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CHARACTERIZATION OF HEALTHY ORTHODONTIC PATIENTS ON THE

BASIS OF METABOLIC TESTS, AS A FUNCTION OF THE

PRESENCE OR ABSENCE OF MODERATE TO SEVERE

GENERALIZED ROOT RESORPTION

by

Stavros D. Papaconstantinou, D.D.S.

A Thesis Submitted to the Faculty of the Graduate School

of Loyola University in Partial Fulfillment

of the Requirements for the Degree of

Master of Science

July, 1981

DEDICATION

To my parents, who always managed to
exceed my expectations, and to
whom I owe my being here

To my uncle George and aunt Viola, my second mother

To my associate in life and in orthodontics,
Robin, with all my love

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VITA

The author of this thesis, Stavros Papaconstantinou, was born on January 18, 1953, in the village of Liopessi, Greece, the son of Dimitrios and Anna.

In 1970, he graduated from the French High School "Lycee Leonin" and the same year he entered the Dental School of Athens University. In November, 1975, he received his D.D.S.

From November, 1975 to June, 1978, he worked as Honorary Assistant at the Orthodontic Department of Athens University where the Chairman was Dr. H. Haralabakis. Parallel to that, he worked for his Doctorate Degree at the Department of Pathology of the Medical School of Athens University under the supervision of Professor Dr. Papacharalampous and Dr. Davaris. The subject of his research was "Regeneration Capacity of Salivary Glands in Rats". He hopes to defend this thesis after his return to Greece. During that period of time, he presented a paper at the Cypress Dental Meeting (1978) and published in Greek Dental Journals, three papers.

In July, 1978, he enrolled for a two year post-graduate course in the Orthodontic Program of Loyola

University, and in the graduate school leading to a Masters of Science in Oral Biology. In July 1980, he received his specialty certificate. From July, 1980 to the present time, he has been an Assistant Professor on the faculty of the Orthodontic Department of Loyola University.

In October, 1980, he presented together with Dr. L. Klapper and Dr. E. Marinakis, a course on Cephalometrics for Oral Surgeons.

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CHAPTER I

INTRODUCTION

Ketcham in 1927, reported a high incidence of root
resorption among his patients. The orthodontic profession
reacted with great concern. Numerous studies have been
performed since then, some of them attempting to elucidate
the mechanism by which root resorption takes place and some
of them striving to clarify the precise etiology.

The understanding of the problem today indicates
that orthodontic mechanics are capable of inducing root
resorption, particularly when excessive forces are used.
The mechanism by which root resorption occurs is quite
clear, at the present time. However, the severe generalized
incidence of root resorption, which appears in about 10% of
orthodontic patients, possesses no definite explanation, and
most clinicians "observe these changes, and in silence,
blame themselves and their mechanics" as Becks wrote, in
1936. Becks inferred then that the susceptibility to root
resorption is controlled by many coexisting factors. The
research on the topic indicates that there should be some
relationship between idiopathic root resorption and

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metabolic and nutritional factors. Nevertheless, that relationship has not yet been definitely shown, and controversy still prevails.

The present investigation will seek to demonstrate how healthy individuals undergoing orthodontic treatment can be distinguished, one from another as a function of the presence or absence of moderate to severe, generalized root resorption. The basis of characterization are measured values of various parameters of calcium and phosphorus metabolism and of certain parameters of the hormonal status, taken individually and collectively for each subject.

The results, seen in this study, if positive, might form a ground upon which a prediction test of susceptibility among orthodontic patients, in regard to root resorption, may be based. This test could be used by clinicians in order to view the problem prospectively, instead of retrospectively.

REVIEW OF LITERATURE

The first reports regarding the resorption of the roots of permanent teeth, as sited by Ketcham[23], were made by Bates in 1856, Chase in 1875, Harding 1878, and the first study concerning apical root resorption with orthodontic procedures was reported in the literature by Ottolengui in 1914. However, it was not until the reports on apical root resorption presented by Ketcham in 1927[23,24] followed by a subsequent report in 1929,[25] that the orthodontic profession reacted with great concern. Ketcham reported that, excluding gross pathological causes, only 1% of 1037 normal individuals x-rayed showed root resorption. This finding is in accordance with the results of Hemley,[16] and similar to the observations of Rudolph[55], who reported a 5% incident of root resorption, perhaps because the gross pathologic causes were not ruled out from his sample.

For patients who underwent orthodontic treatment, the percentages of root resorption were completely different. Ketcham's final report[25] covered over 385 cases treated by himself and other orthodontic specialists

in their private practices. He found that 21% of these cases showed root resorption after treatment. At that time Ketcham stated,"apical root loss was so startling, so potent in danger to the orthodontic patient, so prolific of recrimination to the orthodontist himself", that he "made bold" to present his findings to the orthodontic world. Ketcham's[23] dramatic evaluations acted as a catalyst, challenging every orthodontist to review his own experiences.

Becks[3] (1936) found that 20% of orthodontic cases treated at the University of California showed root resorption. Hemley[16,17], studying 165 treated cases at the New York University, found 21.5% revealing root resorption. These investigators showed remarkable unanimity in their studies. However, Rudolf of the University of Minnesota reported on the work done at the undergraduate clinic and published[55,56] these amazing results: "At the end of the first year of treatment, 49% of the 439 patients showed root resorption; and at the end of the two years of treatment, 75% of the remaining 277 patients demonstrated root resorption." In a subsequent study Rudolf[56] reported that the longer the treatment was and the older the patient, the higher the incidence of root resorption .

In 1951, Henry and Weinman[18] performed a histologic study of the morphologic and physiologic characteristics of the cementum in terms of number, size, distribution and types of resorption areas in the permanent

teeth of 15 cadavers. Their findings disclosed that over 90% of the teeth showed evidence of root resorption. The resorption areas were observed more often in the apical third of the roots (76.8%), than in the middle (19%), or gingival third (4%). There were also more instances of resorption on the mesial and buccal surface, which indicated that resorption occured more readily upon surfaces which are facing toward the direction of physiologic drift. Age, according to Henry and Weinman was a contributing factor in the causation of resorption.

Massler and Malone[36] in 1954, studied 708 sets of x-rays of complete dentitions of normal individuals 12 to 49 years of age and compared them to 81 sets of x-rays of patients 12 to 19 years of age which had undergone orthodontic treatment. It was found that over 80% of the untreated group exhibited root resorption, while in the orthodontic group that number increased to 93.3%. However, the frequency of moderate degrees of root resorption rose from 9.2% in the untreated group to 31.4% in the treated group. The frequency of severe root resorption rose from 0.3% to 10.8% and of the very severe resorption, from .11% to 3.4%. The percentage of teeth which exhibited slight root resorption decreased from 71% to 54.7%.

Concerning the frequency and susceptibility of different teeth to root resorption after orthodontic treatment, there seem to be few disagreements in

epidemiologic studies.[3,17,36] Overall, there is an agreement that the most susceptible teeth to root resorption are the upper and lower incisors, followed by the upper first molars, upper first and second premolars and canines, while the lower canines, lower first and second premolarsand first molars show less susceptibility. There is also evidence[17] supporting the similarity in the order of susceptibility between the treated and untreated populations; the only difference is the severity of root resorption displayed.

Sex was found not to be a variable related to root resorption[16,44]. There seems to be some controversy concerning the influence of the age of the patients which underwent orthodontic treatment as well as the length of the treatment. Rudolf[55,56] found a significant increase of root resorption in older patients and high correlation between root resorption and length of treatment. On the other hand, Phillips[44] did not find any relationship between root resorption and age of patients or length of treatment. Phillips also refuted the observation of Hemley[16] according to which root resorption is related to the amount of movement of the apices of the teeth.

Thus, from these epidiomiologic studies, concerning root resorption it is well established[10,16,17,24,25,36,44,55,56] that the orthodontic treatment can significantly increase both the severity and

the number of teeth which exhibit this defect.

Numerous studies have attempted to elucidate the mechanism by which root resorption occurs and account for changes in supporting structures of the teeth as they relate to orthodontic tooth movements. Present knowledge on that subject is based on experiments on dogs (Sandstedt 1904-05, Gotlieb and Orban 1931, Schwartz 1931, Reitan and Skiellen 1940), on monkeys (Oppenheim 1911, 1933, 1934, 1935, 1936, 1944, Johnson et al 1926, Marshall 1932), on rats, Waldo 1953, Waldo and Rothblatt 1954, Macapanpan et al 1954, Zaki and Van Heysen 1963, Crumley 1964, Kvam 1967, 1972 Azuma 1970, Baumrind and Buck 1970, Rygh and Selvig 1973, Rygh 1972, 1974, 1977 and on human (Herzberg 1932, Reitan 1951, 1971, 1974, Boyde and Lester 1967, Kvam 1972, Rygh 1973, 1977).

Sandstedt[61,62] was the first to experiment on animals in order to study the mechanism of tooth movement, in 1904 and 1905. Using heavy intermittent forces produced by screws, activated daily, he retracted the anterior teeth of adult dogs. Microscopic observation of the teeth and supporting structures revealed the development of a cell free zone in the periodontal ligament of the teeth at the pressure sites. Sandstedt called these zones the "hyalinization process".

Generally, the term hyaline degeneration refers to a regressive cellular change in which the cytoplasm of the

cells takes on a homogenous, glossy eosinophilic appearance. Although pathologists have objected to the excessive use of the word "hyaline" to describe the histologic appearance of a wide variety of unrelated circumstances, the term hyalinization of the periodontal ligament is used in the current literature. It describes the cell free area of the periodontal ligament (P.D.L.) which develops when an excessive force is applied on a tooth. The area acquires a glassy like appearance in hemotoxylin and eosin stained histologic sections.[53]

Sandstedt also described the undermining resorption i.e. a resorption starting from the marrow spaces around a compressed and hyalinized area of the P.D.L.

Johnson, et al,[22] in 1926 induced labial movement of juvenile monkey central incisors with partially formed roots. They described a fulcrum of rotation to exist somewhere in the root of the incisors, causing lingual movement of the apices. This apical section was deformed in comparison to the control side, leaving the tip in its neutral position. They also described a resorption area in the section of the root, where deformation had taken place.

During this period, Ketcham reported on a radiographic investigation[23,24,25] of root resorption among human subjects. His findings revealed that patients treated with lingual appliances with finger springs attached to them, exhibited less root resorption, than the patients

treated with the "pin and ligature appliance". This finding caused discordance between clinicians and investigators, since the first was considered to deliver light continous forces while the latter intermittent forces.

Schwartz in 1931 and 1932[64],[65] stated that intermittent forces are dangerous since they produce the phenomenon of "jiggling". This jiggling, which means a repeated change in the direction and in the amount of pressure applied within a short period of time is thought responsible for extensive root resorption. According to Schwartz , the most favorable treatment was that in which forces were continuous and did not exceed the pressure of the blood capillaries. This pressure in men, as well as in most mammals, is 15-20 mm. Hg., and corresponds approximately to 20-26 gr. per 1 cm^2 of root surface. This pressure is so intensive, that a continuous, rather aggressive resorption takes place in the alveolar bone at the pressure site.

Gottlieb's findings[14] from his experiments in dogs support Schwartz's hypothesis. After creating a traumatic occlusion, he found formation of osteoid tissue at the pressure site of the P.D.L. This finding led him to the conclusion that interruption in the application of forces should be avoided during orthodontic treatment, because each interuption caused the formation of a new alveolar wall at the pressure site by deposition of newly uncalcified bone

(osteoid). He verified that osteoid tissue is more resistant to resorption than the "old" calcified bone, and therefore, if a force is applied again, resorption may attack the tooth surface more easily. Gottlied demonstrated that the teeth of young animals in comparison to adult animals, exhibited considerable resistance to root resorption.

Herzberg[19] in 1932 was the first to study human subjects. He moved orthodontically the first premolar of a patient and then extracted it together with its surrounding supporting tissue in order to study histologically the changes that occurred. He reported that the reaction of the human alveolar bone was quite similar to that of experimental animals.

One person who contributed significantly to our knowledge and understanding on tooth movement was Albin Oppenheim, an outstanding clinician and investigator. He performed numerous experiments on dogs,[38] monkeys[39,40,41,43] and humans[42].

Experimenting on young monkeys[39,40,41] Oppenheim found that when a strong force was used to move a tooth, tipping of the apex towards the opposite direction would occur. The blood vessels and nerves entering the apical foramen appeared to be distorted; a reaction of the bone was lacking, while there appeared numerous resorptions of the cementum. By experimenting with gentle intermittant forces,

he observed comparatively quick recovery of the P.D.L., due
to a rapid re-establishment of blood supply from the
application of pressure extending over a short period of
time. Even if the force was occasionally somewhat stronger,
it soon regained its ability to react biologically, to form
osteoclasts and to resorb bone. In addition, the cementum
quickly regained, through its rapidly re-established normal
blood supply, its orginal resistance against resorption.
Oppenheim stated that continuous forces can lead to a
compression of the blood vessels and anemia of the P.D.L.
more easily than can intermittent forces. This anemia
reduces the vitality of the P.D.L. and creates a situation
which is responsible, on one hand, for the lack of proper
bone reactions, and on the other, for the development of
root resorption. He realistically stated, "orthodontic
procedures, no matter the kind of forces used, are a
violence to nature. We must try to do only the least amount
of damage, for we cannot, by any means, avoid or evade some
damage". Studying human premolars in histologic sections
after being moved orthodontically with light intermittent
forces,[42] Oppenheim observed an abundance of large vessels
and capillaries close to cementum resorptions at the
pressure sites of the P.D.L.. According to his description,
these vascular changes suggested an angioma-like formation.
His explanation depicts this formation as a protective
measure of nature, a sort of cushion, which interposed

between the tooth and alveolar wall and which protects the
structures from increased pressure. While studying the
angioma-like formation, he observed that the endothelial
cells of the capillaries were lying very close to resorption
lacunae, on the cementum and on the alveolar wall. He
concluded that the endothelial cells of capillaries can
exercise osteoclastic or cementoclastic activity, working to
relieve pressure by gaining space. During this process,
osteoblasts could not be identified.

In a subsequent study[43] Oppenheim observed the
reaction of osteocytes to different degrees of force and
described three types of osteoclasts, the primary, secondary
and tertiary. This classification was based on the place
that they would appear, which would be determined by the
intensity of the force applied. Using light forces, he
described compression of the P.D.L. on one side and the
presence of "primary" osteoclasts resorbing the alveolar
wall, while the osteocytes were intact. On the tension
side, there was apposition of osteoid tissue in uniform
layers. Using heavier forces, he found hemorrhagic sites on
the pressure side, hyalinized areas, and "primary"
osteoclasts around the hyalinized areas. The osteocytes
showed signs of degeneration, and "secondary" osteoclasts
appeared in the bone marrow, causing undermining
resorption. On the tension side, many periodontal fibers
were disrupted, some vessels were torn, hemorrhages were

formed, and osteoid tissue was deposited in such a manner as to form spicules. Using heavy forces, he described complete hyalinization of the P.D.L. and disappearance of the osteocytes on the pressure side. Numerous osteoclasts were present in the bone marrow, resorbing the bone, which he considered to be dead after the disappearance of the osteocytes. On the tension side, most of the periodontal fibers were ruptured, and hemorrhages were found throughout. There was a trace of osteoid tissue formation, while numerous tertiary osteoclasts were observed on the tension side.

Reitan[48] discribed two zones of proliferating cells on the tension side. The first was located parallel to the root and close to the alveolar wall. The other zone was located adjacent to the root. Mitotic cell division was observed more often in the zone adjacent to the bone. Concerning the pressure side, Reitan was the first to state that there was great similarity between the nuclei of surrounding fibroblasts and individual nuclei of the osteoclasts. That observation was of prime importance, since it was later verified that one type of multinucleate osteoblast derived from fusion of undifferentiated mesenchymal cells[60].

In the early 1950's, several researchers[31,54,74,75] attempted to develop a new experimental model that would allow study of tissue response to tooth movement in both

qualitative and quantitive ways. That experimental animal
was the rat, which being versatile for its size and
relatively cheap, allowed investigators to use a larger
number of experimental animals. The most important
advantage was that genetic and metabolic variations could be
overcome by using animals from previously developed pure
strains[74]. Tooth movement was usually induced by placing a
rubber band, or a piece of rubber dam between the upper
first and second molars. Using this type of experimental
model, Waldo and Rothbladt[73] found that the tissue
response to orthodontic tooth movement was similar to that
found in other animals. They found inital compression of
the P.D.L., followed by hyalinization and undermining
resorption which was obvious three days after the
application of the force. Small areas of root resorption
were observed in the teeth of the animals in which the
stress of the rubber band was allowed to act from five to
seven days. Accompanying this root resorption was usually
an area of hemorrhage and crushing of the periodontal
fibers, suggesting, according to the investigators, that
such resorption of cementum may result from excessive
stress, even in perfectly normal animals. Another
interesting finding was the histologic evidence of reaction
to applied stress, as a result of occlusal adjustment, in
the lower quadrant corresponding to the experimental side.

In a subsequent study[54] Waldo and Rothblatt found

that hypophysectomized animals as well as rats on lysine-deficient diets exhibited extremely high osteoclastic and cementoclastic activity, and mechanical stress seemed to produce extreme loss of bone.

Macapanpan et al,[31] in 1954, were the first to attempt to quantify the tissue reaction following tooth movement by measuring the mitotic activity of the fibroblasts of the P.D.L. There findings showed that the mitotic activity among the fibroblasts of the P.D.L. in the experimentally induced tension area was three to four times higher than that on the control side, and that periods of maximal mitotic activity followed periods of maximum displacement of teeth after 15 to 18 hour intervals. It was concluded that not only osteoblasts and osteoclasts but also fibroblasts play an important role in the repair following tooth movement. It was speculated that the increased mitotic activity of the fibroblasts was part of the process by which the fiber bundles of the widened periodontal spaces are repaired and re-adapted to the altered interface between tooth and bone. Fibroblasts are capable of synthesizing and degrading collagen[69].

On the pressure side, Zaki[77] found that where hyalinization occured, hyperplastic mesenchymal tissues entered and reorganized the non-vital tissue. This mesenchymal tissue approached the hyalinized areas from different directions: from the normal P.D.L., apical and

marginal to the hyalinized area and through the medullary alveolar margin bone spaces opening into the P.D.L. This proliferating young connective tissue can, and often does, resorb the cementum of the root surface as well as the alveolar bone margin in the vicinity of the hyalinized P.D.L.

Baumrind[1] in 1970 using radioisotopes tried to quantify the metabolic activity of the cells of the P.D.L. after inducing tooth movement. It was found that, on the pressure side, cell replication rates increased at statistically significant levels instead of displaying the predicted decline in activity. On the tension side, cell replication increased as predicted. General metabolic activity appeared to increase but collagen synthesis decreased, both being displayed in the tension and pressure sides concomitently. This latter finding can be explained as an initial drop in collagen production below a rather high base line[9] since it is accepted as fact[9,4,6] that the turnover of the collagen in the P.D.L. is high.

Several electron microscopy studies during the last decade[26,27,28,57,58,59,60] on tissue changes following tooth movement have given us a more accurate portrayal of the situation.

The principal findings of those studies indicate that, after application of force, initial dilation of blood vessels and packing of erythrocytes developed, while platelets and floccular material interspersed between the

cellular elements. The vessel walls appeared to be intact,
at this stage, and, although the erythrocytes had been
pressed against each other, an open lumen in these vessels
remained[58]. During the next stage, part of the
endothelial walls had disappeared along with the basement
lamina thus allowing communication between the lumen of the
blood vessels and the perivascular space[58].
Crystalization of the erythrocytes developed in the P.D.L.
indicating a local degradation of the erythrocytes as a
result of pressure and hemostasis[59]. Cementoblasts,
fibroblasts, and osteoblasts showed no difference in
cellular reaction to the orthodontic force[57] and they all
exhibited various stages of disintegration, characterized by
intracellular swelling, advanced dilation of the endoplasmic
reticulum, moderate swelling of the mitochodria, rupture of
the cell membrane followed by separation of the nucleus from
the cytoplasm and decomposition of the nucleus[57]. This
process indicated that cell death occurs in the cytoplasm,
while the nucleus disintegrated later. Furthermore, it
demonstrated that the previous assumption which held that
the death of a cell is more prominent in the nucleus then in
the cytoplasm, due to the appearance of a pycnotic nucleus,
was not correct. This process would proceed until complete
hyalinization of the P.D.L. at the pressure sites had
occurred. Multinuclear large cells appeared then near the
cementum surface at some distance from the hyalinized

tissues. These cells resorb tooth substance. The
resorption of the cementum appeared under the E.M. as a
resorption from the rear[60]. Once the cementum is
resorbed, there is an indication that the resorption
continues in the dentin at a greater rate. In other words,
the cementum acts as a barrier so that resorption of the
entire root of the tooth does not take place. The P.D.L.
adjacent to the cementum being resorbed from the rear, was
rich in blood vessels and cells[60]. Hyalinized structures
disappeared concommitantly with an invasion of cells and
blood vessels from the neighboring P.D.L.

These finding are common both in animal and human
material[27,28,52] and indicate that the formation of
hyalinized zones on the P.D.L. due to force application lead
to root resorption which occurs during the invasion of new
cells from the healthy periodontium and the bone marrow.

It might be concluded that the mechanism by which
root resorption occurs is presently clear. However, the
sited literature does not contribute substantially to our
knowledge as to why individuals respond to orthodontic
treatment with varying amounts of root resorption.

The cementum can be considered a tissue having
similar morphologic characteristics to bone based on the
following facts. It is produced by cementoblasts cells very
similar to the osteoblasts and it is calcified the same way
bone is and is resorbed by large multinucleate cells which

first remove minerals and then the organic matrix.
Never-the-less it has some differences from bone and one
should to be aware of these differences in order to
understand why cementum is much more resistant to resorption
and why resorption can occur to cementum.

Most likely the reasons why cementum is more
resistant to resorption than bone, are: 1) Cementum has a
higher content of fluoride then bone, 2) Bony tissue has an
ample blood supply, whereas cementum is completely void of
vascular tissue, 3) The cementum is surrounded by older,
more mature collagen, which is more resistant to the actual
chemical changes than bone,[12] and 4) The cementum is
covered by a layer of unmineralized precementum, called the
cementoid, which like the osteoid, is considered as a
resorption resistant coating.[14,52]

It is reasonable to consider that variations of the
above factors can greatly influence the resistance of
cementum to resorption, particularly when a local stimuli
changes the equilibrium of the P.D.L.

Since cementum is considered to be very closely
related to bone, it would be logical to speculate that the
mechanisms which induce cellular activity in order to form
or resorb bone would influence the latter in forming or
resorbing cementum.

Many observations have shown that bone is formed
from cells that proliferate from the vascular endothelium of

thin-walled sinusoid vessels[70,71]. Cells that form these vessels are often called osteogenic precursor cells and they are the same as those which some authors refer to as undeferentiated mesenchymal cells. A variety of factors operate to influence the proliferation of these cells, some of which are common to all connective tissue cells and some specific for bone.

Common to all these cells is the need for an adequate supply of energy before cell division can take place.[6] Since energy production is brought about by means of oxidation of certain celluler high energy products, a plentiful supply of oxygen is needed for cell proliferation and activity.

In the P.D.L. the undeferentiated mesenchymal cells, become osteoblasts, which lay down the bone matrix. If a decreased oxygen supply occurs, the amount of osteoid matrix produced decreases, or ceases altogether. Equally important for cell division is the local concentration of carbon dioxide. Too high or too low concentrations of carbon dioxide inhibit cell proliferation. Since local concentrations of oxygen and carbon dioxide are partly regulated by the rate of blood flow, the latter should be an important practical consideration.

Another regulating mechanism for cell division and intercellular matrix production is the balance of anabolic and catabolic hormones.[29]

There are two types of osteoclasts described. Both types are multinucleated cells, and secrete enzymes that hydrolyze and degrade bone tissue, and thus, are able to resorb bone.

One type of osteoclast is formed by the coalescence of undeferentiated mesenchymal cells in the presence of excess cortisol or corticosteroids.[30] Osteoclasts formed in this manner, although showing considerable cytoplasmic activity, remain in one place, still being attached to neighboring cells.

The second type of osteoclast is freely-moving, and is formed from macrophages. These cells are formed in the bone marrow and have phagocytic capability. Before the macrophages can coalesce, the cells enlarge. This is prevented by cortisol or corticosteroids[11] so that these catabolic agents inhibit the production of the freely-moving osteoclast. The presence of parathyroid hormone is required before macrophages can coalesce to form osteoclasts.[7] With an excessive amount of parathyroid hormone present, these osteoclasts display a correspondingly exuberant activity. The presence of thyroid hormones seems to be necessary for parathyroid hormone activity.[29]

When the rate of flow of the blood diminishes, as on the pressure side of the P.D.L., the available oxygen is decreased and at the same time, the rate of removal of carbon dioxide is decreased. With a diminished blood flow,

therefore, fewer osteoblasts and less osseous tissue are
formed and, at the same time, the osteoclasts which are
formed from the undifferentiated mesenchymal cells are also
reduced in number. However, it has been demonstrated[29]
that as the rate of flow of blood through bone is reduced,
macrophages increase in size and coalesce to form phagocytic
osteoclasts. This mode of osteoclastic activity and bone
removal is therefore enhanced.

The different hormones regulate bone metabolism in
order to maintain a constant level of extracellular
calcium.[46,76] Calcium is an important substance and is
required: 1) as calcium phosphate and calcium carbonate in
order to form the principal chemical constituents of bone,
cementum and enamel, 2) for the coagulation of blood
(clotting formation), and 3) for the regulation of neural
function by keeping the excitability of nerve endings at a
normal level.

It is believed[46] that the maintenance of a
constant extracellular calcium concentration depends mainly
on the dual reciprocal control of bone resorption by
parathyroid hormone (PTH) and calcitonin (CT). Other
important factors controling calcium homeostasis and bone
resorption are: the level of extracellularphosphorus
(PO_4), the presence of vitamin D, the thyroid hormones
(T_3, T_4),[7] and the corticosteroids, while some
secondary factors are: sucrose, fatty acids, heparin, serum

proteins, male and female hormones, etc.[46]

The PTH has both a regulatory and a permissive role in bone resorption. The overall resorption rate is maintained by continuous secretion of PTH, which can be increased or decreased in response to calcium concentration.[7,46] The hormone must also be present for changes in bone resorption to occur locally in response to immobilization.[7] The PTH raises the calcium blood level by causing osteoclastic resorption of bone, and by increasing the excretion of PO_4 from the kidneys causing inhibition of reabsorption of PO_4 from the tubules and by inhibiting calcification of newly formed bone.

Two types of hyperparathyroidism are distinguished. The primary hyperparathyroidism is usually caused by a tumor of the parathyroid gland and the secondary, which can be caused by calcium deficient diets, vitamin D deficiency and kidney insufficiency.

Experimentally, it was reported[46] that repeated injections of phosphates can lead to one type of secondary hyperparathyroidism, as the organism tries to increase the excretion of phosphates through the kidneys.

Weinman and Sicher[76] stated that latent hyperparathroidism which is developed through moderate renal insufficiency, causes sometimes localized and minute bone changes in areas which have suffered a mechanical or infectious injury. They hypothesized that these localized

changes were the response of the sensitized skeleton to a localized injury.

Vitamin D deficiency primarily causes the reduction of absorption of calcium and secondarily of the PO_4, from the intestinal tract.[76]   This function occurs because calcium in the gastrointestinal lumen combines with the PO_4 to form insoluble $Ca_3 (PO_4)_2$.   This results in a secondary hyperparathyroidism in order to maintain the blood level of calcium normal.   The PO_4 deficiency is increased by the hyperactivity of the parathyroids.

Vitamin D is found to be permissive for P.T.H. stimulated bone resorption.[46]   They are considered to be physiologic synergists that act not at the same receptor site in bone-resorbing cells, but at separate sites linked so that the effects of one can enhance the response of the other.   When lack of vitamin D occurs, experimental animals become unresponsive to all but extraordinarily large doses of PTH, while large doses of vitamin D has hypercalcemic effects.[4]

Calcitonin together with the PO_4 blood concentration are considered to be the two physiologic inhibitors for bone resorption.   These factors work synergistically.[20]   Calcitonin mainly causes inhibition of mineral resorption in vivo, while PO_4 concentration primerily causes inhibition of matrix resorption by increasing the deposition of mineral on collagen and

therefore blocking its resorption. Another way by which PO_4 can inhibit bone resorption, is by enhancing increased deposition of calcium minerals on bone surfaces which are less mineralized.[13] In contrast to the parathyroid hormone which causes bone resorption along with release of calcium by stimulating collagenolytic and proteolytic enzymatic activity, the calcitonin and PO_4 block calcium release without inhibiting enzyme release.[73] This indicates that while PTH acts directly on the cells, the CT does not do so.

Thyroid hormones regulate calcium homeostasis by controlling the renal secretion of calcium and phosphates. Consequently, the changes in bones are expected to be a response to depletion of calcium. Reduced bone apposition and increased bone resorption in cases of hyperthyroidism are to be understood as an attempt of the organism to mobilize enough calcium and PO_4 to compensate for the increase loss of these elements.[76] In addition to that, thyroid hormones seem to be necessary so that PTH can act on the cells.[28]

The complicated interplay of hormones, which can be influenced by local or generalized factors (primary endocrine malfunction, diet, renal insufficiency, gastointestinal problems, etc.), influences the cellular activity in forming or resorbing bone. Based on the similarity ofcementum and bone, it has been

assumed[2,3,32,33,34,45,66] that these factors should
influence the resorption of the cementum.

Orthodontists have speculated for a number of years
about hormonal and dietetic influences on root resorption
and several researchers have attemmpted to study these
relationships. Marshall (1931, 32,33,34)[32,33,34,35]
experimenting on monkeys, concluded that independent of the
type of appliance used, "absorption" on either the lateral
or apical aspect of the root occurred under conditions where
unusual force was applied. This process seemed to develop
more rapidly and procede farther when the diets of the
experimental animals were deficient in ingredients
containing vitamin A. Furthermore, when experimental
animals were maintained on diets adequate in protein,
vitamins, mineral salts, fats and carbohydrates, new tissue
was always found in the areas where slight absorption had
previously occured, thus restoring the original contour.

Becks and Weber, in 1931,[2] reported that diets
with normal salt mixtures, as well as those with low calcium
salt mixture, both being devoid of cod liver oil (vitamin D)
given to a series of twenty-five dogs for a period of seven
to twelve months, led to atrophic and dystrophic bone
changes of the active skeleton. These changes were
accompanied by marked root resorption.

In a subsequent study, in 1936,[3] Becks examined
100 patients who exhibited root resorption. Half of them

had undergone orthodontic treatment previously. Based on a complete physical examination, urinalysis, differential blood count, dietary survey, clinical and roentgenographic examination of the teeth and jaws, determination of basal metabolic rate and determination of the serum and saliva calcium and PO_4, it was reported that 60% of the orthodontic group and 40% of the non-orthodontic group exhibited a definite hypothyroidism. Hypothyroidism together with other endocrinopathies accounted for another 20% in the orthodontic group and 26% in the non-orthodontic group. Hyperpituitarism was also noted in his study and correlated with root resorption as well as intestinal problems, the latter causing disturbances in mineral metabolism and therefore leading to pathologic bone formation.

In 1951, Tager[68] searched for medical evidences of endocrine and metobolic disease in 100 children, presenting special orthodontic problems, among them, root resorption. Basal metabolic rate, calcium and PO_4 serum concentration, sugar tolerance, protein bound iodine (P.B.I.) and serum cholesterol were measured. It was concluded that only 10% of the children revealed a "frank endocrinopathy". One case presented hypopituitarism and the remainder of the 10 cases were hypothyroid. The greatest proportion of these cases revealed neither specific endocrine disease nor congential anomalies. What did appear significant was evidence that

certain types of orthodontic defects, more specifically root
resorption and architectural abnormalities of the bone,
repeated themselves in a particular type of accelerated
growth pattern connected with puberty. This observation led
Tager to the notion of a "relative metabolic insufficiency",
meaning insufficiency of a hormone or nutrients in the bone,
not in an absolute sense, but insufficient in respect for
the greater demands made by the accelerated growth pattern.

Pinsker in 1962,[45] studied the influence of
hydrocortisone on the development of root resorption on
monkeys. His finding was that in the hypercorticosteroid
group, some of the animals exhibited mild root resorption.

Finally, Newman in 1975,[37] attempted to screen 47
orthodontic patients exhibiting moderate to severe root
resorption on a minimum of three teeth, from the genetic
endocrine and nutritional aspect. His conclusions
concerning the genetic aspect was, that no definite
relationship could be drawn, and the metabolic aspect was,
not at all related to root resorption.

In the sited literature, there are indications that
a probable relationship between metabolism and root
resorption, particularly in patients which exhibit tendency
towards generalized root resorption should exist.
Unfortunately, the research findings, to date, have not been
able to demonstrate that relationship in a convincing
manner. Therefore, additional research in the field is

needed in order to clearly demonstrate the relationship
between hormonal function, metabolic status and root
resorption.

CHAPTER III

MATERIALS AND METHODS

The subjects in this study consisted of 12
individuals, six of whom were undergoing root resorption
with the other six as control. The sample was selected from
the patients of the Orthodontic Department of Loyola
University, who were under active orthodontic treatment. Of
the patients undergoing root resorption, three were male and
three female, while of the control patients, four were male
and the rest female. All subjects appeared to be healthy
with essentially negative medical histories.

Three criteria for the selection of patients who
displayed root resorption were used: (1) The first was the
amount and degree of root resorption presented. All
patients had to exhibit roentgenographic evidence of
moderate to severe root shortening of the incisors, premolar
and canines in both upper and lower arch. A tooth was
considered "severely" shortened if the root loss was greater
than, or equal to, one third of the normal root length. A
"moderately" shortened root was designated if more than 2
mm., but less than one third, of the root was resorbed. In

order to evaluate the amount of root resorption exhibited,

recently exposed intraoral or panoramic radiographs were

reviewed from more than 500 patients who were currently

under orthodontic treatment. These radiographs were

compared to the ones taken prior to treatment and

determinations were made concerning the conditions of the

roots. These x-rays had been taken routinely from all

patients as a method of monitoring the progress of their

treatment. (2) The second was the age of the patients. The

patients selected were between 17 and 22 years of age in

order to secure a homogenous population in regard to their

metabolic status. (3) The third was the length of

treatment. One principal criterion of selection was that

patients exhibiting root resorption had to be in treatment

for less than 18 months. The control patients could be in

treatment for a longer time. Thus, it was attempted to

exclude patients whose root resorption could be readily

attributed to excessive and prolonged trauma of the

supporting tissues of the dentition. Sex was not considered

as a necessary criterion of case selection. Consent forms

were signed by each patient.

Blood specimens were drawn pre-prandially before

10:00 a.m. by venal puncture in non-heparinized vacu-tubes.

Approximately 15 ml. of blood was drawn and the serum was

immediately separated by centrifusion. Half of the serum

obtained was used for routine determination in SMAC, to

determine the levels of: (1) serum calcium (Ca), (2) serum

phosphorus (PO_4), (3) alkaline phosphatase, (4) serum

creatinine. The remaining portion of the serum was frozen

to be used later for the determination of certain hormones.

Using the double antibody radio-immuno assay method the

following assays were carried out: (1) triiodothyronine

(T_3), (2) tetraiodothyronine (T_4), (3) cortisol, (4)

parathyroid hormone (PTH),and (5) calcitonin (CT).

In addition, the patients were asked to collect

total volume urine samples over two separate 24 hour periods.

Special containers were furnished. These urine samples were

used for the determination of the 24 hour output of: (1)

calcium (Ca), (2) phosphorus (PO_4) and (3) creatinine.

Collectively for every patient, the following

clinical values were obtained:

1. serum Ca level,

2. serum PO_4 level,

3. 24 hour urine Ca,

4. 24 hour urine PO_4,

5. tubular resorption of PO_4,

6. blood level of alkaline phospatese,

7. blood level of T3,

8. blood level of T_4,

9. blood level of cortisol,

10. blood level of PTH,

11. blood level of calcitonin.

The tubular resorption of PO_4 was determined using the following mathematical formula:

$$TRP = 100 \left(1 - \frac{\underline{urine\ PO4\ \ x\ serum\ creatinine}}{serum\ PO_4\ x\ urine\ creatinine}\right.$$

The T.R.P. value reveals the percentage of filtered phosphate that is reabsorbed by the renal tubules. The value is used as an aid for the determination of parathyroid and renal function.

The blood level of alkaline phosphatase was observed because it relates to the metabolic status of bones. Alkaline phosphatase plays an important role in bone formation, and it increases in ricketts, bone atrophy, osteoporosis, while moderately increased values have been found in hyperparathyroidism.

Based on these data, it would be possible to investigate the relationship between these urine and serum values, individually and collectively, and root resorption.

In order to investigate the significance between the two groups, two-sample t tests will be run on each variable by subject and group.

Further, the possible relationship of all the variables, taken as a biochemical mosaic, to root resorption, will be noted using direct and step-wise discriminant statistical analysis.

The direct discriminant analysis weighs, and linearly combines, the discriminating variables in such a

fashion, so that the groups are forced to be as statistically distinct as possible.[66] The stepwise discriminant analysis begins by selecting the best discriminating variable. Subsequent variables are then selected according to their ability to contribute to further discrimination.[66] The significance of the separation of these patients in two groups, as well as the combination of each variable in achieving that separation can be demonstrated by means of histograms, as will be shown subsequently.

In addition to these analytical procedures, the probability for each patient to belong in one or the other group will be shown.

These statistical analyses are used widely in medecine[15] for the classification of microorganisms and mental disorders. Although it was not possible to find applications of these analyses on human studies, it is beleived[15], that use of these analyses can healp the classification of desease and the development of prediction tests which will determine the predisposition of individuals to them. The discriminant analyses used in this study can be found under the S.A.S.[63] (Statistical Analysis System) and the S.P.S.S.[66] (Statistical Package for the Social Sciences).

In order to present each patient as a biochemical composite, or mosaic, the ranges of each laboratory test,

furnished by the laboratory where the tests were performed, will be interconnected, one with another as a function of each test listed systematically in a vertical dimension. The result of such a composite presentation is shown in Fig. 1. The actual observed biochemical values for each variable will then be plotted with respect to the normal range and interconnected in the same fashion as the normal range pattern. Thus, each patient will possess a "fingerprint" to be discriminated statistically and placed into a group of his own kind.

FIGURE 1

Graphic representation of the normal ranges[*] of biochemical tests
interconnected one with another in a vertical dimension.

Serum Calcium	9	11 MG/DL
Serum Phosphorus	2.5	4.2 MG/DL
24 h.Urine Calcium	55	400 MG
24 h. Urine Phosphorus	.34	1.30 MG
T.R.P.	79.6%	90.4%
Alk. Phosphatase	30	110 U/L
T₃	80	160 NG/DL
T₄	5	12 UG/DL
Cortisol	6	25 UG/DL
P.T.H.	430	1860 PG/ML
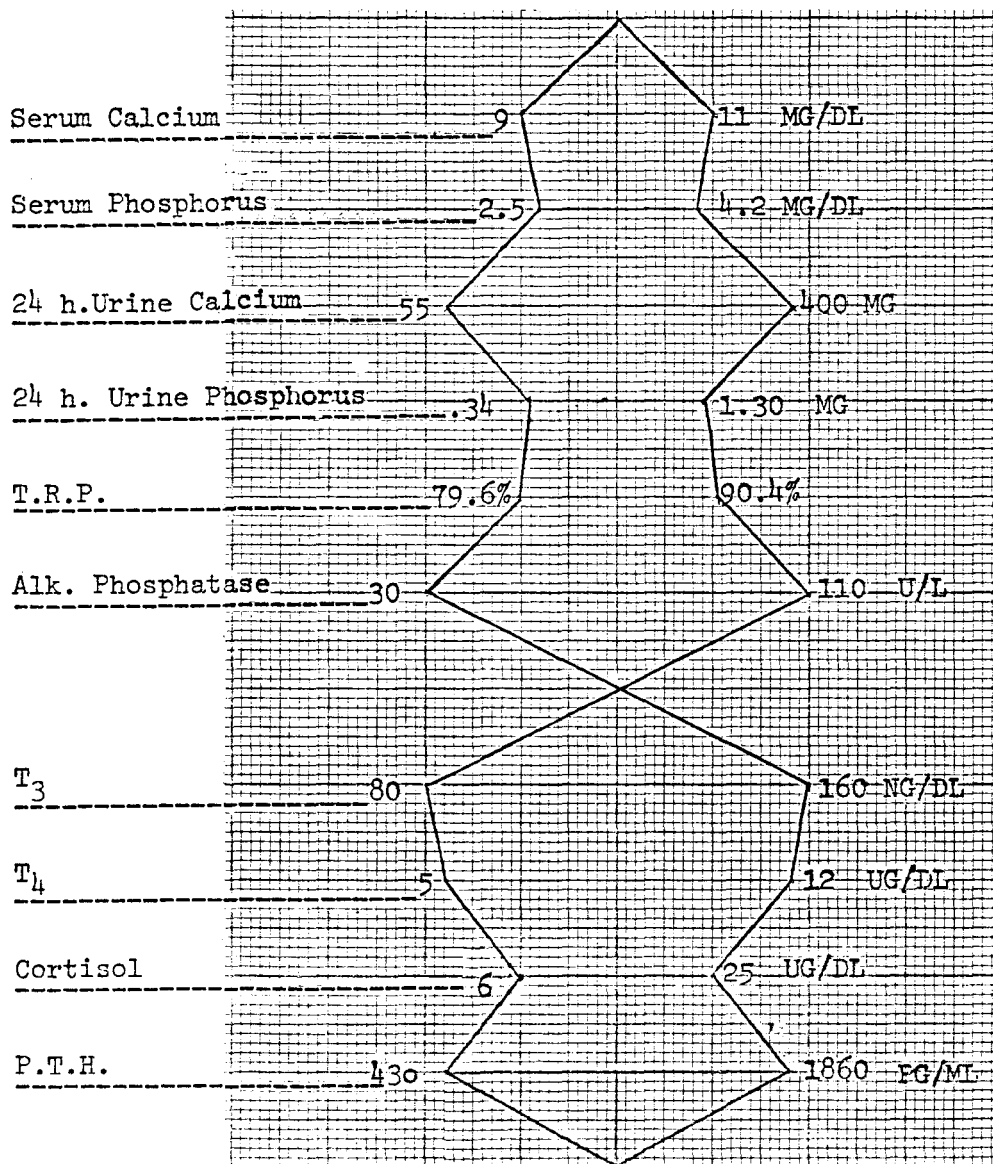
*Normal ranges were furnished by the clinical laboratories which
performed the biochemical tests.

CHAPTER IV

RESULTS

Table I shows the initials of the name of each patient, their corresponding sex and age, and the group in which they were placed, according to the root condition. Twelve patients participated in the study. The control group consisted of four male and two female patients, with an age range from 17 to 22 years. The root resorption group consisted of three male and three female patients, with an age range from 17 to 23 years.

The results of the laboratory tests for all the control and root resorption patients are displayed in Tables II and III. On the bottom of these charts, the mean and standard deviation of all the variables and the normal range of each was included. These normal ranges were furnished by the clinical laboratories, which performed the tests.

Figures 2 to 13 display, graphically, the results of the laboratory tests, for each patient separately, as they relate to the normal ranges, given by the clinical laboratories. These graphs are separated in two parts: the upper one, which includes the results given by the S.M.A.C.

37

and the urinalyses, and the lower one, which includes the results of the hormonal analyses. The continuous line, which forms the periphery of the diagram, represents the normal range of the variables, interconnected one with another vertically. The dotted line, represents the result of laboratory tests, also interconnected one with another. With these diagrams an attempt was made to present each patient as a separate biochemical unit and graphically illustrate the results of the laboratory tests as they relate one to another, and as they relate to their normal ranges.

From the Tables II and III which display the raw data and from the Figures 2 to 13 the following findings could be demonstrated: (1) Within the control group, the values of all the variables fell within their normal ranges, with the only exception being the T.R.P. of patient L.D., which exhibited a low value of 64.6% and of patient F.G., which exhibited a low value of 76.1%. (2) Within the root resorption group, only patient S.K. exhibited the values of all the laboratory tests falling within their normal ranges. The remaining five patients exhibited one or more of their tests to fall outside their normal ranges. Patient W.R. exhibited a high amount of PO_4 in his 24 hour urinary collection. Patient M.R. exhibited low values of serum Ca, 24 hour urnine Ca, T.R.P. and high values of T_3 and cortisol. Patient V.L. showed low value of the 24 hour

urinary PO_4, and low value of the T.R.P. Patient M.M.
displayed low value of the T.R.P., and high value of the
PTH. Patient D.M. displayed low value of T.R.P.

Table IV is a tabulation of the mean values and
standard deviations of all the variables of the control and
root resportion group. It also displays the t values and
the significance of the difference of each variable between
the two groups, as they resulted after two-sample t tests
were performed. No variable displayed any significant
difference at P = .10, between the control and root
resorption patients.

Figures 13 to 24, are the histograms displaying the
results of the S.P.S.S. discriminant analysis.

The application of the S.P.S.S. discriminant
analysis to the data, produced a set of coefficients which
determine a line. The best separation between the groups
occur when the values, which represent each patient are
plotted along this line[66]. In the histograms, the x-axis
is the line of best separation. Point zero is the point of
separation of the two groups, and lies midway between their
centroids, which are the average positions of all the
patients in a group. The position of each patient along the
x-axis is computed from the sum of the products of the
z-scores and the standard coefficients for each variable[66].
The height of each bar indicates the number of patients in
that position.

Figure 14 is the histogram which displays the result of the S.P.S.S. direct discriminant analysis when all the variables, except CT, were used. Separation of the groups is observed, without overlap. However, one of the control cases is classified into the root resorption group.

The S.A.S. discriminant analysis (Table V) indicates that with the exception of the control patient F.D., which was classified as a root resorption patient with a probability of 90%, all the patients were assigned to the correct group with a probability ranging from 93% to 100%.

Figures 15 to 24 are histograms showing the progressive separation achieved by the S.P.S.S. step-wise discriminant analysis.

According to the S.P.S.S. step-wise discriminant analysis, the best separating variable is the T_3. The sequence by which the rest of the variables are added to the T_3 according to their significance in contributing to further separation is: T_4, 24 hour urine Ca, serum PO_4, T.R.P., Serum Ca, Alkaline Phosphatase, 24 hour urine PO_4, P.T.H., and Cortisol.

Examining these histograms, we observe that a minimum of four or five variables is required for the visible separation of the groups.

TABLE I

Tabulations of the patients according to their sex, age, grouped according to root condition.

Patient	Sex	Age	Group*
F.D.	M	18	I
F.S.	F	18	I
L.D.	M	22	I
F.G.	M	22	I
H.M.	M	18	I
K.J.	F	17	I
W.R.	M	23	II
M.R.	F	21	II
S.K.	F	17	II
V.L.	M	18	II
M.M.	M	18	II
D.M.	F	18	II

*Group I represents the control patients. Group II represents the root resorption patients.

TABLE II

Serum and urine analyses in patients without root resorption subsequent to orthodontic treatment (Group 1, Control).

Pat.	Serum Ca	PO$_4$	24 hour Urine Ca*	PO$_4$*	T.R.P.	Alkaline Phosph.	Serum T$_3$	T$_4$	Cort.	P.T.H.	CT
F.D.	9.5	3.5	261, 188	1.18, 1	82.4%	62	125	8.3	19	765	<50
F.S.	9.2	3.3	25, 102	0.61, 1.15	80%	75	106	6.6	15	800	<50
L.D.	9.5	2	170, 172	1.1, 1.2	64.6%	39	134	9.1	23	680	<50
F.G.	9.5	2.7	132, 185	1.17, 0.89	76.1%	83	118	6.9	25	755	<50
H.M.	9.7	3	318, 174	1.1, 1	79.9%	100	114	7.1	20	680	<50
K.J.	9.4	3.8	45, 90	0.68, 0.72	83.7%	105	116	8.2	11	1015	<50
Mean	9.4	3.05	154.3	1	77.8%	77.3	118	7.7	18.8	782	<50
S.D.	.19	.64	77.8	.17	6.9	24.5	9.6	.9	5.1	123	
Norm** Range	9-11 MG/DL	2.5-4.2 MG/DL	55-400 MG	0.34-1.30 MG	85%±5.4	30-110 U/L	80-160 NG/DL	5-12 UG/DL	6-25 UG/DL	430-1860 PG/ML	20-50 PG/ML

*These numbers represent the values of two separate 24 hour urine collections.
**Normal values were furnished by the clinical laboratories where the analyses were performed.

TABLE III

Serum and urine analyses in patients with root resorption subsequent to orthodontic treatment (Group 2, Root Resorption).

Pat.	Serum		24 hour Urine		T.R.P.	Serum					
	Ca	PO$_4$	Ca*	PO$_4$*		Alkaline Phosph.	T$_3$	T$_4$	Cort.	P.T.H.	CT
W.R.	9.5	3.5	241, 372	1.28, 1.52	81%	42	114	7.7	25	950	<50
M.R.	8.9	3.1	48, 56	0.6, 0.5	77.6%	42	168	10.5	37	915	<50
S.K.	10	3.3	170, 150	0.64, 0.52	84.4%	66	152	10.6	11	605	<50
V.L.	9.5	3.1	353, 185	1.62, 1.81	70.5%	105	110	6.2	10	735	<50
M.M.	9.9	3.3	157, 249	1.03, 1.13	75.5%	93	115	6.3	18	1970	<50
D.M.	9.1	3.4	87, 160	0.73, 1.12	77.7%	79	124	6.3	12	715	<50
Mean	9.48	3.28	185.5	1.04	77.7%	71	130.5	7.9	18.8	981	<50
S.D.	.43	.16	93.9	.45	4.7	26.1	23.8	2.1	10.5	501	
Norm** Range	9-11 MG/DL	2.5-4.2 MG/DL	55-400 MG	0.34-1.30 MG	85%±5.4	30-110 U/L	80-160 NG/DL	5-12 UG/DL	6-25 UG/DL	430-1860 PG/ML	20-50 PG/ML

*These numbers represent the values of two separate 24 hour urine collections.
**Normal values were furnished by the clinical laboratories where the analyses were performed.

TABLE IV

Means, standard deviations, t values and level of significance for between group comparisons of each variable.

Variables	CONTROL GROUP		ROOT RESORPTION GROUP		t values	P
	Mean	S.D.	Mean	S.D.		
Serum Ca	9.4	0.19	9.48	0.43	0.417	.10*
Serum PO_4	3.05	0.64	3.28	0.16	0.854	.10
24 h. Urine Ca	154.3	77.8	185.5	93.9	0.627	.10
24 h. Urine PO_4	1	0.17	1.04	0.45	0.204	.10
T.R.P.	77.8%	6.9	77.7%	4.7	0.029	.10
Alkaline Phosph.	77.3	24.5	71	26.1	0.431	.10
T_3	118	9.6	130.5	23.8	1.117	.10
T_4	7.7	0.9	7.9	2.1	0.214	.10
Cortisol	18.8	5.1	18.8	10.5	0	.10
P.T.H.	782	123	981	501	0.945	.10

Calcitonin was not included because no absolute values of that variable were furnished by the laboratory.

*The difference between the groups is not significant at P = 0.1

TABLE V

Probability of classification of the sample in two groups on
the basis of biochemical results according to the S.A.S.
discriminant analysis*.

Patient	Group**	Probability of membership, according to the S.A.S. discriminant analysis in:	
		Group 1***	Group 2****
F.D.	1	0.0928	0.9072
F.S.	1	0.9998	0.0002
L.D.	1	0.9994	0.0006
F.G.	1	1.0000	0.0000
H.M.	1	0.9996	0.0004
K.J.	1	0.9999	0.0001
W.R.	2	0.0620	0.9380
M.R.	2	0.0002	0.9998
S.K.	2	0.0038	0.9962
V.L.	2	0.0005	0.9995
M.M.	2	0.0001	0.9999
D.M.	2	0.0003	0.9997

*All variables used, except calcitonin.

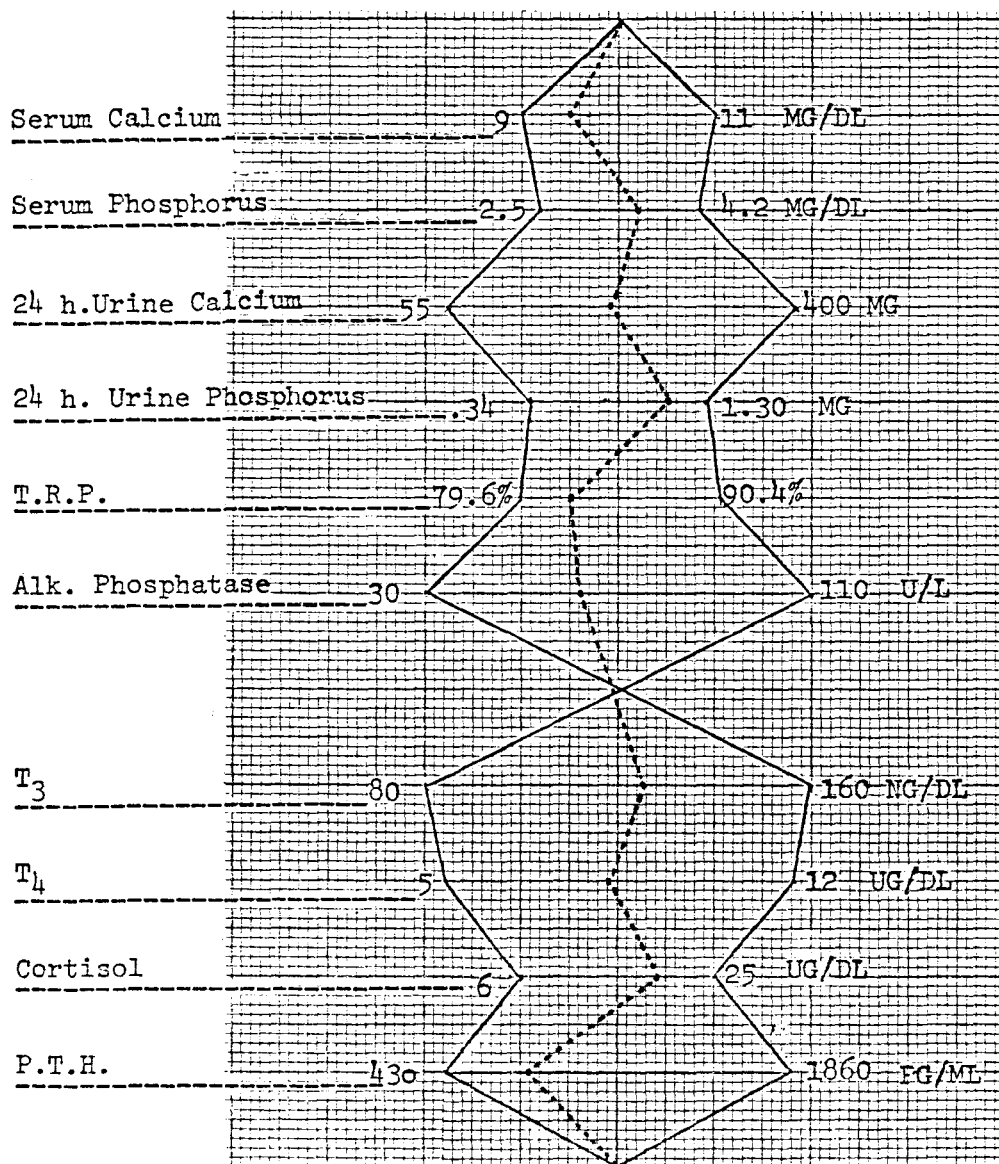**Actual placement of the subjects according to root
condition.

***Group 1: Control group

****Group 2: Root resorption group

FIGURE 2

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

Patient: F.D. , Sex: M , Age: 18 , Control

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 3

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

Patient: F.S. , Sex: F , Age:18 , Control

Serum Calcium ——————9———————11 MG/DL

Serum Phosphorus ————2.5————4.2 MG/DL

24 h.Urine Calcium ———55————400 MG

24 h. Urine Phosphorus ——.34————1.30 MG

T.R.P. ————79.6%————90.4%

Alk. Phosphatase————30————110 U/L

T₃ ————80————160 NG/DL

T₄ ————5————12 UG/DL

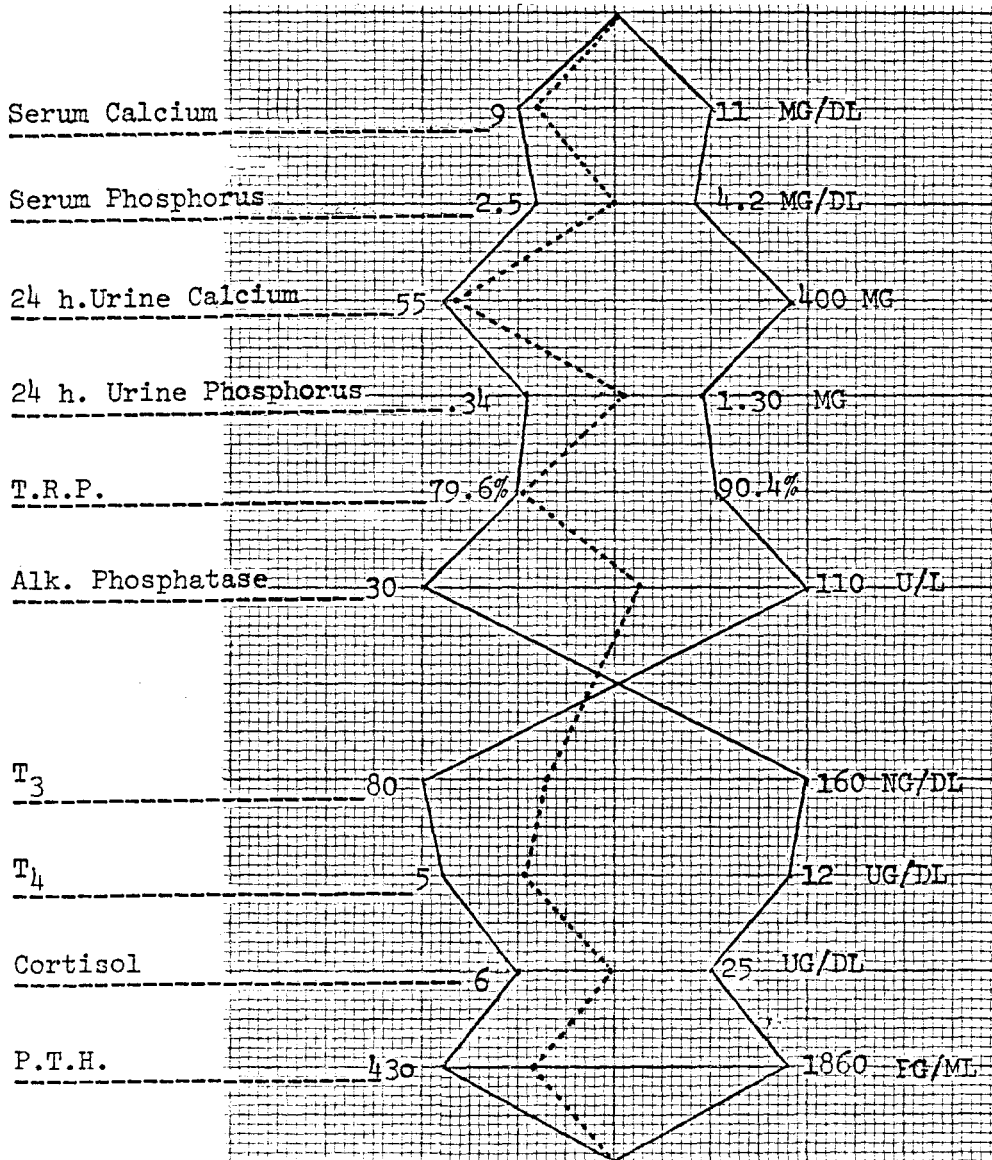Cortisol ————6————25 UG/DL

P.T.H. ————430————1860 PG/ML

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 4

Graphic representation of all variables, resulting from the biochemical
tests, as they relate one to another, and to their normal ranges.(Dotted
line represents the observed values connected to each other.)

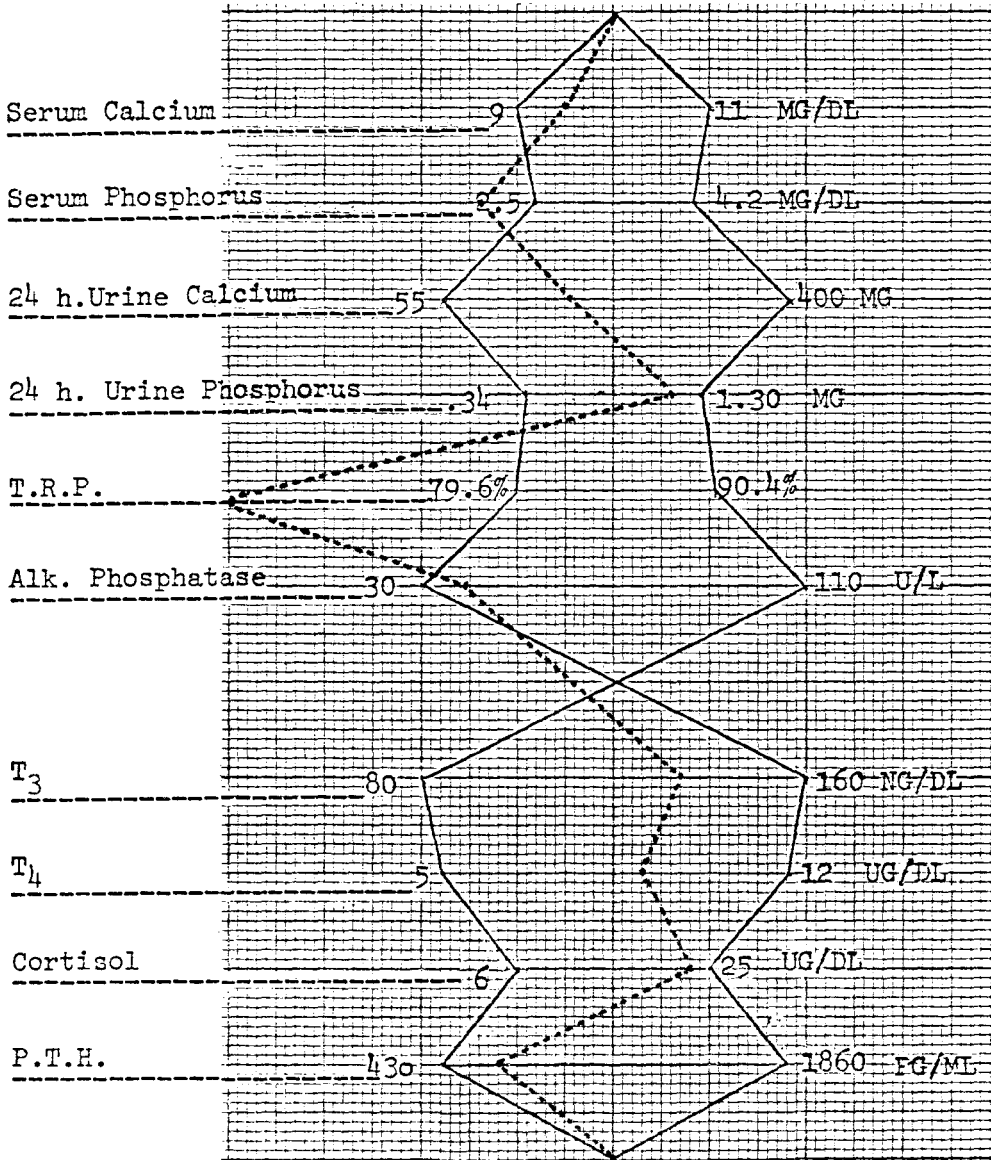Patient: L.D. , Sex: M , Age: 22 , Control

1. The ranges used for the variables, were furnished by the clinical
   laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that
   variable were given by the clinical laboratory (reported as less
   than 50 PG/ML).

FIGURE 5

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

Patient: F.G.., Sex: M , Age: 22 , Control

Serum Calcium   9   11 MG/DL

Serum Phosphorus   2.5   4.2 MG/DL

24 h.Urine Calcium   55   400 MG

24 h. Urine Phosphorus   .34   1.30 MG

T.R.P.   79.6%   90.4%

Alk. Phosphatase   30   110 U/L

T_3 80   160 NG/DL

T_4 5   12 UG/DL

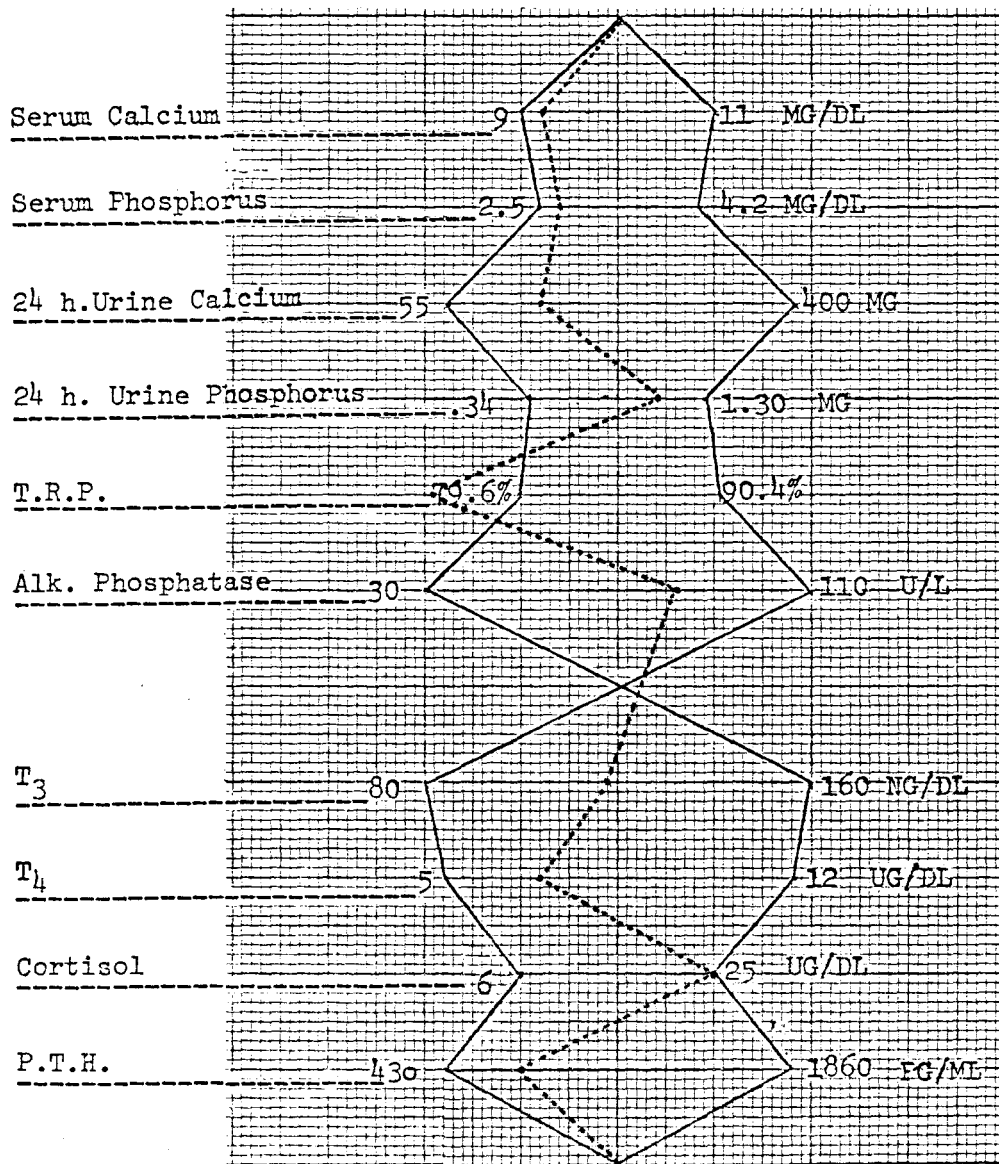Cortisol   6   25 UG/DL

P.T.H.   430   1860 PG/ML

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 6

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

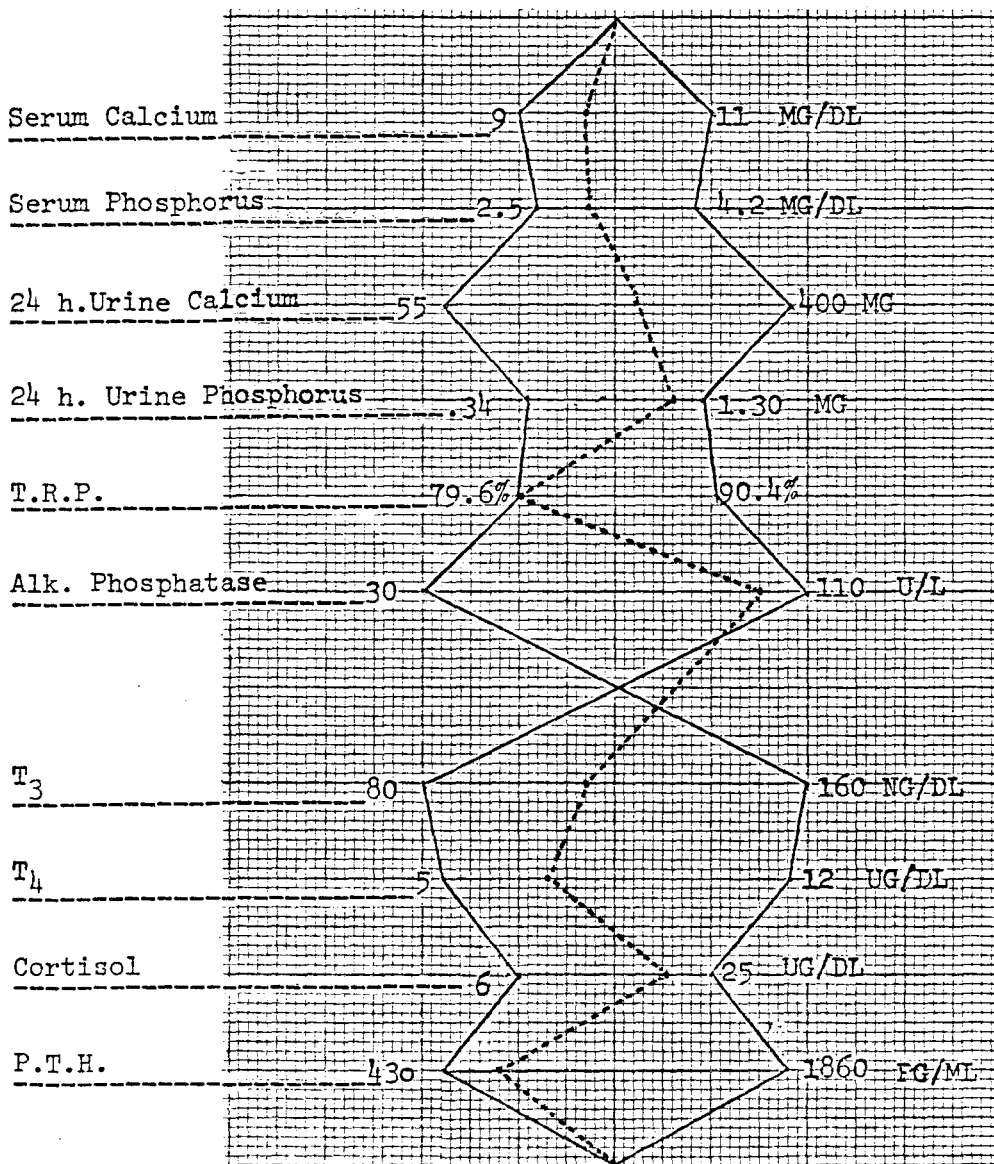Patient: H.M. , Sex: M , Age: 18 , Control

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 7

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

Patient: K.J. , Sex: F , Age: 17 , Control

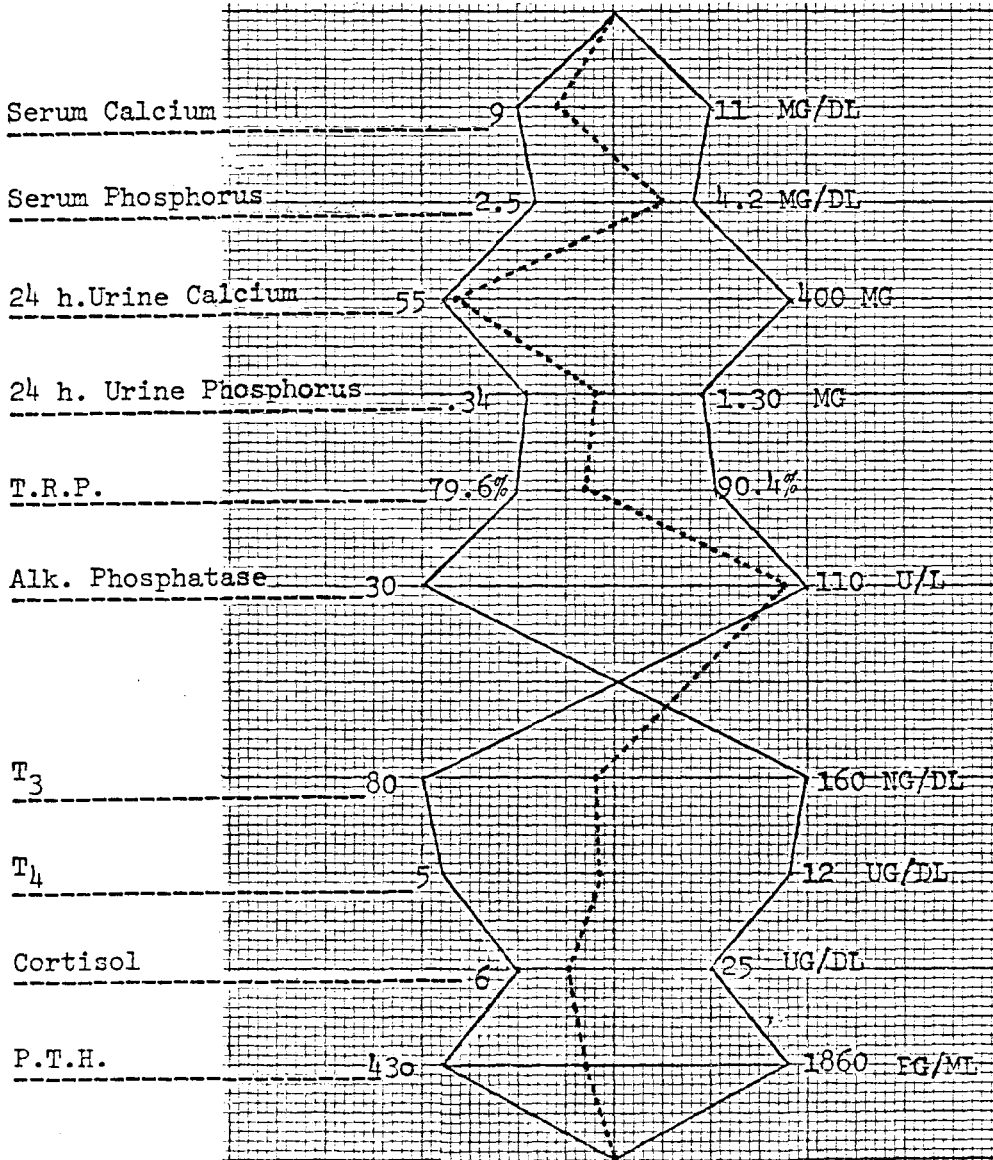|		
Serum Calcium	9	11 MG/DL
Serum Phosphorus	2.5	4.2 MG/DL
24 h.Urine Calcium	55	400 MG
24 h. Urine Phosphorus	.34	1.30 MG
T.R.P.	79.6%	90.4%
Alk. Phosphatase	30	110 U/L
T_3	80	160 NG/DL
T_4	5	12 UG/DL
Cortisol	6	25 UG/DL
P.T.H.	430	1860 PG/ML

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 8

Graphic representation of all variables, resulting from the biochemical
tests, as they relate one to another, and to their normal ranges.(Dotted
line represents the observed values connected to each other.)

Patient: W.R. , Sex: M , Age: 23 , Root Resorption
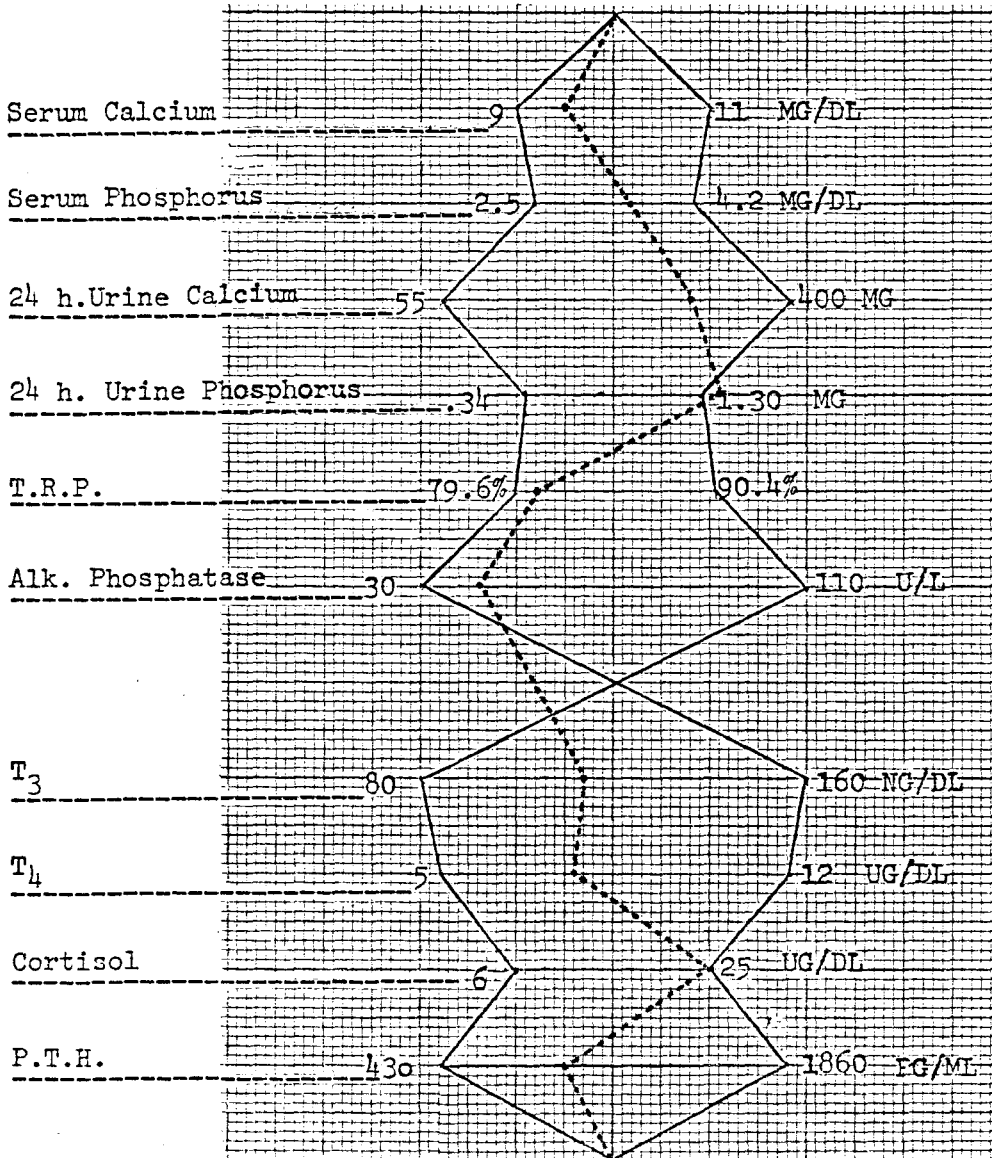
1. The ranges used for the variables, were furnished by the clinical
   laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that
   variable were given by the clinical laboratory (reported as less
   than 50 PG/ML).

FIGURE 9

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

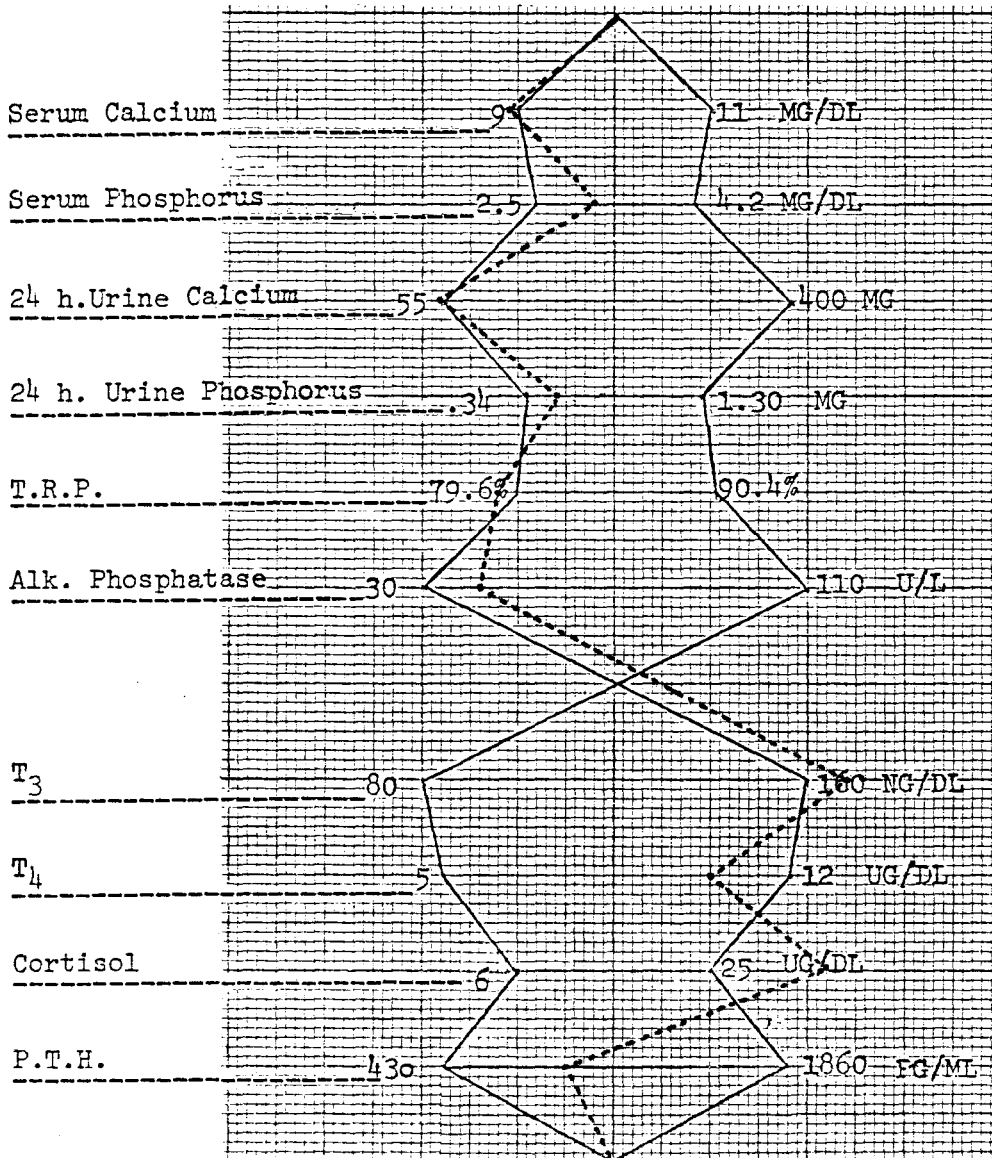Patient: M.R. , Sex: F , Age: 21 , Root Resorption

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 10

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

Patient: S.K. , Sex: F , Age:17 , Root Resorption

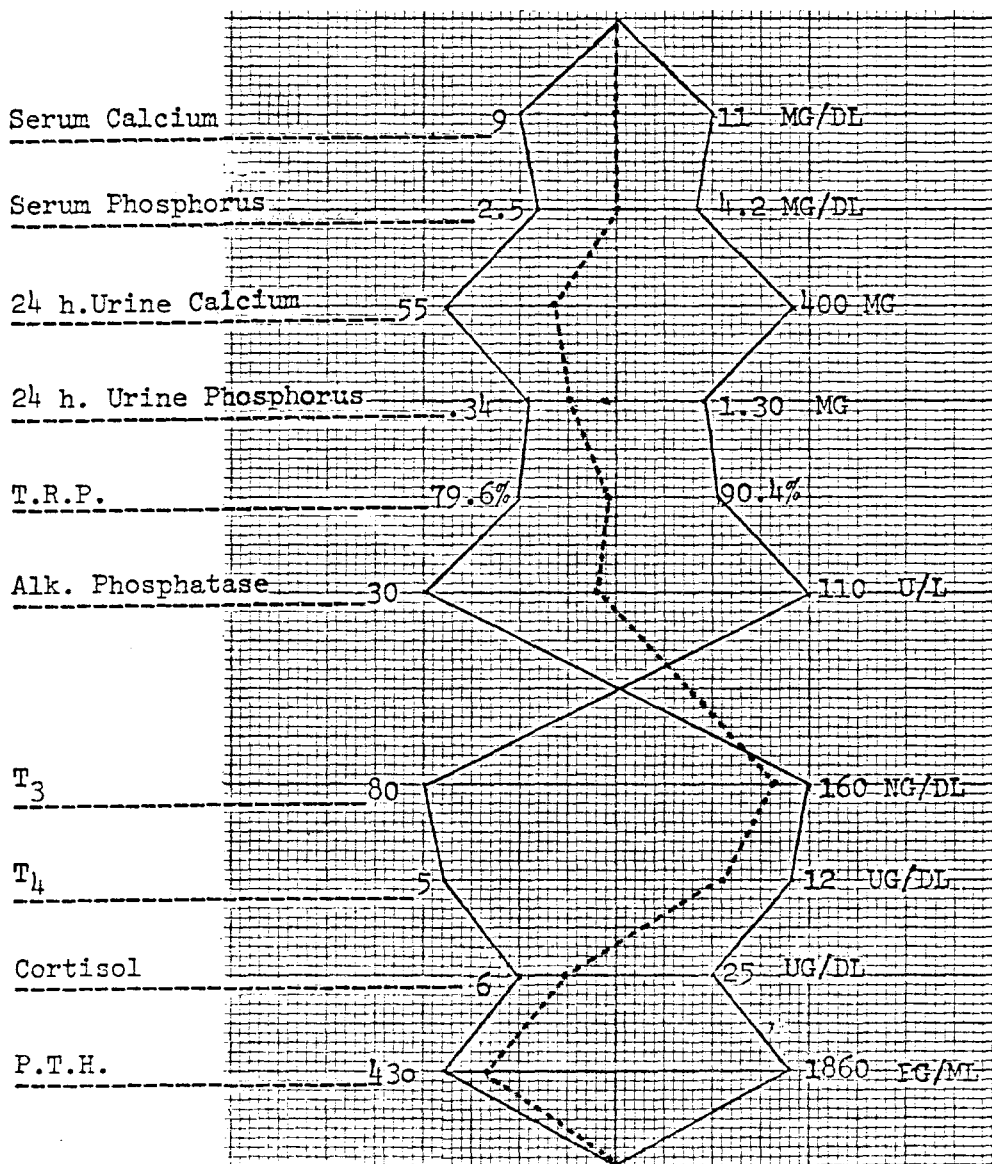| Serum Calcium | 9 | 11 MG/DL |
Serum Phosphorus	2.5	4.2 MG/DL
24 h.Urine Calcium	55	400 MG
24 h. Urine Phosphorus	.34	1.30 MG
T.R.P.	79.6%	90.4%
Alk. Phosphatase	30	110 U/L
T3	80	160 NG/DL
T4	5	12 UG/DL
Cortisol	6	25 UG/DL
P.T.H.	43o	1860 PG/ML

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 11

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

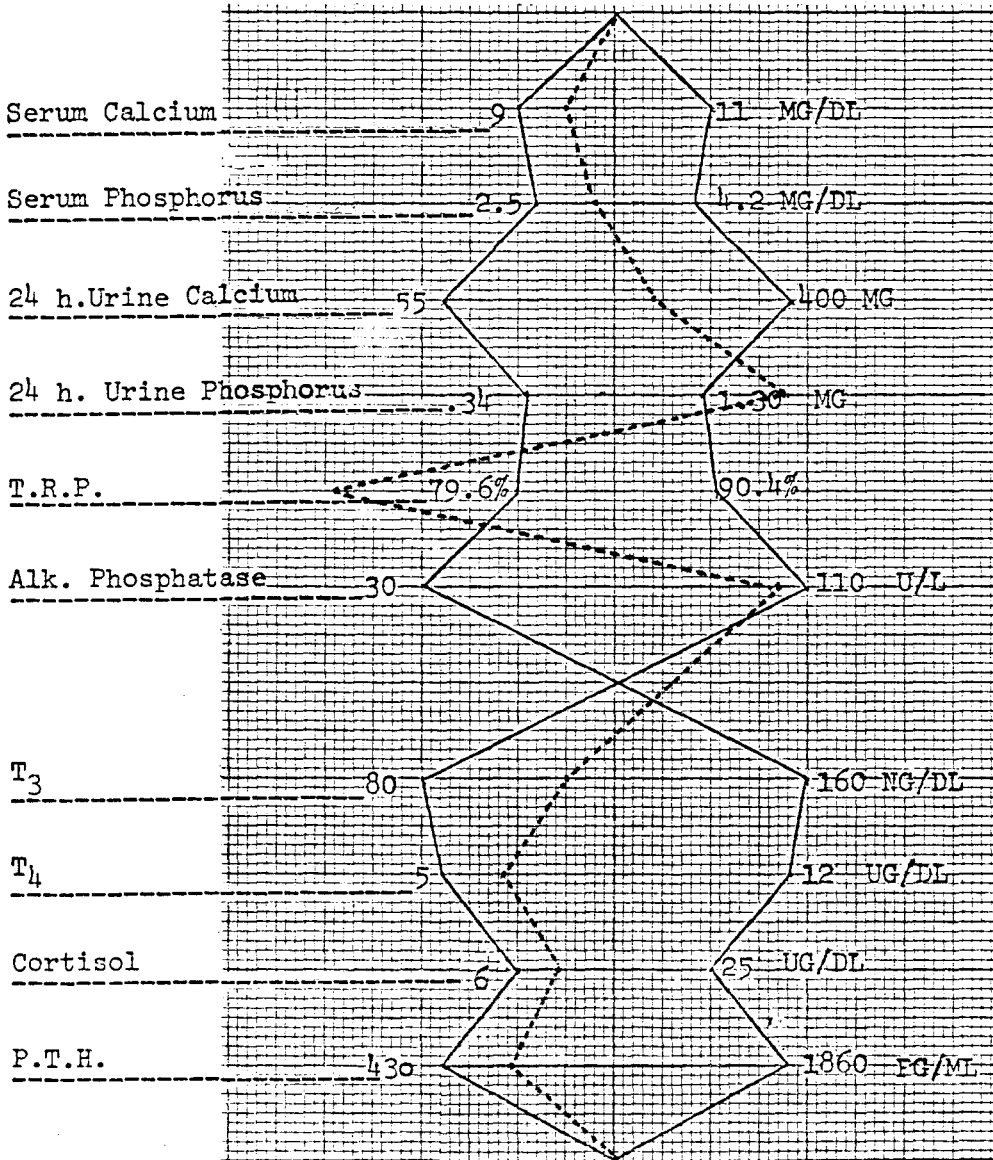Patient: V.L. , Sex: M , Age: 18 , Root Resorption

1. The ranges used for the variables, were furnished by the clinical laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that variable were given by the clinical laboratory (reported as less than 50 PG/ML).

FIGURE 12

Graphic representation of all variables, resulting from the biochemical tests, as they relate one to another, and to their normal ranges.(Dotted line represents the observed values connected to each other.)

Patient: M.M. ,   Sex: M ,   Age: 18 ,   Root Resorption

Serum Calcium ———— 9 ———— 11 MG/DL

Serum Phosphorus ———— 2.5 ———— 4.2 MG/DL

24 h.Urine Calcium ———— 55 ———— 400 MG

24 h. Urine Phosphorus ———— .34 ———— 1.30 MG

T.R.P. ———— 79.6% ———— 90.4%

Alk. Phosphatase ———— 30 ———— 110 U/L

T_3 ———— 80 ———— 160 NG/DL

T_4 ———— 5 ———— 12 UG/DL

Cortisol ———— 6 ———— 25 UG/DL
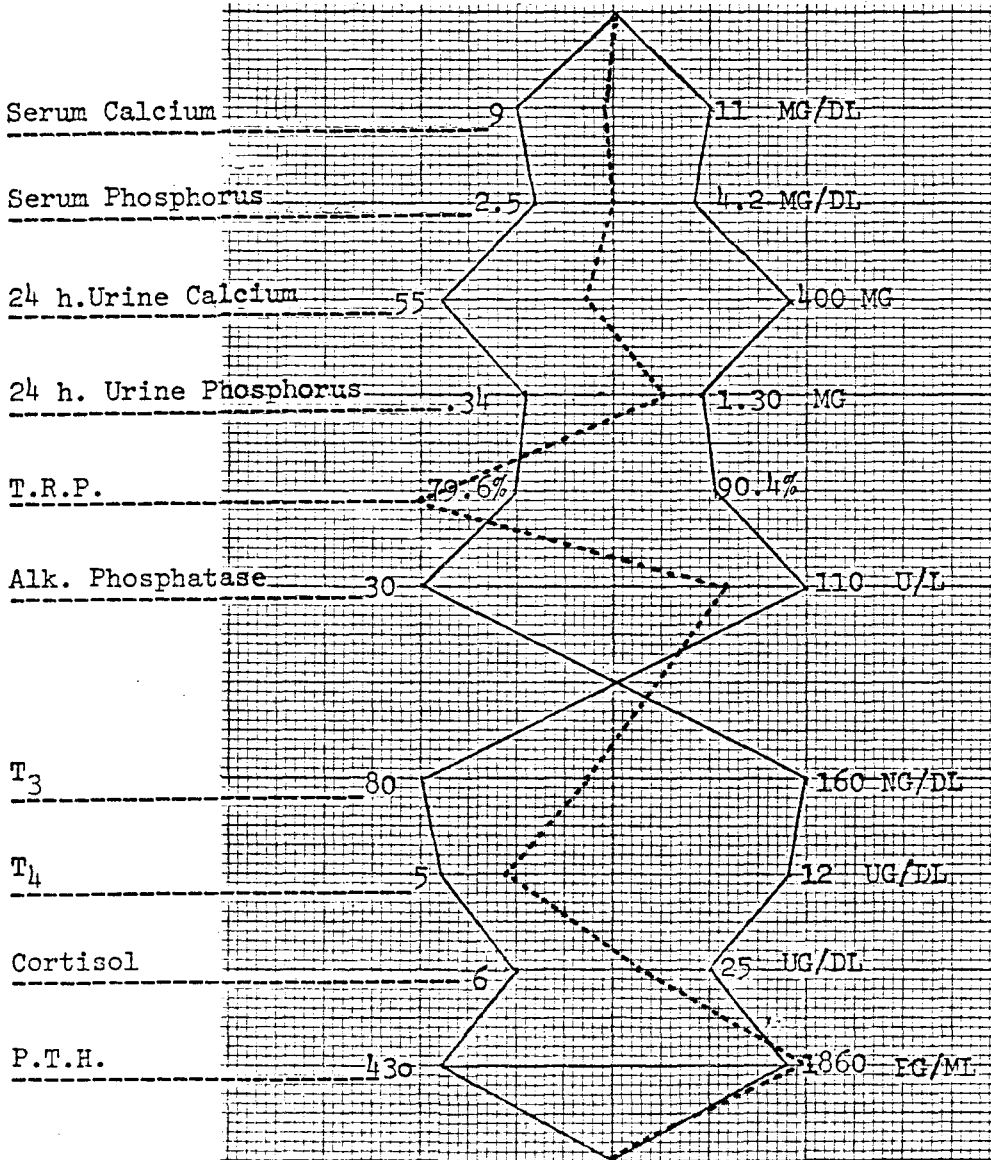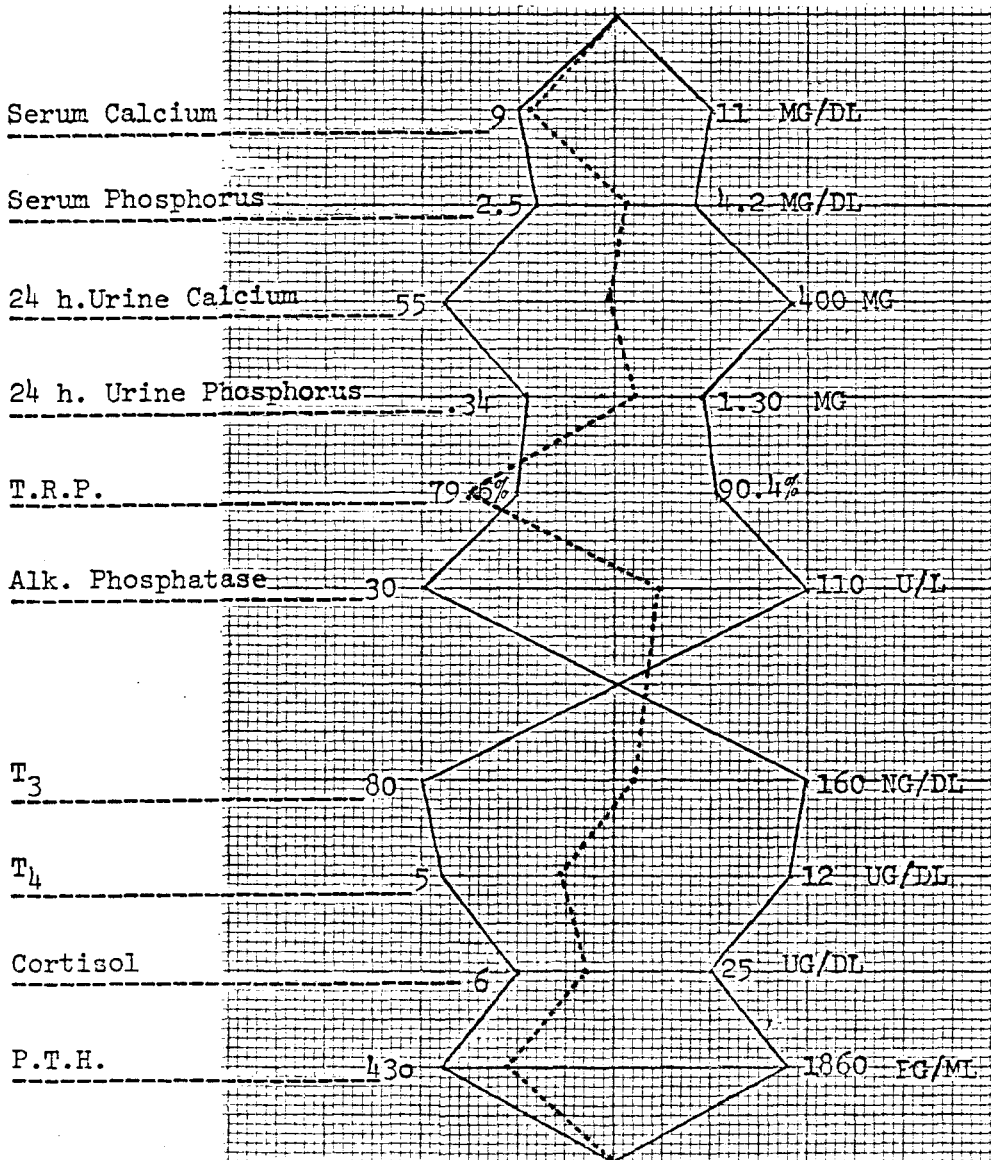
P.T.H. ———— 430 ———— 1860 PG/ML

1. The ranges used for the variables, were furnished by the clinical
    laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that
    variable were given by the clinical laboratory (reported as less
    than 50 PG/ML).

FIGURE 13

Graphic representation of all variables, resulting from the biochemical
tests, as they relate one to another, and to their normal ranges.(Dotted
line represents the observed values connected to each other.)

Patient: D.M. , Sex: F , Age: 18 , Root Resorption

Serum Calcium 9 11 MG/DL
Serum Phosphorus 2.5 4.2 MG/DL
24 h.Urine Calcium 55 400 MG
24 h. Urine Phosphorus .34 1.30 MG
T.R.P. 79.5% 90.4%
Alk. Phosphatase 30 110 U/L
T_3 80 160 NG/DL
T_4 5 12 UG/DL
Cortisol 6 25 UG/DL
P.T.H. 430 1860 PG/ML

1. The ranges used for the variables, were furnished by the clinical
laboratories, where these tests were performed.

2. Calcitonin was not included, because no absolute values of that
variable were given by the clinical laboratory (reported as less
than 50 PG/ML).

FIGURE 14

Histogram of the classification of the sample in two groups by the S.P.S.S. direct discriminant analysis (all variables included except Calcitonin).
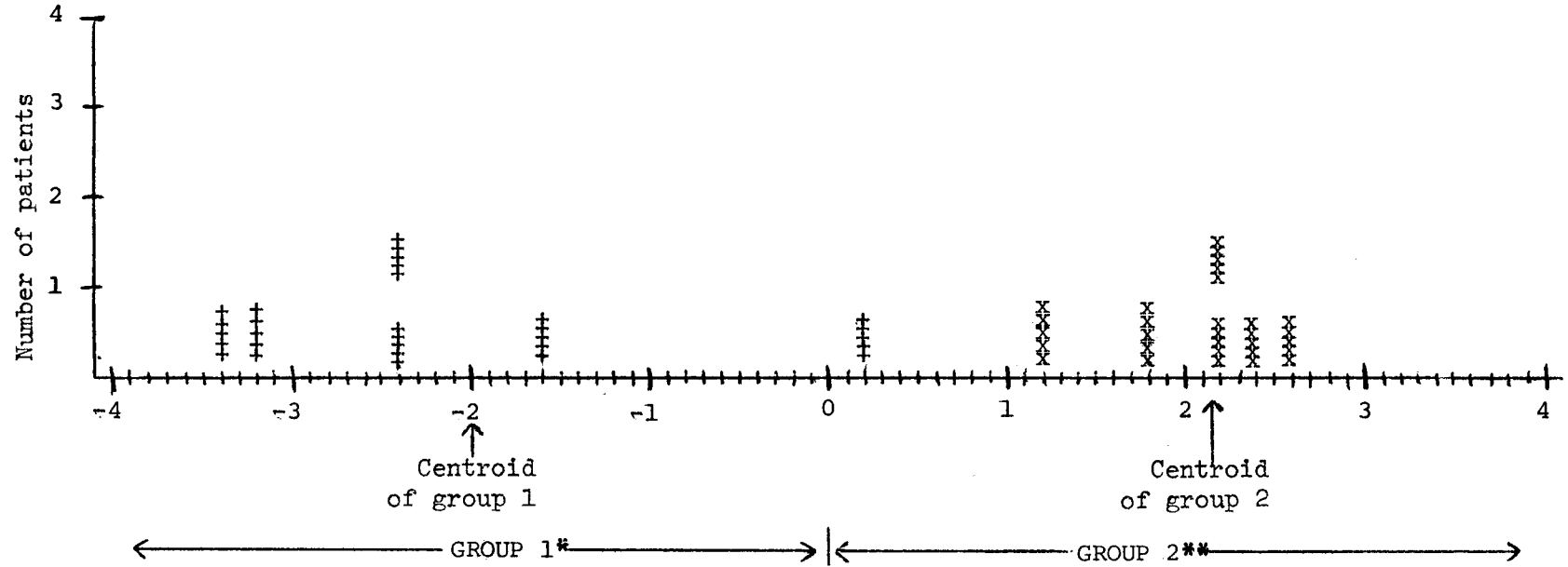
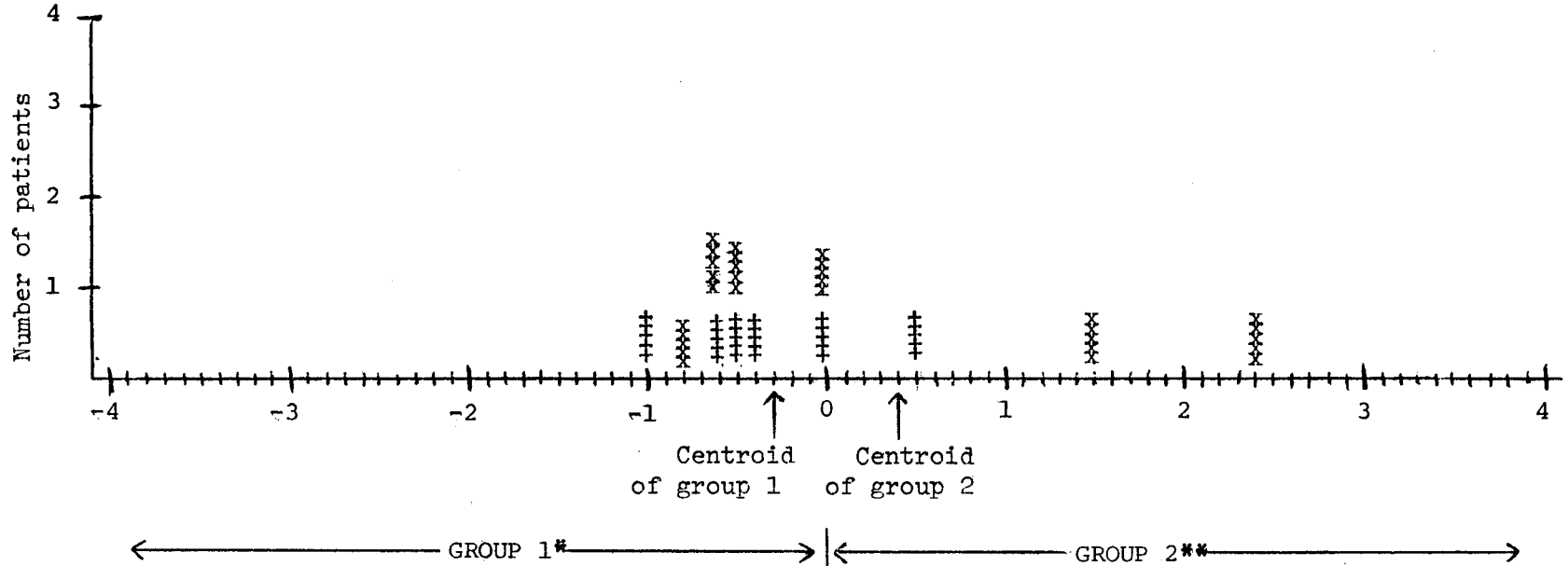Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✗ represents: one control patient, as selected according to the root condition.

  *Group 1:   Control group
**Group 2:   Root resorption group

FIGURE 15

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 1. Variable used: T_3)

Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✗ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 16

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 2. Variables used: T_3, T_4).
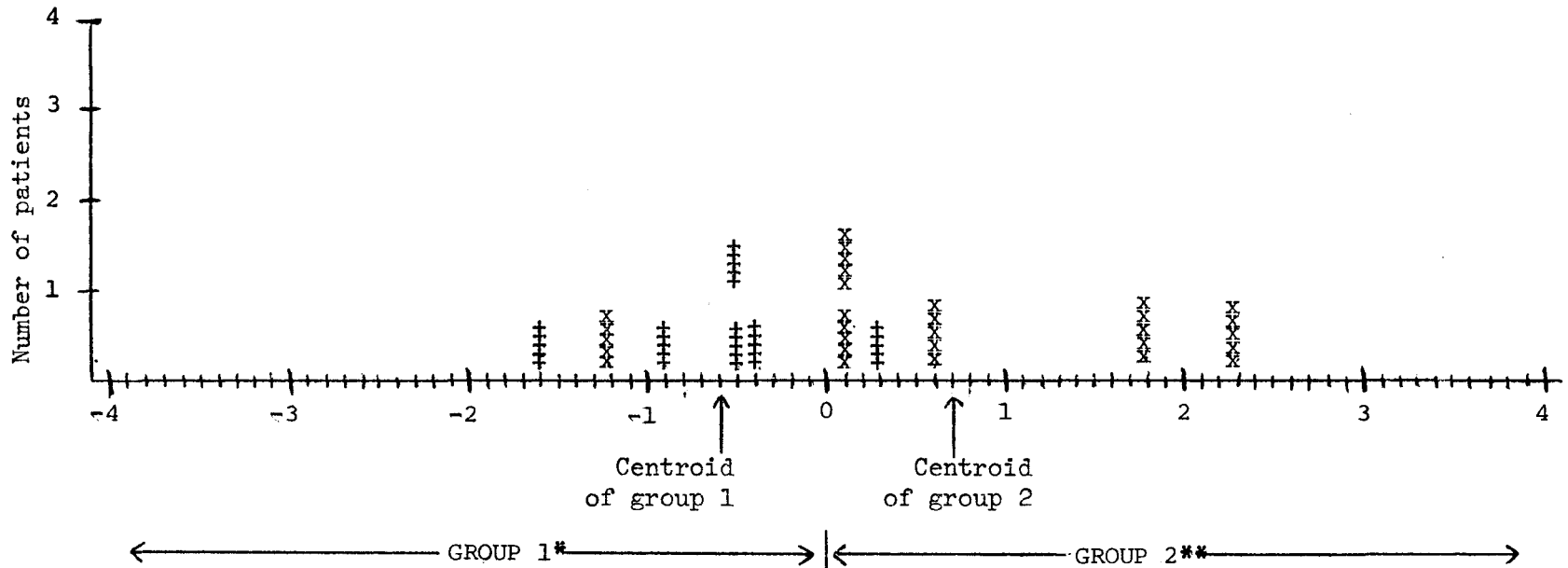
Centroid of group 1

Centroid of group 2

GROUP 1* ⟶|⟵ GROUP 2**

Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✕ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 17

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 3. Variables used: T_3, T_4, 24 hour urine Ca).

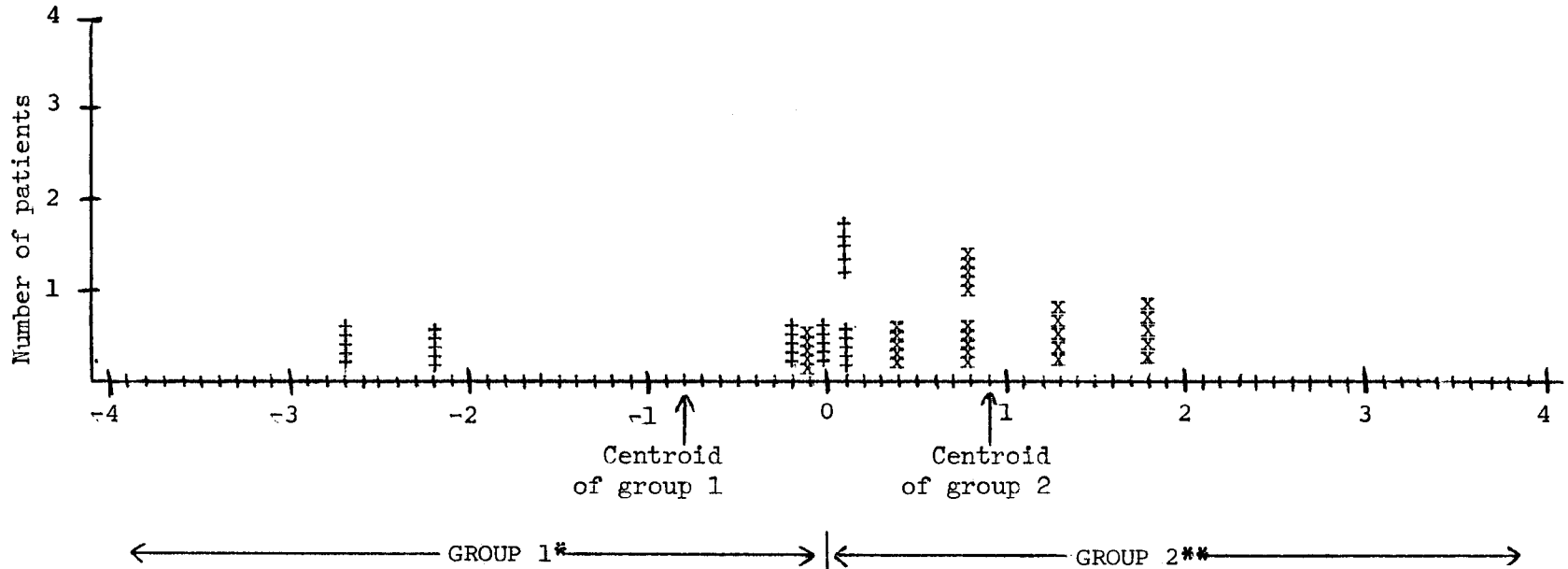Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol X represents: one control patient, as selected according to the root condition.

 *Group 1: Control group
**Group 2: Root resorption group

FIGURE 18

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 4. Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4).

Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✗ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 19

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 5.   Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4, T.R.P.).
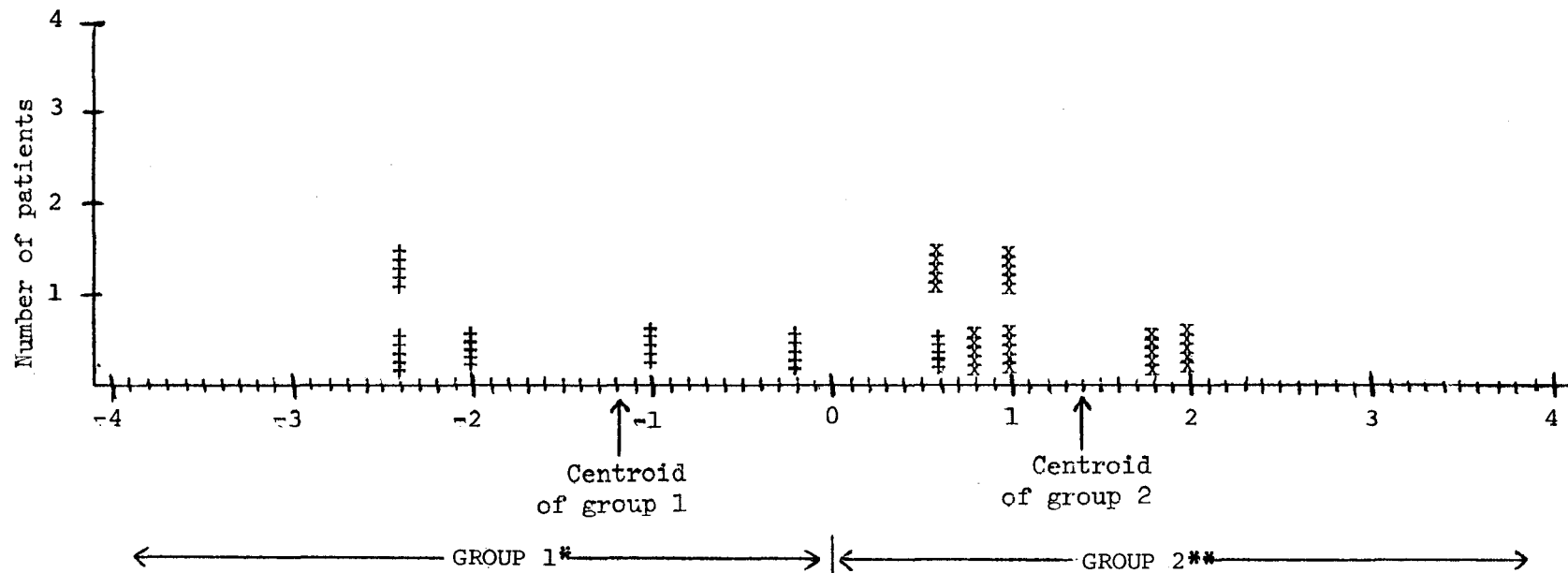
Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ‡ represents: one control patient, as selected according to the root condition.

  *Group 1:   Control group
**Group 2:   Root resorption group

FIGURE 20

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 6. Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4, T.R.P., serum Ca).

Number of patients

Centroid of group 1

Centroid of group 2

GROUP 1* | GROUP 2**

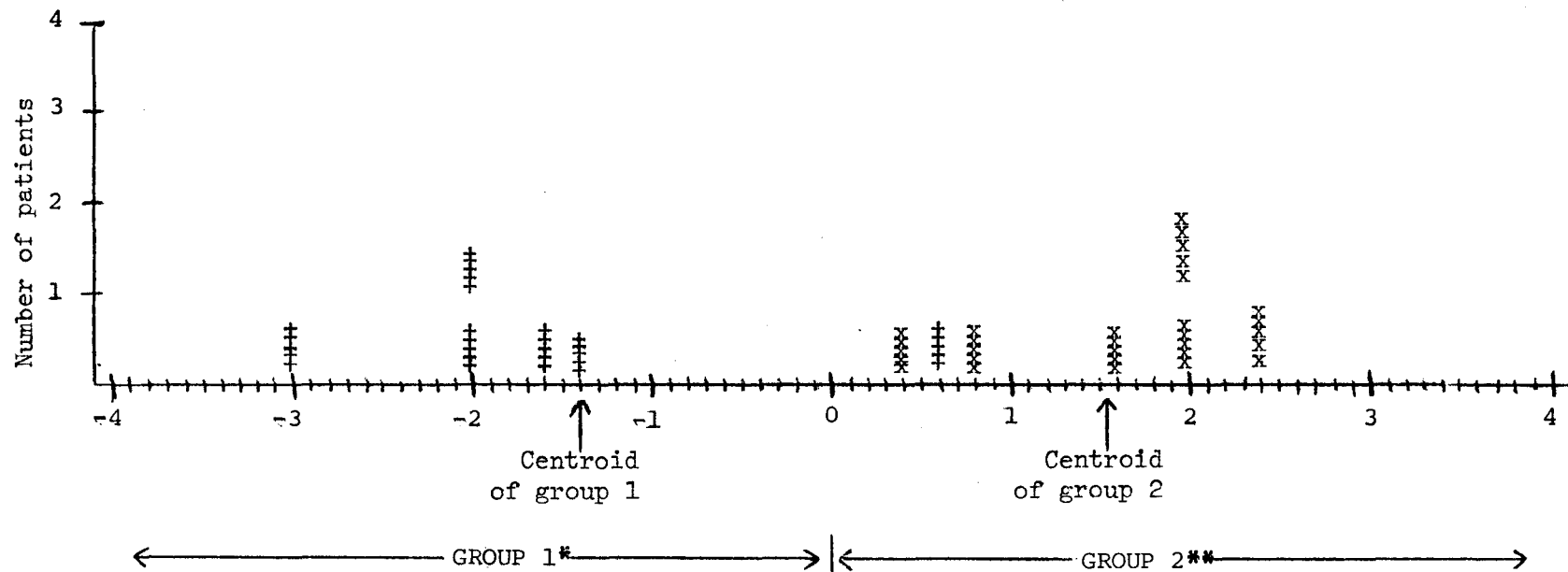Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✗ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 21

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 7. Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4, T.R.P., serum Ca, Alk. Phosph.).
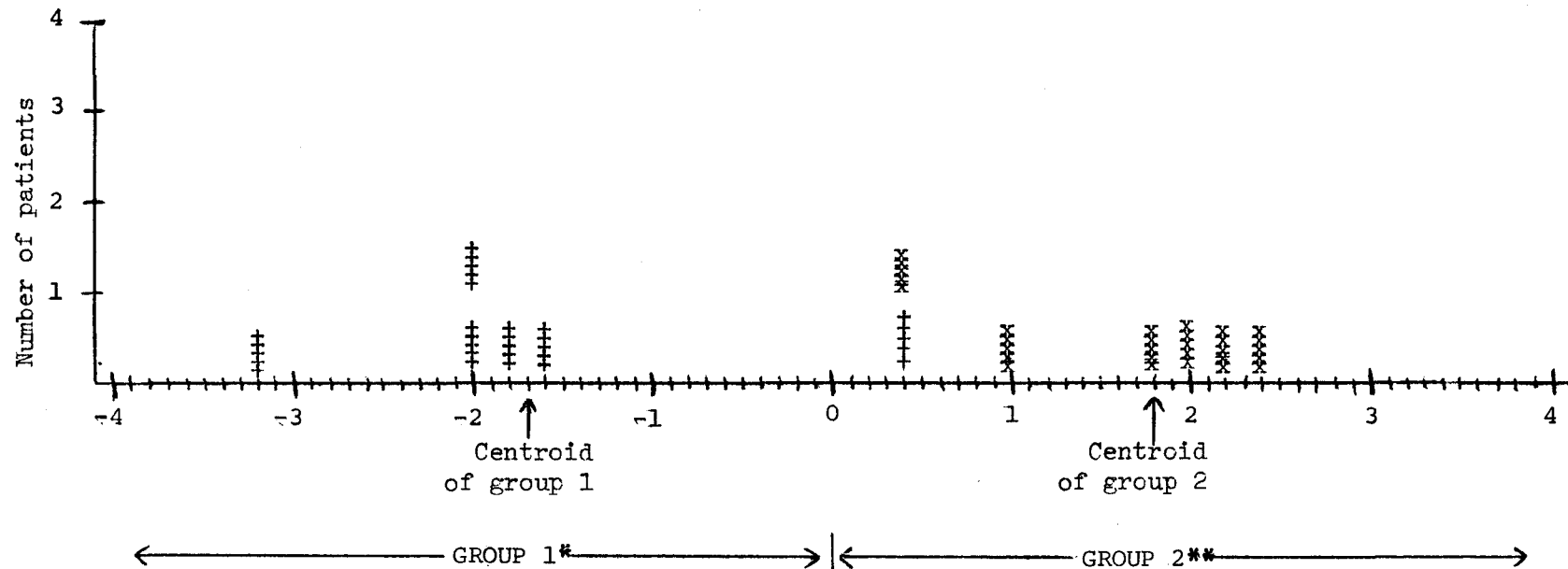

Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✗ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 22

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 8. Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4, T.R.P., serum Ca, Alk. Phosph., 24 h. urine PO_4).

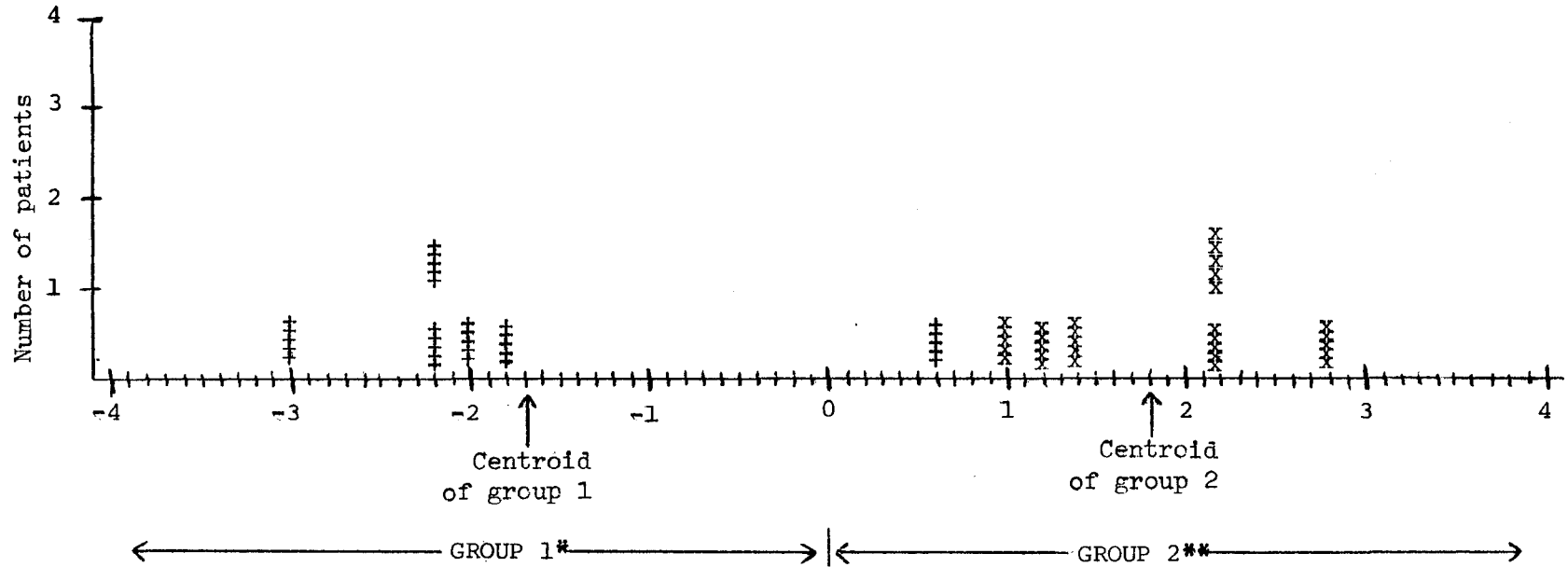Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✕ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 23

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 9. Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4, T.R.P., serum Ca, Alk. Phosph., 24 h. urine PO_4, PTH).
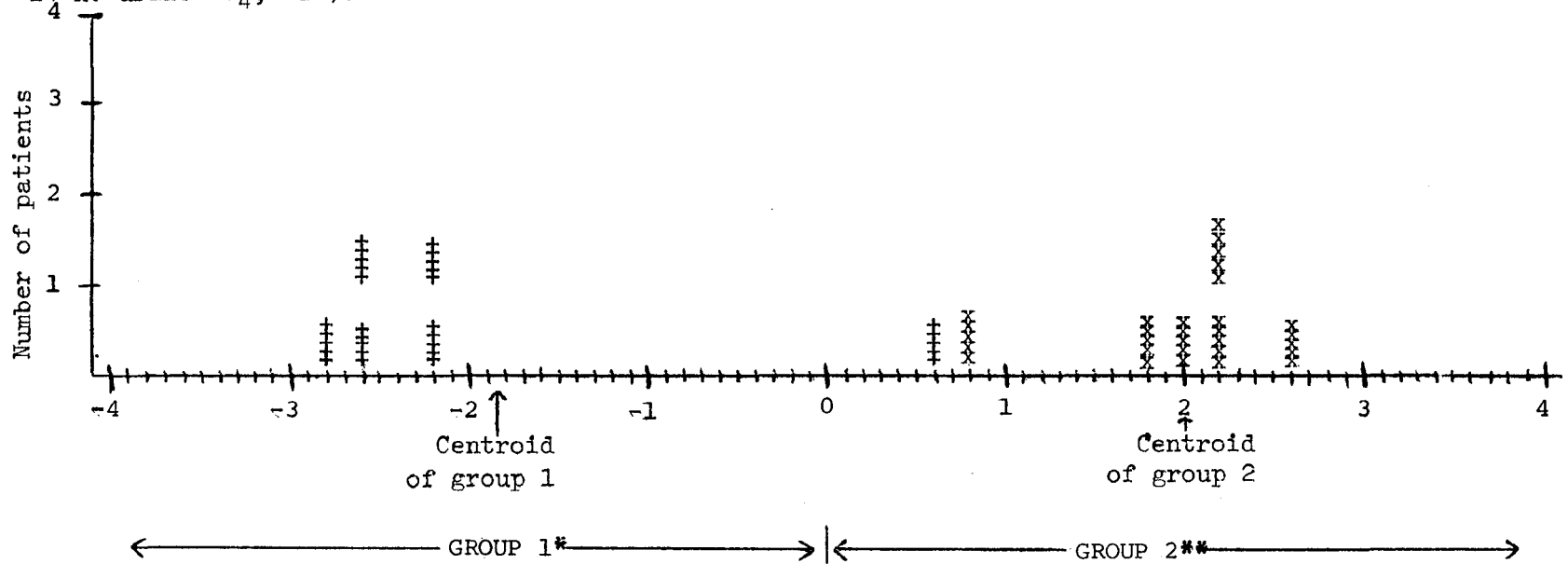
Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✗ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

FIGURE 24

Histogram of the classification of the sample in two groups by the S.P.S.S. step-wise discriminant analysis (Step 10. Variables used: T_3, T_4, 24 h. urine Ca, serum PO_4, T.R.P., serum Ca, Alk. Phosph., 24 h. urine PO_4, PTH, cortisol).

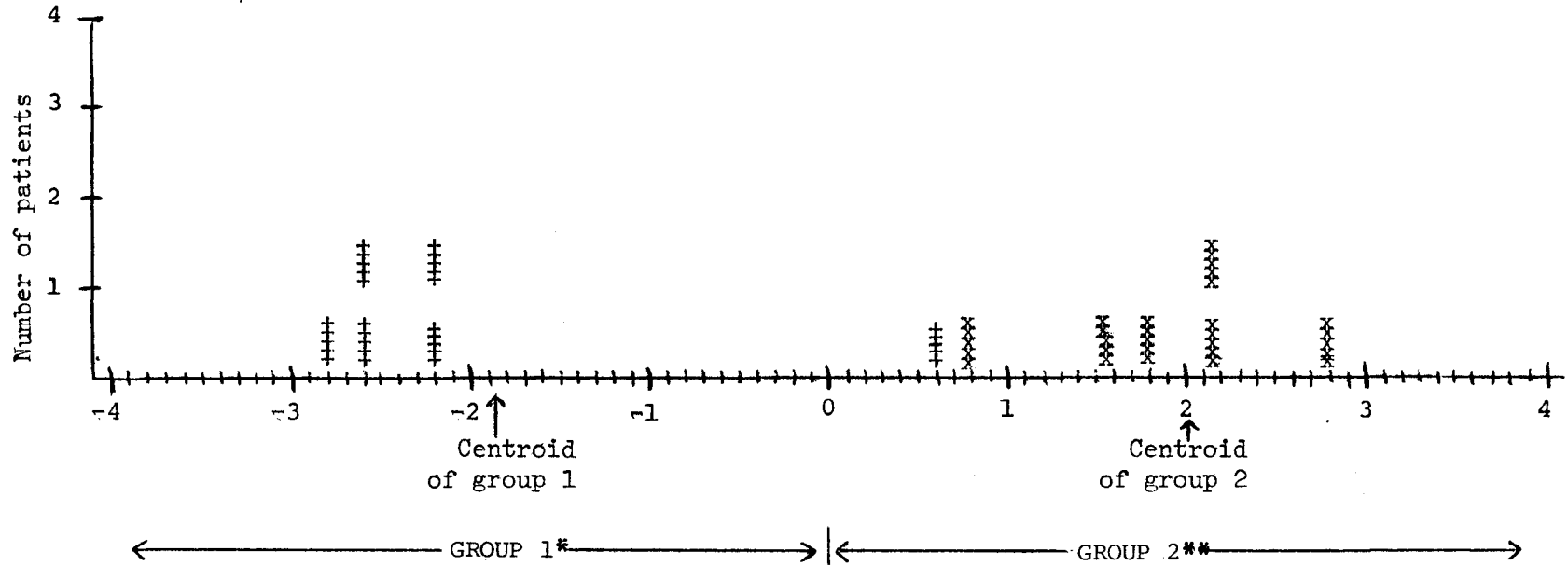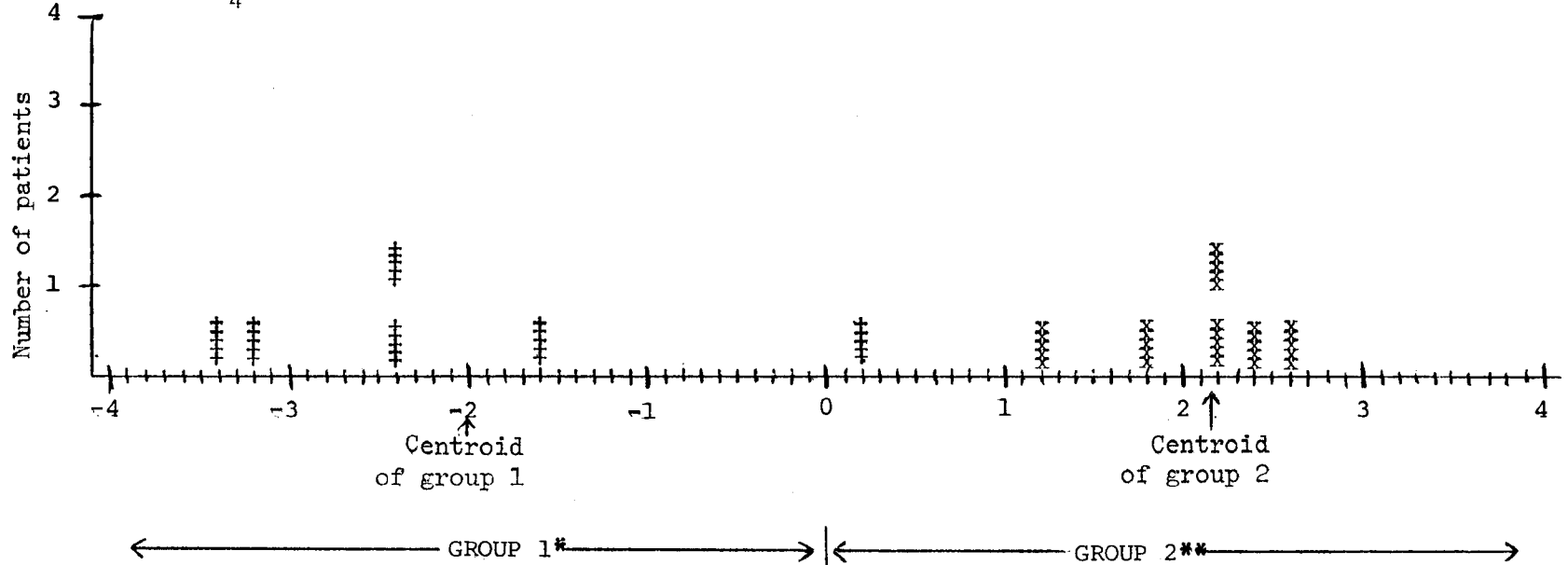Symbol ‡ represents: one root-resorption patient, as selected according to the root condition.

Symbol ✕ represents: one control patient, as selected according to the root condition.

*Group 1: Control group
**Group 2: Root resorption group

CHAPTER V

DISCUSSION

The purpose of this study was to demonstrate how normal patients undergoing orthodontic treatment could be adequately distinguished, one from another, based on their metabolic fingerprint, when some of them exhibited generalized root resorption and some not. This was in contrast to previous studies[3,37,68] which attempted to establish a metabolic characteristic of the root resorption patient by comparing the results of several laboratory tests to their normal ranges.

The results of this study demonstrate a strong relationship between the overall metabolic picture and generalized root resorption which appears in patients during the first year and a half after the initiation of orthodontic treatment.

Since it has been shown that orthodontic treatment can cause root resorption, very strict criteria for the sample selection were placed. Orthodontic patients, in order to qualify for the root resorption group, had to exhibit moderate to severe generalized root resorption and

be in treatment for a relatively short period of time. In
these patients, the observed root resorption could not be
attributed readily to the applied orthodontic mechanics and
the characteristic term, "idiopathic", could be used in
discribing that condition. Furthermore, these resorption
cases constitute a source of concern to both orthodontist
and patient. The prognosis in these cases, for both the
orthodontic treatment and the future health of the dentition
is poor. Orthodontic patients, in order to qualify for the
control group in this study, did not exhibit any
radiographic evidence of root resorption.

The sample was highly selected. It is obvious that
comparisons between two extreme situations were attempted.
The percentage of orthodontic patients exhibiting idiopathic
root resorption is not more than 10%, while the large
majority of the orthodontic patient population exhibits some
minor degree of root resoprtion.

A noteworthy result of this study is that, in order
to demonstrate the relationship between metabolism and root
resorption, the metabolic fingerprint of each patient had to
be used rather than individual metabolic variables. An
attempt to relate, statistically, individual metabolic
variables to root resorption failed, although some greater
variability among the values of some metabolic factors can
be observed. Also, occasional, values outside their normal
ranges could be seen in the root resorption group. If the

study was ended at that point, the conclusions drawn would
had been similar to those of Newman [37]. Newman, in 1975,
after examining the relationship of T_4, PBI, serum Ca,
serum PO_4 and Alk. Phosph. to root resorption, came to the
conclusion that systemic factors and metabolic problems were
not at all related to root resorption.

Use of direct discriminant analysis allowed the
measurments of each patient to be taken as a biochemical
unit. By using this metabolic fingerprint, we attempted to
determine the significance of the separation of those
patients in two groups. The result of that statistical
analysis demonstrated that the control and root resorption
patients were classified in two separate groups with a
certanity ranging between 93 to 100%, with the exception of
one control patient which was classified as a root
resorption case. This divergent datum indicates that, in
addition to the choosen variables, there should be others
also influencing root resorption. It can be suggested that
some of these additional variables should be related to the
anatomy of the root and the P.D.L. and to the chemical
composition of the cementum. Another possible explanation
for divergence could be that the chemical analyses give a
metabolic fingerprint at a particular time. Perhaps that
patient would have been classified as a control, if the
tests were performed at an earlier and perhaps that patient
will develop root resorption as the treatment progresses.

Becks[3] in 1936, after studying 100 patients with root resorption, stated that 66% of the orthodontic patients and 86% of the nonorthodontic patients exhibited definite hypothyroidism. The findings of Becks were based mainly on readings of their basal metabolic rate. The present study, using more precise methods for the determination of thyroid function, does not support this finding. On the contrary, it is shown that in the root resorption group, there was one patient exhibiting a high value of T_3 and also the mean values for the T_3 and T_4 were greater, although statistically, not significant, when compared to the mean values exhibited in the control group.

The results of Tager[68] could not be evaluated and compared to this study, because his study sample included patients with several problems, i.e. delayed tooth eruption, tooth deformities and root resorption.

The step-wise discriminant analysis, shows that the single most important separating variable is the T_3, while the factor which enhances best the separating action of T_3, is T_4. This result indicated that thyroid function is closely related to root resorption. Nevertheless, it is apparent that the separation of the sample in two groups is insignificant and only after five variables are included in the discriminant analysis, can one observe the sample separation (Figures 15 to 20). The sequence by which the variables were included one after another in the step-wise

analysis, is based on the potential of each variable to increase the separating action of the previously added variables and does not necessarily imply any biological mechanism, nor does the sequence follow any biological pertinency. An impression was gained that the sequence by which the variables were included in the step-wise discriminant analysis do not express a particular pattern or syndrome, not detectable in the graphical two dimensional representation of each case. On the contrary, it is tempting to speculate, based on the small differences between the mean values and the large standard deviations, shown in Table IV, that there could be several biological mechanisms involved, some of them possibly related to nutritional status, as Marshall and Becks have shown, and some of them to renal and gastrointestinal problems, as Sisher and Weinman suggested, and some of them to primary endocrinal problems.

This study described clearly a definite relationship between the metabolic picture of the patients, as given by the tests which were selected, and generalized root resorption. Furthermore, it is suggested that the procedure applied in this study could be use prospectively as a prediction test concerning the behavior of the roots of the dentition of future orthodontic patients.

It is further suggested that the following studies should follow this preliminary study.

1.   Replication of the same study while using a large number of patients, selected with the same strict selection criteria used in this study. The results of this study will enhance the calibration of the discriminant analysis.

2.   Addition of orthodontic patients exhibiting less than moderate degree of root resorption. This study will determine if these patients can be classified, based on their metabolic fingerprint, in a way corresponding to their root condition.

3   Application of the derived prediction test prospectively, to future orthodontic patients.

These studies are needed for the development of an accurate and cost effective prediction test, which could be applied in the Orthodontic profession.

SUMMARY AND CONCLUSIONS

This study was designed to test: (1) The significance of the variation of individually selected metabolic variables (test values) between orthodontic patients exhibiting moderate to severe generalized root resorption and others exhibiting no radiographic evidence of that condition. (2) The possibility of classifying these patients in two separate groups on the basis of their metabolic fingerprint.

The sample consisted of 12 orthodontic patients, six of whom exhibited root resorption; the other six none.

The selected metabolic variables which were also used to compose and describe the metabolic fingerprint of each patient, were as follows: serum calcium, serum phosphorus, 24 hour urine calcium, 24 hour urine phosphorus, tubular reabsorption of phosphorous, triodothyronine, tetraiodothyronine, cortisol and parathormone.

The two-sample t test showed no significant differences between individual test values between groups. The S.P.S.S. direct discriminant analysis was performed and

it was possible to classify the patients into two groups with a probability of group membership better than 90%. One control case was classified incorrectly.

The results of this study indicates that it is possible to separate healthy orthodontic patients, exhibiting generalized root resorption, from patients without root resorption.The success relates to each patient's metabolic fingerprint and the application of the S.P.S.S. discriminant analysis in characterization of the fingerprint.

On the basis of our findings, it is suggested that the described method: (1) could be used as a prediction test for moderate to severe generalized root resorption in prospective orthodontic patients, and (2) should be used as a basis for further research, so that an even more accurate and more versatile prediction test may be developed.

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APPENDIX A

APPENDIX A

Copy of consent form which patients were requested to sign, prior to participation in this study.

IRB Number: 1/80-5c

LOYOLA UNIVERSITY MEDICAL CENTER
MAYWOOD, ILLINOIS
SCHOOL OF DENTISTRY
Orthodontics and
Preventive Dentistry and Community Health

INFORMED CONSENT

Patient's name:_____Date:_____

Project title: Some Metabolic Aspects of Root Resorption, A
                Preliminary Study in Normal, and Orthodon-
                tically Treated Patients

PATIENT INFORMATION

This study is an attempt to relate some minerals of the
blood and hormones controlling the minerals, to root
resorption, which appears in some orthodontically treated
patients.

Description and explanation of procedure:

   1.   Blood will be drawn to perform complete biochemical
         screening of the patient. The results will indicate
         physiologic function of various organ systems
         including enzymes and hormones that may vary within
         normal limits as the function of mineral metabolism.

   2.   Twenty-four hour urine tests which will allow us to
         determine renal function concerning some minerals.

Risks and discomforts:

   1.   Not to have breakfast before the drawing of the
         blood which has to be taken in the morning between 8
         a.m. and 10 a.m.

   2.   The collection of 24 hour urine.

Potential benefits:

     As a result of this study, it might be possible to predict the degree of root resorption which may occur in a patient, normally or when certain orthodontic procedures are done.

Alternatives: There are no alternatives, except no participation.

<div align="center">CONSENT</div>

I have fully explained to   _____
                       (patient, parent, legal represen-
                       tative)
the nature and purpose of the above-described procedure and the risks that are involved in its performance. I have answered and will answer all questions to the best of my ability.

                       _____
                       (principal investigator)

     I have been fully informed of the above-described procedure with its possible benefits and risks. I give my permission for my/my child's participation in this study. I know that _____ or his/her associates
          (prinicipal investigator)
will be available to answer any questions I may have. If at any time, I feel my questions have not been adequately answered, I may request to speak with a member of the Medical Center Institutional Review Board. I understand that I am free to withdraw this consent and discontinue participation in this project at any time without prejudice to my/my child's medical care. I have received a copy of this informed consent document.

     I understand that biomedical or behavioral research such as that in which I have agreed to participate, by its nature, involves risk of injury. In the event of physical injury resulting from these research procedures, emergency medical treatment will be provided at no cost, in accordance with the policy of Loyola University Medical Center. No additional free medical treatment or compensation will be provided except as required by Illinois law.

In the event you believe that you have suffered any physical injury as the result of participation in the research program please contact Dr. R.J. Blumenthal, Chairman, Institutional Review Board for Portection of Human Subjects at the Medical Center, telephone (312) 531-3384.

_____
(Signature: patient/parent/legal representative)

_____
(Signature: witness to signatures)

APPROVAL SHEET

The thesis submitted by Stavros Papaconstantinous, D.D.S. has been read and approved by the following committee:

> Hoerman, Kirk C., D.D.S., M.S.
> Director, Dental Auxiliary Utilization Program,
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> Klapper, Lewis, D.M.D., M.Sc.D., D.Sc.
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> Hospital, Hines
> Professor of Medicine, Loyola

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the thesis is now given final approval by the Committee with reference to content and form.

The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Science.

7/ 14/81
_____   _____
Date   Director's Signature