunting of gingival margin)
2	Moderate hyperplasia (less than 1/2 of crown length)
3	Marked hyperplasia (greater than 1/2 of crown length)

The vertical and horizontal scores were added, thus giving a hyperplasia score for each gingival unit. The maximum score obtainable using this method is five. As 20 gingival units were examined, the degree of hyperplasia around upper and lower anterior teeth was expressed as a percentage (Seymour et al 1985).[12]

The horizontal component of the hyperplastic index, developed by Seymour et al 1985[12] measured the degree of gingival thickening on both the labial and lingual direction (horizontal).

For a gingival unit:

Grades	*Criteria*
0	Normal width of free gingival margin
1	Thickening from the normal up to 2 mm
2	Thickening from the normal and > 2 mm

Procedure for quantification of fibroblastic and phogocytic cells in the PHT-induced connective tissues. Quantification of fibroblasts and phagocytic cells can be done by making smears from the PHT-induced gingival enlargement biopsies.

Before biopsy was taken complete oral prophylaxis was done. After reviewing the case for a period of 15 days, biopsy was taken.

Biopsy

The biopsy specimens were obtained from all the 24 patients belonging to the two groups under local anesthesia (lignocaine hydrochloride 2% with adrenaline). In the PHT-induced gingival enlargement cases, the hyperplastic tissue is taken as the biopsy. In the control group, the lingual mucosa adjacent to lower left second premolar and first molar was taken as biopsy tissue. The technique employed to obtain the specimen was incisional biopsy technique. The biopsy material was immediately fixed in 10% potassium buffered formalin following adequate fixation, they were processed by conventional methods and paraffin blocks were made and sectioned on a Reichert Histostat rotary microtome, sections made and stained with hematoxylin and eosin solutions.

The slides were examined under a compound microscope with a magnification of ×100. In the histopathological view of the slides, the number of fibroblasts, macrophages, lymphocytes, the amount of papillary proliferation, the amount of collagenation, whether their is acanthosis or not and degree of inflammation was seen. As it is impossible to count the number of different cells in the sections, we have graded them into 0, +, ++ and +++ depending on the number of cells present in the sections.

- 0: Zero or negligible number of cells in some sections.
- +: Cells present in all the sections but in medium density in few sections.
- ++: Cells present in all the section but in high density in limited section.
- +++: Cells present in all the sections of the slide in high density.

RESULTS

A total of 24 patients were taken for the study. They were divided into two groups.

Group I: Test group—this consists of 12 patients taking PHT with gingival hyperplasia (Fig. 1). Group II: Control group—this consists of 12 patients taking PHT and without gingival hyperplasia (Fig. 2).

Results of group I: It consists of 12 epileptic patients under PHT therapy. Of all the 12 patients, clinically examined five patients showed grade II gingival enlargement and remaining seven patients showed grade III gingival enlargement. None of these cases had grade I enlargement (Fig. 3).

On histopathological examination, the section with these second degree of gingival enlargement showed the following changes in the submucosal layer. One case showed less degree of fibroblastic proliferation and remaining four cases of second degree drug enlargement showed moderate degree of fibroblastic activity (Fig. 4).

In third degree enlargement cases, except one case all the remaining cases, showed dense degree of fibroblastic activity. The remaining cases showed moderate degree of fibroblastic activity. Three out of five in second degree enlargement cases show minimum amount of macrophages infiltration, one case showed moderate amount of macrophages and remaining one case showed dense infiltration of macrophages. Figure 5 showing basal epithelium, fibrous stands, groups of inflammatory cells.

In cases showing third degree enlargement, two cases showed minimum amount of infiltration of macrophages, one case showed moderate amount of infiltration of macrophages, remaining four cases showed the dense infiltration of macrophages. Moving on to the infiltration of lymphocytes, all the second degree enlargement cases have minimum amount of infiltration. In the third degree enlargement, three cases showed minimum amount of infiltration of lymphocytes, three cases showed moderate degree of lymphocytic infiltration and remaining one case showed dense infiltration of lymphocytes (Fig. 6).

Collagenation and capillary proliferations in all the cases followed the degree of enlargement. The grade of inflammation seen in the slides made from the gingival enlargement biopsy followed the grading of enlargement.

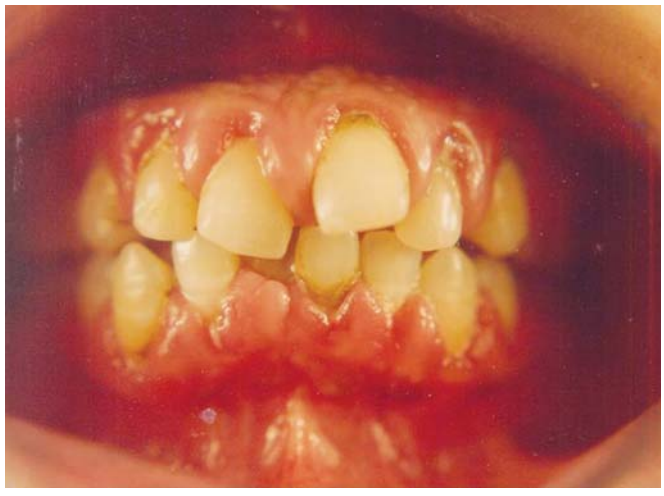


Fig. 1: Grade I: Phenytoin gingival hyperplasia

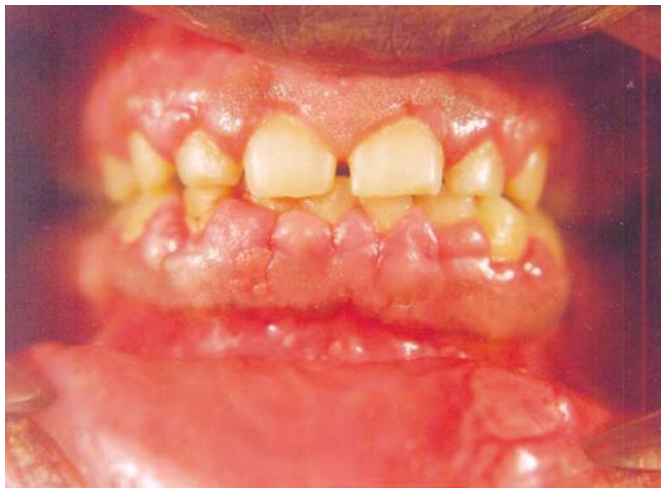


Fig. 2: Grade II: Phenytoin gingival hyperplasia

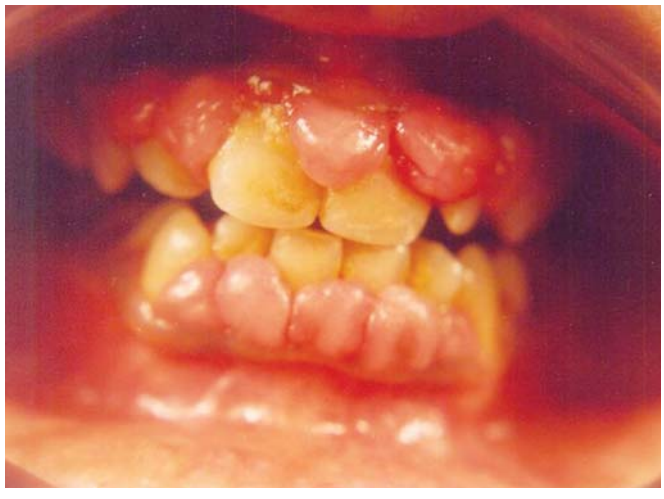


Fig. 3: Grade III: Phenytoin gingival hyperplasia

All the second degree enlargement showed signs of second degree of inflammation and in cases of third degree enlargement except one case all the other cases showed signs of third degree of inflammation. The left over cases showed second degree of inflammation (Fig. 7). Phenytoin gingival

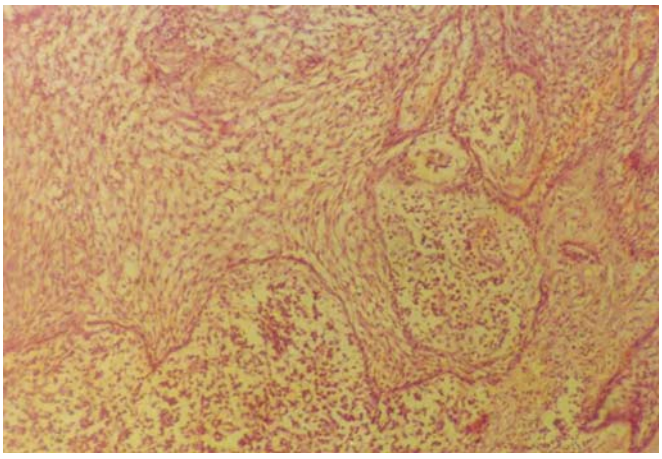


Fig. 4: Phenytoin gingival hyperplasia—lining epithelium—shows some degree of acanthosis with inflammatory cells beneath

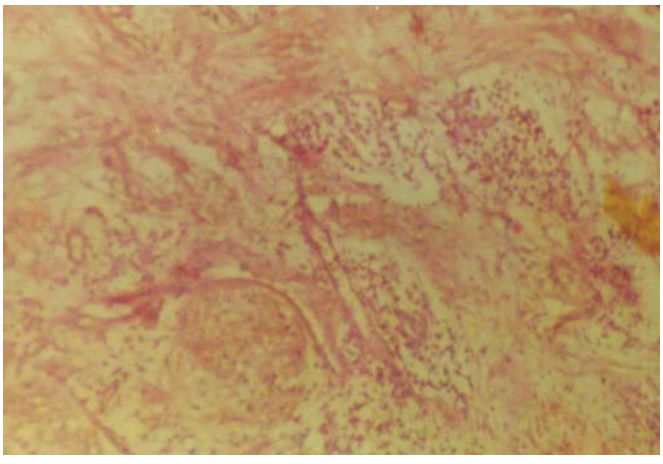


Fig. 5: Basal epithelium, fibrous stands, groups of inflammatory cells and showing edema in deeper plane with occasional macrophages

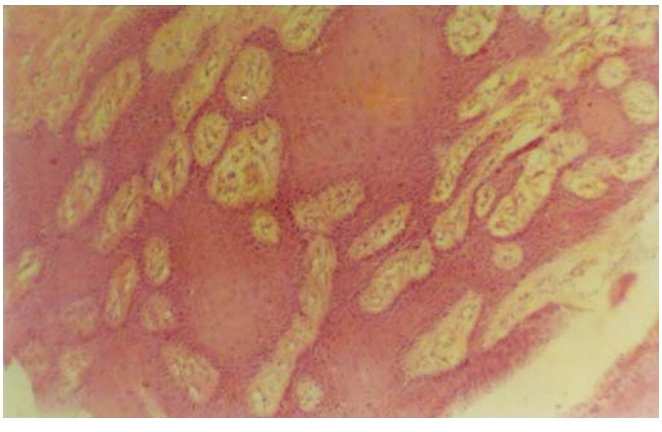


Fig. 6: Phenytoin gingival hyperplasia—epithelium with marked plaxiformacanthosis showing inflammatory cells infiltrate, thickened fibrous bands showing some degree of edema (×100)

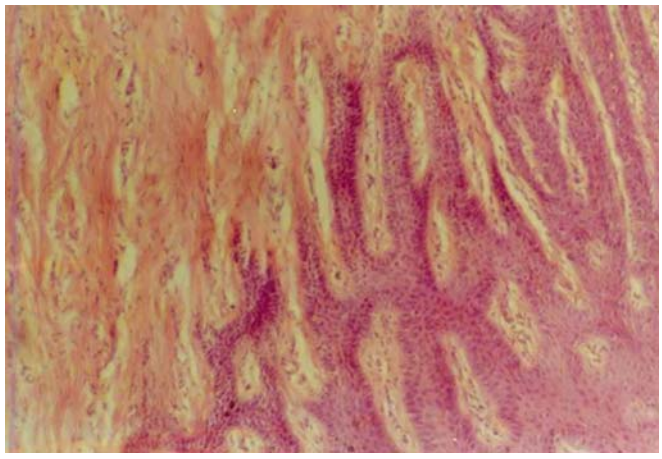


Fig. 7: Phenytoin gingival hyperplasia epithelium showing normal plaxiform pattern and normal subepithelial connective tissue comprising fibrous tissue in various discrepences and accompanying vascular structures. No evidence of inflammatory infiltrate (×100)

hyperplasia epithelium showing normal plaxiform pattern and normal sub-epithelial connective tissue comprising fibrous tissue in various discrepancies and accompanying vascular structures. No evidence of inflammatory infiltrate (magnification 100%).

Group II: This group consists of 12 epileptic patients under DPH therapy. On clinical examination none of the cases showed gingival enlargement. In this group, only five patients showed minimum amount of fibroblastic activity and the remaining seven cases showed nil or negligible amount of fibroblastic activity. Like fibroblastic activity, the degree of infiltration of macrophages is also followed, only five cases showed minimum amount of infiltration and lymphocyte infiltration is also seen only in three cases in minimum degree. Collagenation and capillary proliferation followed the degree of inflammation as only five cases showed the signs of minimum degree of inflammation (see Table 2).

Plaque index means are as follows:

- Test group: 1.17356
- Control group: 0.7427833

Though the test group showed slight difference in plaque index, it is not of much significance. Gingival index means are as follows:

- Test group: 1.17356
- Control group: 0.7427833

There is no significance difference in gingival index according to means.

Table 2: Comprehensive histopathologic changes in the gingival tissues of patients

	Fibroblast		*Macrophage*		*Lymphocytes*	
	Test	*Control*	*Test*	*Control*	*Test*	*Control*
Means	2.3333	0.4166	2.0833	0.4166	0.9166	0.25
SD	0.6513	0.51493	0.90003	0.5149	0.5624	0.452
SE	0.1486472		0.2993927		0.20832	
T test	12.87		5.5667		3.19988	
p-value	<0.001		<0.001		<0.01	

DISCUSSION

The introduction of PHT as an epileptic drug in human beings in 1938 marked the beginning of a new stage in the history of epileptic patients in particular grand mal epileptic patients and decreased significantly not only the epileptic attacks but also improving the quality of life. PHT, however, also produces several side effects, including hypertrichosis, hirsutism, vestibulocerebellar syndrome, megaloblastic anemia and gingival overgrowth. The first reports of PHT-induced gingival enlargement was made by Kimbal OP in 1939 and subsequent studies further confirmed this finding. Despite the large number of research studies on this subject, the etiology of PHT-induced gingival overgrowth and associated factors that contribute to its development has not yet been properly established. For each potentially associated factor, like PHT concentration in blood, plaque accumulation, inflammation, genetically determined, etc. conflicting results have been reported. A comprehensive study of the various factors, covering a sufficiently large sample to reach conclusions with a high degree of statistical significance, might help to clarify this issue.

The present study was conducted to investigate whether there is any relationship between the degree of enlargement and their histopathologic sections and quantify the different varieties of cells and to see whether there is any relationship between them, degree of hyperplasia and inflammation. As I see in my study that increase in the degree of gingival hyperplasia coincides with the degree of inflammation. This is in agreement with the Kimbal and Horan, Glickman I and Lewitus[15] Store and Leyarelli, Staple PH and Reed, Hall WB,[16] Nuk LK and Copper SH,[17] Tigaran S[18] and Philstrom, Hardwick, Band Park SS.[19] They all observed significant relationship between the gingival hyperplasia and the inflammation. In the phenytoin enlargement smears, there is increase in number of cells particularly fibroblasts, macrophages and lymphocytes than the control group.

There is an increase in collagenation, capillary proliferation is also seen in the phenytoin enlargement areas. Para or hyper keratosis and epithelial pearls also seen some times in the phenytoin enlargement cases.[20,21]

Glickman I and Lewitus, Ohyumi M and Sooriya Murthy N, Gowe DB and Elcy BM stating that phenytoin induces changes in connective tissue followed by epithelium. It is observed in the present study that there is comparative increase of fibroblast along with macrophages. There is no significant difference between two groups in plaque index and gingival index between test and control groups. It is observed in the present study that there is a significant difference between the smears of phenytoin enlargement and control group.[22,23]

SUMMARY AND CONCLUSION

Based on the unprecedented success in preventing the attacks of epilepsy, it appears that the clinical use of PHT may increase significantly in the near future. Consequently, cases of PHT-induced gingival hyperplasia could become a far more common problem confronting the dental profession. As a result, the services of dentists, dental hygienists and dental specialists, particularly periodontists, would be sought for prevention control and treatment of this type of gingival hyperplasia. There is significance difference in gingival index according to means.

Many periodontists presently treat patients who exhibit gingival hyperplasia induced by PHT therapy. It is observed that less than 1% of the population is on chronic PHT therapy and that of these, approximately 50% will exhibit atleast minimal gingival hyperplasia. As the patients on PHT is on rise, this figure may increase. Although these observations do not exclude other phagocytic cell types, e.g. neutrophils or fibroblasts, they strongly support the hypothesis that at some point during the course of PHT-induced connective tissue proliferation, there are significantly larger numbers of macrophages present.

Thus, in some ways, PHT appears to mimic endogenous signals for wound repair or remodeling. At the usual therapeutic dose level, these PHT effects must be at subthreshold. However, in inflamed gingiva, a tissue normally expressing a high rate of remodeling, the effects of PHT could act synergistically with endogenous signals resulting in excessive repair or overgrowth. The growth promoting effects of PHT are not limited to the gingiva, but are found in other types of connective tissue. This fact is borne out by the results of this study. PHT must therefore be considered to have rather broad effect on connective tissues, the connective tissue of the gingiva being one of the most susceptible.

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ABOUT THE AUTHORS

Rosaiah Kanaparthy

Professor and Head, Department of Periodontics, People's Dental Academy, Bhopal, Madhya Pradesh, India

Correspondence Address: HIG-3, PDA Staff Quarters, People's Campus, Bhanpur, Bhopal, Madhya Pradesh, India, Phone: 9893050554 e-mail: drrosaiah@gmail.com, medha98@gmail.com

Aruna Kanaparthy

Reader, Lecturer, Department of Conservative Dentistry, People's Dental Academy, Bhopal, Madhya Pradesh, India

Kamala Devi

Principal and Head, Department of Periodontics and Oral Implantology Government Dental College and Hospital, Hyderabad, Andhra Pradesh, India