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# Hyperparathyroidism : anatomic, physiologic, pathologic, and clinical considerations

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HYPERPARATHYROIDISM

ANATOMIC, PHYSIOLOGIC, PATHOLOGIC AND CLINICAL CONSIDERATIONS


BY

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# TABLE OF CONTENTS

# INTRODUCTION

It is the purpose of this paper to present a review of the literature on the subject of hyperparathyroidism, to show that this condition is one which may have any of several clinical manifestations, and to demonstrate that it is in reality a rather common condition which should be of interest to the internist, surgeon, urologist, pediatrician, orthopedist, dermatologist, and neurologist.

Although we are primarily interested in the clinical phases of the subject, sections on the normal anatomy and physiology of the parathyroid glands have been included. Some knowledge of these fundamentals is essential to an adequate understanding of the physio-pathology of the disease and to a clear picture of the problems incident to parathyroidectomy and irradiation therapy. Regarding the various clinical syndromes, rather complete reviews of the literature have been made on those diseases in which overactivity of the parathyroid glands has been definitely proved to be the etiological factor. On the other hand, in those conditions where a parathyroid factor is only suspected, but not proved, only that information which pertains directly to the possible association has been used. To aid in the location of various items in the paper, brief outlines of the subject matter to follow have been inserted at the beginning of certain of the chapters.

It is not claimed that a complete review of all publications pertaining to hyperparathyroidism has been made. The almost innumerable contributions to the literature on this subject in very recent years has made such a task a tremendous one. We have reviewed all those papers available which offer any original work or contribute in any essential way to an understanding of the subject. The bibliography, for the most part, contains only those references which have been cited in the body of the paper, and which have been personally studied by the writer. The few exceptions to this statement have been adequately explained and credit rightfully given, either in the text proper or in the bibliography.

# PART I

## ANATOMY OF THE PARATHYROID GLANDS

### Outline

Gross Anatomy

      History
      Present Concept of Morphology
      Relations
      Blood Supply
      Nerve Supply

Histology

Embryology

# ANATOMY OF THE PARATHYROID GLANDS

## GROSS ANATOMY

### History.

Credit for the first description of the parathyroid glands
is usually given to Sandström who wrote of the external (inferior)
pair in 1880, but many previous investigators had observed the
organs and given sketchy anatomical reports concerning them. As
an example, in a lecture delivered in 1863 Virchow (161) commented
on isolated, separate, pea-sized, reddish knots which he had found
very frequently connected with the thyroid gland through loose
connective tissue. He remarked that they appeared to be either
small lymph glands or parts of the thyroid gland. Although Sand-
ström's original article has not been available to us, other re-
view of the literature indicate that he gave a very accurate des-
cription of the inferior glands and reported them to have been
constantly present as paired structures in a series of fifty,
human cadavers. (101 and 165). He called them "glandulae para-
thyroideae" and believed them to be embryonic residues of thyroid
tissue.

It remained for Kohn in 1895 (101) to begin the task of
differentiating between the parathyroids or "Epithelkorperchen",
as he preferred to call them, and true accessory thyroid tissue.
In the former he was never able to demonstrate colloid acini and

he believed that they never assumed thyroid function. In addition
to the external pair, mentioned by Sandström, Kohn described an
internal pair of "Epithelkorperchen" imbedded in thyroid tissue
and he remarked on the structural similarity of the two types.
At about this same time Gley (68) was beginning to work out the
relation of the glands to tetany, and it became definitely known
that the parathyroids were glandular entities. In 1897 Welsh (165)
after a study of forty human glands wrote an anatomical descrip-
tion which serves as the basis for our present day knowledge. The
only significant contributions to the anatomy since his time have
been those referring to physiological variations in size and loca-
tion.

## Present Concepts.

The parathyroid glands are usually four in number, rarely
two or three, and occasionally more than four. In addition, small
groups of parathyroid cells, called accessory glands, are quite
commonly found scattered over a wide area in the regions of the
thyroid, trachea and thymus. (119). In the infant the glands are
a light yellowish red color which gradually darkens to a yellowish
brown or mahogoney color in the adult. (123). Overlaid fat tissue
may superimpose a yellow or pale white color, however, as seen in
gross dissection. The glands are usually oval, rarely approximat-
ing a circular outline, and have molded edges. There is a definite
indentation on one side at the point of entrance of the blood
vessels so that the whole resembles a lima bean. (102). At times

one extremity tapers off to a fine point, running along a thin
stalk attached to the thyroid gland, but the parathyroid tissue
ceases before the stalk reaches the thyroid. (165). The presence
of surrounding fat tissue may also modify the external appearance
so that the organ appears more globular in shape, without molded
edges. The fibrous capsule is smooth and glistening. (123).
The normal glands vary in length from three to ten millimeters,
in width from two to six, and in thickness from one to four.
Pappenheimer and Wilens (135) have made an extensive investigation
of the weight variations and report as follows:

        Right Upper---62 cases---0.027 grams.
        Right Lower   51 cases   0.032 grams.
        Left Upper    59 cases   0.027 grams.
        Left Lower    58 cases   0.031 grams.

The combined weight varied in their series from 0.117 to 0.118
grams. The total weight was 20% greater in males than in females.
Gilmore and Martin (67) have investigated a much larger series of
glands and do not agree with this last statement. In their series,
the female glands were heavier than those of males--the mean weight
of the former being 0.1313 grams and the latter 0.1176 grams. In
the females they found a progressive increase in the combined
weight of the parathyroids up to the age of fifty years. In the
male, the glands reached a maximum weight between the ages of
twenty-one and thirty years.

Relations.

    With the development of surgical interest in the parathyroids

in recent years much work has been done on the normal and anomalous variations in the positions of the glands. Classically we think of a superior pair and an inferior pair, all on the posterior capsule of the thyroid gland. As early as 1897, however, Welsh recognized the fact that there was considerable diversity in location, but it remained for later writers to fully cover this subject. Lahey (102) has found the two most common positions to be: first, on the back of the thyroid close to the point where the inferior thyroid artery enters the gland, below the lateral exit of the middle and lower thyroid veins, and second, on the posterior lateral aspect of the upper pole of the thyroid, where it rests against the laryngeal cartilage. According to Millzner (119) in 30% of all cases one or more parathyroids are located on the true anterior or lateral thyroid capsule, instead of posteriorly. Of these, one-third are truly anterior. These variations appear to be associated definitely with atypical arrangements of the thyroid vessels. In addition parathyroids have been found embedded in thyroid tissue, (115), and between the trachea and the esophagus, as well as closely associated with the thymus gland either high or deep in the mediastinum. There are no reports of tumors or glands posterior to the deep cervical fascia resting on the longus colli muscles, and none anterior to the middle cervical fascia which lies just beneath the sternohyoid and sternothyroid muscles forming the so-called outer capsule of the thyroid gland. Within these fascial boundaries, however, parathyroids have been described in almost every conceivable

location from the pharynx above down to an almost unknown distance in the mediastinum. (Churchill and Cope, 40). The superior glands are more constant in position than the inferior pair. (119).

Blood Supply.

The blood supply of the organs is rather characteristic and constant and helps in the finding of them at dissection or operation. The inferior parathyroid arteries arise on each side from the inferior thyroid arteries or from one of the larger branches of the latter at a point near the lower pole of the thyroid gland. The superior parathyroid arteries arise on each side from one of the branches of the inferior thyroid artery or one of the anastomotic vessels between the superior thyroid trunk and the inferior thyroid artery. Occasionally it may come directly from one of the larger branches of the superior thyroid artery, proper. (Millzner, 119). Each gland receives but one artery, which enters at the hilus. Almost immediately the artery breaks up into large arterioles which in turn give way to large sinusoidal capillaries which run along the trabeculae. The parenchymal cells lie immediately adjacent to the endothelium of the capillaries. (123). Curtis (49) using an injection method in cadavers, came to the conclusion that the glands had a rich collateral circulation, even when all four arterial trunks were ligated. More recently, however, Morgan (123) has found that the arteries are of a terminal type with no anastomosis and that ligation will thus always cause infarction.

Venules accompany the arterioles and empty into a central channel. The latter communicates with numerous other channels which lie immediately under the capsule, forming a delicate reticulum. The final drainage is into the esophageal, tracheal or thyroidal veins. (165).

### Nerves.

Rhinehart (141) of Indiana University was the first to make an extensive investigation of the nerve supply to the parathyroids. He described a set of sympathetic fibers which arose from large nerve bundles around the thyroid and continued as nerve plexuses around the parathyroid arteries. These resemble the perivascular plexuses of the thyroid vessels, but differ in not being nearly so elaborate and in consisting of single fibers. The smaller arterial twigs in the gland carry with them a single nerve fiber, and there are no nerves around the veins. Rhinehart is of the opinion that these sympathetic nerves are entirely vasomotor for the supply of the blood vessels and that there are no special glandular or secretory nerves in the organs. None of the fibers leave the supporting connective tissue and penetrate into the cell groups. No ganglion cells have been reported. In addition to the above, a parasympathetic innervation has been described by Herrman (82). The inferior parathyroid nerve comes off the recurrent laryngeal at the point at which the latter crosses the main branch of the inferior thyroid artery. The superior parathyroid nerve is described as a

fine filament coming off the external branch of the superior laryngeal nerve as it passes downward to supply the cricothyroideus muscle. Herrman states that these nerves regularly join the corresponding arteries to form four, constantly present "stalks". These are constant, regardless of the number of parathyroids present. Any of the stalks, however, may supply two or more glands.

## HISTOLOGY

Kohn (101) in 1895 gave a brief and inadequate histological description of the parathyroids, and again it remained for Welsh (165) writing two years later to clarify this subject and lay down the basis for our present conception of the microscopic structure of these glands. Welsh described two main cell types, the principal cells and the oxyphile cells and listed four variations of each type. More modern writers have contined to use this classification essentially, but have limited the variations to two of each main type. The distinctions are not well defined, however, and it is generally agreed that all of the various types represent merely different maturation stages in the development of a single original cell type. Thus Morgan (123) calls the stem cell--the pale principal cell (chief cell of others) and believes that in progressive metamorphosis it becomes the dark principal cell, then the dark oxyphil and finally the pale oxyphil. He emphasizes

the fact that transitional forms may be seen between each of these types.

The pale, principal cells (chief cells) make up the bulk of the gland throughout life, but decrease in number relatively in old age. They are cuboidal to polyhedral in shape, measuring 7 to 15 microns in diameter. (123). The nucleus is large, irregularly round, measuring 5 to 6 microns in diameter and filled with chromatin granules. The cytoplasm is scant and in the process of fixation it retracts, giving rise to large vacuoles and an eccentric location of the nucleus. (36). These cells are essentially basophilic. Erdheim (62) believes that the fat content of these cells increases with age, but does not vary with the state of nutrition of the individual.

The dark principal cell (Wasserhelle Celle) represents the next step in the maturation of the parathyroid cell. Although Castleman and Mallory (36) state that it is not seen before puberty, Morgan (123) insists that it is present in infancy and increases relatively with age. The cell varies from 6 to 12 microns in diameter. The nucleus measures from 3.5 to 5.0 microns in diameter and is considerably more hyperchromatic and pyknotic than in the first type discussed. This staining of the nucleus is the chief method of differentiation between the two principal cells.

The next stage in development is represented by the dark oxyphil cells, which are relatively few in number. These cells are

6 to 14 microns in diameter, polygonal in shape and filled with granules of fairly uniform size. The granules stain bright red with the ordinary iron-hemotoxylin preparation. (123). The nuclei are small, measuring 4 to 5 microns and are definitely pyknotic. Most investigators are agreed that these cells first appear when the individual is about 10 years of age. (62 and 123). If it is true, as assumed, that these cells represent a later stage of development than the dark, principal cells, then we must agree with Morgan that the latter are present before puberty.

The end product of the metamorphosis is the pale oxyphil cell. It is present in greater numbers than the preceeding type. The cell is large and irregularly polygonal, varying from 13 to 15 microns in diameter and possessing a sharply defined margin. (36 and 123). Castleman and Mallory have stated that the cytoplasm of this cell shows no vesiculation, but Morgan describes a varying amount. The latter's material for study included more than three hundred normal human parathyroid glands, all carefully prepared in the Harvard laboratories. Consequently we are inclined to accept Morgan's statement in this regard. The nucleus of the pale oxyphil cell is large (4 to 5 microns), somewhat pale and has a homogeneous appearance.

Morgan reports that all the cells of the gland have a high glycogen content but it is most pronounced in the principal cell group. The cells are variously grouped into irregular masses, rows

or columns. Some of the groups or masses have a central alveoli lined by low columnar or cuboidal cells, usually of the principal cell type. The alveoli generally contain a clear colloid material which stains evenly with eosin. Maresch (114) described these in 1916 and believed them to be secondary, degenerative changes, but Morgan believes they are not the result of degeneration. From the deep surface of the capsule of the gland fibrous septa may be given off which penetrate the gland and produce an irregular lobule formation, rarely well marked. (165). In general there is no particular distribution of the various cell types throughout the gland.

## EMBRYOLOGY

Ludwig Schreiber (148) was among the first to investigate the origin of the parathyroids, but he erred in thinking that both pairs of glands developed from the fourth branchial pouch of the embryo, with later fragmentation. We know now that both the third and fourth pouches are concerned. Bodwin (69) of Cornell has very recently published an excellent paper on this subject, and his findings represent the present conception. The parathyroid primordia arising from the endoderm of the third pouches are closely associated with the primordium of the thymus until the embryo has a crown-rump measurement of 15 mm. (In the dog embryo).

Soon thereafter this relationship is lost, and during the separation
the accessory parathyroids mentioned above may appear. Small clus-
ters of cells break off from the main bodies and shift caudally in
close association with the cephalic portions of the thymus. During
the descent of the complex III as a whole, these fragments shift
caudally more rapidly than does the comples itself. But even the
latter descends a considerable distance and finally comes to lie
below the primordia of IV. Thus, the inferior parathyroids are
derived from the third branchial pouch. (123).

The superior glands are derived from the fourth pouch and first
appear in the dog in the 8.5 mm. embryo, when the complex IV is
connected to the pharynx by a still open but quite narrow duct. On
the dorse-lateral surface of the complex the parathyroids may be
identified as a definitely thickened area of small, darker-staining
cells. In the 12 mm. embryo the primordium of parathyroid IV has
the shape of a cone with the apex at the internal surface of the
complex and the base forming a portion of the external surface.
The organ then expands caudally, sometimes forming a surprisingly
long thin sheet of parenchymatous material. It then undergoes a
process of constriction and fragmentation. Various of the frag-
ments so formed may and are caught in the growth shiftings and are
separated by a considerable distance in the adult. (69). Thus,
accessory parathyroid material may be present near the superior
laryngeal nerve, along the carotid artery both cephalad and caudad
to the thyroid gland, as well as in the anterior mediastinum and

within or associated with the thymus itself.

In view of the above shown multiple origin and coincident, surrounding developmental shiftings in the region of the neck, the various anomalous positions of the parathyroids mentioned above becomes readily understandable. The fragmentary, accessory gland material scattered throughout the neck and mediastinum also suggests the possibility of tumor growth in this tissue, without actual involvement of the parathyroids proper, at all.

# PART II

## PHYSIOLOGY OF THE PARATHYROID GLANDS

### Outline

Early History

Calcium Metabolism

Parathyroid Extracts

Action of the Hormone
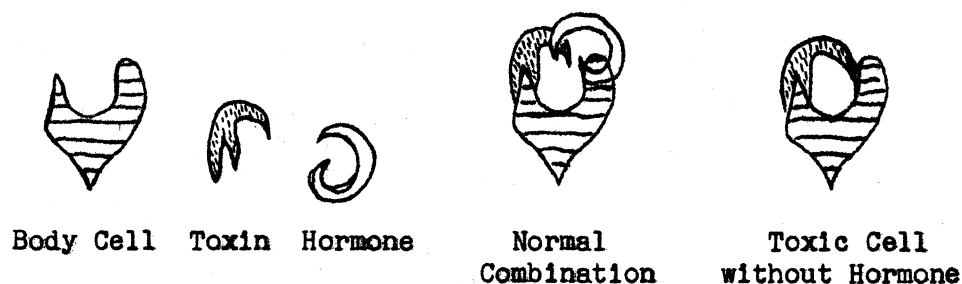
Parathormone and Vitamin D

Summary

# PHYSIOLOGY OF THE PARATHYROID GLANDS

## Early History.

The first inkling of the physiological importance of the parathyroid glands came in 1893 with Gley's (68) discovery that the tetany so commonly seen in experimental animals after thyroidectomy could be completely prevented by the preservation of two or even a single one of the "glandules thyroïdes", which we know as the parathyroids. Erdheim followed and confirmed Gley's work in 1906 (63). In the meantime various investigators were attempting to relieve tetany by the administration of various parathyroid extracts, without remarkable results. Finally Halsted (76) in 1907 reported having secured benefit not only from the use of serum but also from feeding both dried and fresh beef parathyroids, thus accomplishing what many others had failed to do. In addition he developed a method of successfully transplanting parathyroids in the posterior sheath of the rectus abdominis muscle.

The mechanism by which the active principle of the parathyroids prevented tetany became a much disputed question. In 1906 Mac-Callum (108) believed that tetany was caused by certain poisons in the body which normally would be neutralized by a hormone produced in the parathyroid tissue. This theory was bolstered up as late as 1916 by Paton and Findlay (136) after a long and elaborate series of experiments designed to prove that the toxic product causing tetanic convulsions was methylguanidine. They contended that the

secretions of the parathyroids rendered this substance innocuous.
Vines was still defending this conception in 1922. (160). Blum
(25) in 1925 discarded the guanidine conception but maintained the
idea of some toxic substance in the etiology of tetany. He form-
ulated an intricate theory based on a complement-fixation scheme,
as follows:



Body Cell   Toxin   Hormone         Normal              Toxic Cell
                                  Combination        without Hormone

## Calcium Metabolism.

It is unfortunate that these various investigators had so
solemnly followed MacCallum's suggestion, because in a paper pub-
lished only three years after his original one MacCallum, himself,
outlined the real key to the problem, which is one of calcium
metabolism. (MacCallum and Voegtlin, 109). This represents a
major step in the development of the physiology of the parathyroids.
MacCallum' group contended that calcium salts had an important
relation to the excitability of the nervous system, and that tetany
might be regarded as an expression of hyperexcitability of the
nerve cells due to some change in the calcium salts of the body
fluids. They then undertook studies of the metabolism in para-
thyroidectomized animals and found a marked reduction in the calcium
content of the tissues, especially of the blood and brain, an increased

output of calcium in the urine and feces, an increased output of
nitrogen in the urine, and increased output of ammonia in the
urine with an increased ammonia ratio, and an increased amount of
ammonia in the blood. They concluded that the parathyroid secretion
in some way controlled the calcium exchange in the body. It does
not come within the scope of this paper to discuss the many theories
as to the ultimate nature of tetany. Suffice it to say at this
time that parathyroid tetany, at least, is intimately concerned
with calcium metabolism.

Further studies on the calcium of the blood were made in
1913 by Rona and Takahashi (143) of Berlin. They dialyzed the
blood serum and found that both the diffusible and the non-diffusible
portions contained calcium. Additional biochemical investigation
revealed that the calcium of the non-diffusible portion was chief-
ly in a protein combination and that no inorganic calcium was
demonstrable. 50% of the total serum calcium was found to exist
in this form and the other 50% in the form of the freely diffus-
able, ionized, calcium hydrocarbonate. In 1920 Cushny's work (50)
led him to believe that 60% of the serum calcium was diffusible.
In 1922 Neuhausen and Marshall (128) reported that 10 to 20% of
the total existed in ionic form. These percentages were revised
again by McLean and Hastings in 1935. (116). These men developed
a frog-heart method of detecting the presence of calcium ions in
very great dilution and set about to determine the exact amount of
ionization of the calcium in the diffusible fraction. Their anal-
ysis of the serum calcium was as follows:

```
Calcium proteinate-------------5.0 mg.%.
Calcium ions-------------------4.5 mg.%.
Non-ionized calcium citrate----0.5 mg.%.

            Total-------10.0 mg.%.
```

They further demonstrated that the calcium proteinate and the calcium ions are in chemical equilibrium and the relationship depends upon the total amount of protein present. Thus, they found that an indirect method of analysis, involving the determination of the total serum calcium and total serum protein and consequent calculation of the calcium ion concentration gave results closely coinciding with those obtained in their direct analyses. The parathyroids control the amount of ionized calcium present, and consequently the activity of these glands can be measured by the determination of the calcium ions in the serum. We are reproducing a chart of McLean and Hastings which allows one to make this calculation, knowing only the total serum calcium and the total serum protein. (See following page). This chart has come to be of great value in ascertaining the existence of abnormal parathyroid states, in doubtful cases, and will be referred to again when we come to a consideration of the diagnosis of hyperparathyroidism.
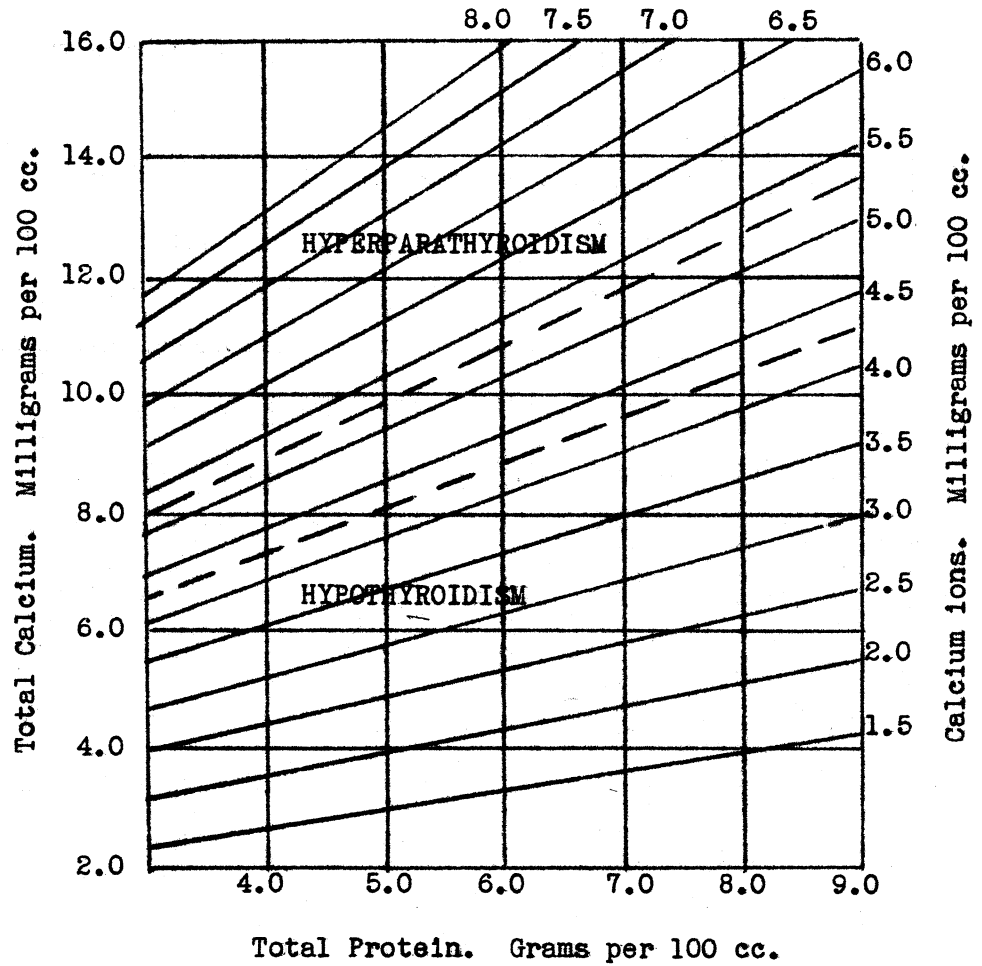
CHART FOR CALCULATION OF CALCIUM IONS
From McLean and Hastings (116)

The dotted lines on the chart represent the limits of the normal range of calcium ion concentration, from 4.25 mg.% to 5.25 mg.%. Above this there is hyperparathyroidism and below there is hypoparathyroidism. Knowing the total serum calcium and the total serum protein, the calcium ion concentration may be read directly from the graph.

Ninety-nine per cent of the calcium in the body is present in the skeletal system in the form of calcium orthophosphate and calcium carbonate. This calcium is in equilibrium with the blood calcium, so that the latter can be kept at a constant concentration by a shift of calcium from the bones to the blood or from the blood to the bones. (147).

## Parathyroid Extracts.

While the above mentioned chemical work was in progress other experimenters were busy along another line of research, that of developing a potent extract of the parathyroid glands. Probably about the first extract containing the active principle was made by Hanson of Minnesota (80) in 1924. His first preparation, "Hydrochloric-X", was essentially a hydrochloric acid extract of fresh bovine glands. A variation was "phosphotungstic acid precipitate" made by adding 1% phosphotungstic acid to the "hydrochloric-X" until a precipitate was obtained. Hanson believed that intramuscular injections of his products built up general body resistance by increasing the ionic calcium of the blood. With typical enthusiasm he proceeded to use the preparations in varicose ulcers, duodenal ulcers, urticaria, pruritus ani and a host of other miscellaneous conditions, and strangely enough, claimed good results in all of them. Vines (160) claimed similar results in England at about the same time. These therapeutic uses are still a matter of controversy and need not concern us farther.

At about the same time Collip (46) of Canada was working on the extract problem also. He demonstrated that he had obtained the active principle by using it to completely replace parathyroid tissue in experimental animals. He has kept animals with no thyroid or parathyroid glands living for five months with its use. In purifying his extract he used a salting out process, followed by dialysis and isoelectric fractionation. This extract has become known as "parathormone-Collip." It appears to be a complex protein deriviative or else intimately associated with such a compound. Collip established a unit of potency as one one-hundredth of the amount of extract which will produce an average increase of five milligrams percent in the blood serum calcium of normal dogs of approximately twenty kilograms body weight in fifteen hours. With the development of such an extract, capable of standardization, more exacting studies concerning the physiological action of the active principle could be made.

The Action of the Hormone.

Certain facts concerning the relationship of the parathyroid hormone to the calcium content of the blood serum seem fairly well established. The administration of the hormone results in a rise of the serum calcium. Long continued injection of even small amounts always result in death, while a single massive injection appears to be harmless. A total serum calcium of 18 mg.% has been seen after one injection, however. A value of 20 mg.% is as high as has been observed experimentally, but Snapper (153) reports a

human case of hyperparathyroidism with successive serum calcium determinations of 19, 21.4 and 23.6 mg.% respectively. The hyper-calcemia remains about constant at this level for some time and then gradually falls, to rise again just before death. (46). In experimental animals the first sign of toxicity is vomiting. The mechanism of the production of these essential changes, however, is a much disputed point and many theories have been proposed and vigorously defended.

Greenwald and Gross (72 and 73) believe that the parathyroid hormone is the substance that keeps calcium phosphate in solution in the blood or at least that the hormone is necessary to the preparation of some such hypothetical substance. In addition they believe that this substance actually dissolves the calcium phosphate. Consequently, with removal of the parathyroid glands there is a prompt shortage of the hypothetical substance and calcium phosphate is precipitated with a tendency to a lowering of both the phosphorus and calcium in solution. The concentration of the phosphate in the plasma, however, is kept at normal or even above by phosphates derived from the metabolism of proteins, phosphatides, etc., but the calcium content must fall unless calcium salts are administered. Thomson and Pugsley (157) have called attention to a serious fallacy of this theory. They point out that if it were true that parathormone makes the plasma a better solvent for calcium compounds then with the administration of calcium and hormone together, the blood should immediately assimilate the added calcium and the blood level

should rise. Experimentally this does not obtain. The blood calcium falls and rises only later, apparently coming from the bones. This last feature has lead these same authors, Thomson and Pugsley, to consider that the primary action of the hormone is in the bone tissue itself, where it promotes an osteoclastic activity with mobilization of bone calcium. This conception is given some experimental proof by the work of Selye (149). He found that if 14 day old rats are given one dose of 10 units of hormone, histologic bone studies will show an increase in the number of osteoclasts in 6 hours. However, it must be remembered that the blood calcium changes may appear much more quickly than this.

Still another theory is strongly advocated by the Massachusetts General Hospital group (5) and Ellsworth (61). After extensive experimental work, the Massachusetts group published the following findings in 1929, (4):

Following parathyroid hormone administration the following events take place in order stated:

1. Urinary phosphorus is increased abruptly, while the fecal phosphorus is little affected.

2. The serum phosphorus is decreased.

3. The serum calcium rises gradually. (Effect more marked when patient on high calcium diet.)

4. Gradually there is an increase in the urinary calcium excretion while the fecal calcium remains unchanged.

If, however, the serum calcium rises above a critical point at about 14 to 15 mg.%, then the urinary

phosphorus excretion falls and the blood phosphorus rises.

Following cessation of hormone administration the following events take place in order stated:

1. Urinary phosphorus abruptly decreases.

2. Urinary calcium gradually decreases to a level below that found before administration.

These findings are interpreted to mean that the primary effect of the hormone is on the phosphorus metabolism rather than on the calcium metabolism. Later Ellsworth (61) experimented upon four hypoparathyroid human patients with parathormone injections with similar results and a similar conclusion. The Massachusetts' group is still strongly defending this conception at the present writing (1,3,4,7,and 9), but there are some well defined defects that must be mentioned. One of the chief stumbling blocks to its general acceptance, as pointed out by Thomson and Pugsley (157) is that in dogs the intravenous injection of hormone may result in a simultaneous rise of both calcium and phosphorus. Aub (11) believes that the phosphorus never rises, however, except when calcium is given excessively and there is resulting kidney damage. Collip and Thomson (47) have thrown further doubt on this conception by the following reasoning, quoted directly from their paper:

"If

we suppose the ratio of ionized serum calcium to total calcium to approach constancy, and further that phosphate ions are at any given pH a constant small fraction of the total inorganic phosphate, and finally that the relation $(Ca^{..})^3 \times (PO_4^{...})^2 = K$ holds--this being the only logical

means of correlating calcium and phosphorus--then rough
calculation shows that decrease of inorganic phosphate
from 4 to 2 mg.% permits a rise of calcium only from
10 to 16 mg.%. It seems to us that the observed changes
in total phosphate in parathyroid overdosage, in clin-
ical hyperparathyroidism and especially in parathyroid
tetany are inadequate to explain the observed changes
in calcium on this theoretical basis."

Jaffe (92) believes that the function of the hormone is to
induce a state of acidosis which requires compensation through the
withdrawl of minerals from bone. Following this decalcification
of the bone, osteoclasts proliferate secondarily and phagocytose
the decalcified bone matrix. Stewart (156) gave the original im-
petus to this theory in 1927 when he showed that the administration
of calcium chloride or ammonium chloride caused a rise in the blood
calcium. But he admitted at the same time that parathormone seem-
ed to have no effect on the carbone dioxide combining power of the
blood. Without confirmation along this line, the acid-base bal-
ance theory cannot be definitely accepted.

As has been emphasized above, the usual effect of parathormone
on serum calcium is to cause an increase of the latter, but certain
variations in this relationship have been observed. Selye (149),
working with albino rats, demonstrated that with long continued
sublethal doses of parathormone, there was first an increase of
blood calcium with bone rarefaction and fibrous transformation in
the bone marrow and osteoclastic activity. Eventually, however,
with continued administration, the osteoclasts disappeared and

osteoblasts appeared, with resulting bone apposition. It even
lead to an increased calcium deposition in the bones. This is
the so-called "parathyroid hormone immunity". He further demon-
strated that very small doses may even result in the bone appos-
ition without going through the bone resorption stage at all.
Thus the effect of the hormone on the bone calcium seems to depend
upon the dosage given and the duration of administration.

Bodansky, Jaffe and Blair (28) have shown that under certain
conditions parathormone may be administered without any change in
blood calcium at all. This may occur when there is an increased
rate of excretion of calcium, or in the presence of an alkalosis
from some extraneous cause. The last situation was also reported
by Stewart (156). The feeding of phosphate solutions by mouth will
reduce a high blood calcium and a lack of vitamin D will also cause
a low serum calcium. (Barr and Bulger, 32).

Hoffman of Berlin (88) found in 1933 that in human pregnancy
the parathormone content of the maternal blood begins to rise above
the normal level about the third or fourth month, increases slightly
up to the eighth month and is greatly increased at the end of preg-
nancy. In spite of this, there was no demonstrable change in the
calcium content of the blood. The amount of the hormone present was
determined by an ingenious method of concentration and subsequent
bio-assay on dogs. This work has been confirmed in 1936 by Hamilton,
Dasef, and others at the University of Chicago. (77).

Blood volume changes subsequent to administration of parathyroid extract have been reported by Collip (46). In a normal dog receiving 5 cc. every four hours, the blood volume reached a peak at twelve hours and then gradually declined to below normal in about thirty-six hours. This was determined by repeated hemoglobin estimations. Blum (25) has demonstrated that the hormone is thermo-stabile, not dialyzable and is transmitted in mother's milk.

## Parathormone and Vitamin D.

No discussion of parathyroid physiology and calcium metabolism would be complete without some mention of the relationship to vitamin D. About ten years ago, through the work of Nonidez and Goodale (129) and Higgins and Sheard (83) it was shown that deprivation of ultraviolet rays in chickens also deprived of other sources of vitamin D regularly led to hypertrophy and hyperplasia of the parathyroid glands. It would seem that the parathyroids compensated for the lack of vitamin D. Wilder, Higgins and Sheard (168) continued with this work in 1934 and found that with a deprivation of vitamin D insufficient to cause rickets in chicks, the hypertrophy of the parathyroids could be prevented by the injection of parathormone. If, however, the vitamin D deficiency was great enough to cause definite rickets, the glands hypertrophied even in spite of parathormone injections. This interesting relationship between parathyroids and rickets will be mentioned again in a later paragraph. It is also to be mentioned at this time, that vitamin D in itself

tends to increase the serum calcium, probably through increased absorption of the mineral from the intestinal tract. Thus, given a high blood calcium because of parathormone activity, the administration of vitamin D only serves to accentuate the hypercalcemia. This fact has profound clinical importance to be discussed later.

Summary.

The parathyroid hormone:

1. Its presence in the blood stream usually results in an increase of the ionized portion of the blood calcium with bone rarefaction and an increase in the number of osteoclasts. Under certain conditions, however, the hormone may cause bone apposition and increase the osteoblasts, without material change in blood calcium.

2. A negative calcium balance and increased urinary excretion of calcium is promoted by the hormone.

3. The hormone usually promotes some change in the amount of inorganic serum phosphate, this change usually being a decrease but sometimes an increase.

4. The hormone tends to cause a negative phosphorus balance.

5. A decrease of the hormone available results in increased excitability of the neuro-muscular system, resulting in tetany. A low serum calcium is associated.

6. The hormone causes some increase in blood volume.

7. The amount of the hormone in the blood stream normally

increases during the last months of pregnancy.

    8. The hormone is thermo-stabile and not dialyzable.

    9. The hormone compensates for an absence of vitamin D. Vitamin D will increase a parathyroid hypercalcemia.

The Blood chemistry of normal hormonal balance:

    1. Blood calcium.

```
Calcium proteinate-----------------5.0 mg.%.
Calcium ions-------------------4.25 to 5.25 mg.%.
Non-ionized calcium------------------0.5 mg.%.

Total serum calcium------------9.0 to 11.5 mg.%.
```

These proportions will vary with the total serum protein value.

    2. Blood phosphates.

Inorganic serum phosphate--

```
In adults----------3 to 4 mg.%.
In children--------4 to 6 mg.%.   (131).
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PART III


THE FUNDAMENTAL AND ESSENTIAL PHYSIO-PATHOLOGY

OF HYPERPARATHYROIDISM


Outline

Changes in the Parathyroid Glands

      History
      Present Concept

Clinical Chemistry of Hyperparathyroidism

      Hypercalcinuria
      Hypercalcemia
      Phosphorus Balance
      Sources of Variations
      Rabbit test.
      Summary

Muscle Excitability

      Skeletal Muscle
      Use of Electrocardiogram

# THE FUNDAMENTAL AND ESSENTIAL PHYSIO-PATHOLOGY
# OF HYPERPARATHYROIDISM

We are primarily concerned in this paper with the clinical state of over-secretion of the parathyroid glands or hyperparathyroidism. It has become apparent in recent years that the manifestations of this state may be and are greatly varied, sometimes taking the form of a bone dyscrasia, sometimes posing as a kidney disease, and perhaps even invading the realms of dermatology and ophthalmology. If these diverse conditions are secondary to hyperfunction of the parathyroids, they all must have some features in common--the state of hyperparathyroidism must have certain characteristics which are constant in spite of the multiplicity of possible secondary developments. It now behooves us to determine the nature of these characteristic features. It should be immediately apparent that in the face of hypersecretion, we should find some changes in the parathyroid glands themselves. In addition, since the parathormone has been demonstrated to have profound effects upon the body chemistry and metabolism, we should expect to find some fundamental features of the disease in careful chemical studies. We shall discuss these various phases of the question in separate paragraphs.

## CHANGES IN THE PARATHYROID GLANDS

At this time we shall make no effort to correlate the various

pathological changes in the parathyroids with any definite clinical entity. Where such correlations exist will be pointed out later in the discussion of the individual manifestations of hyperparathyroidism.

## History.

As early as 1895 Kohn (101) intimated that the parathyroids could give rise to new growths. Credit is usually given to de Santi (56) for the first accurate description in 1900, however. Benjamins (21) followed in 1902 by describing a non-malignant parathyroid tumor which was so large that it caused a marked deviation of the trachea to the opposite side of the neck. Various investigators then followed with more exacting gross and microscopical descriptions of tumors of these glands. (Erdheim, 62, Harbitz, 81, Molineus, 121 and Schlagenhaufer, 145). Maresch (114) was one of the first to clearly differentiate hypertrophic and adenomatous growths of the glands. The early reported tumors were chiefly benign in character, but Kocher reported among the first of a malignant type. Wellbrock (164) of the Mayo clinic added another malignant tumor to the literature, describing a polymorphism of cells, hyperchromatic nuclei with many mitotic figures and invasion of the neoplasm through the gland capsule.

## Present Concept.

In the past few years the contributions on this subject have increased tremendously and various classifications of parathyroid

pathology have been proposed. We believe that the most comprehensive and generally accepted of these is the one proposed by Castleman and Mallory (36 and 37). It is given below with some modifications as indicated.

## Pathological Classification

I. Hyperplasia

    A. Wasserhelle, Generalized.

        The gland consists essentially of the Wasserhelle or dark principal cells with a tendency to acinar arrangement and a basal orientation of the nuclei. In appearance it resembles a renal adenocarcinoma.

    B. Chief Cell Type.

        This consists of normal sized chief and pale oxyphil cells arranged in pseudoglandular and papillary formations. There is very little fat and no Wasserhelle cells. There is an increase in the number of cells as shown by widening of columns, development of compact areas where columnar arrangement is no longer discernible and a tendency to acinar arrangement. The oxyphil cells are more numerous than is normal for the age of the individual. Grossly there is slight to moderate enlargement, a creamy gray color, and a consistency which is firmer than normal.

II. Neoplasia

    A. Chief Cell Types.

        1. Chief cell alone. (Found to be the most common)

            In these tumors there is no fat, no Wasserhelle or

pale oxyphil cells and only rare dark oxyphil cells. There is no mitosis observable. The cells are arranged in pseudo-glandular and columnar formation.

2. Chief cell type with Giant Forms.

This is similar to the type with chief cells alone but has the added feature of giant forms of exceptionally hyperchromatic chief cells measuring up to thirty microns in diameter. Many of these giant cells are multinucleated. There are no Wasserhelle or pale oxyphil cells present.

3. Transition Wasserhelle-Chief cell Type.

The cells are all closely packed together with no glandular arrangement. Oxyphil cells are usually absent. The main bulk of the cells appear to be intermediate forms between the Wasserhelle and chief cells.

4. Transition Oxyphil-Chief cell Type.

This represents an intermediate point between the chief and pale oxyphil cells. They are arranged in glandular and pseudoglandular formation. There are no true oxyphil cells present.

5. Glandular Cystic, Chief cell Type.

- This is made up of slightly enlarged chief cells lining and surrounding numerous cystic and glandular spaces.

B. Wasserhelle Celle Types.

1. Wasserhelle, Generalized.

This is an encapsulated tumor with a rim of normal tissue. There are no mitoses and no multinucleated cells.

2. Wasserhelle, Focal Type.

This is an encapsulated tumor composed of both
chief and Wasserhelle cells. The latter are arranged in circum-
scribed masses making up more than one-half of the tumor.

C. Oxyphil Types. (163)

These are composed of varying mixtures of the oxyphil
elements.

Castleman and Mallory add that they have collected ten cases
from the literature and two from their own series where there were
multiple tumors in each patient. In differentiating hyperplasia
from tumor the same authors stress the following features. In
hyperplasia there is microscopically a monotonous uniformity of
cellular arrangement with a uniformly increased stroma. In tumor
there is a gigantism of nuclei with hyperchromatism. The cells
present a protean picture, even in a single field and the stroma is
irregular in distribution with localized proliferative processes.
These criteria have been confirmed by Warren and Morgan (163).
It is mentioned that hyperplasia may be due to continuous, extern-
al stimulation, while tumor is determined by local autonomous fac-
tors. (36). It seems that all forms of parathyroid cells are
capable of producing hyperparathyroidism. (163).

If a graph is drawn showing the relationship between parathy-
roid hyperplasia or tumor formation and age groups of patients,
the peak of the curve is reached between the ages of 40 to 59 years.

This was determined from a study of 174 cases in the literature, of which 122 were females and 52 were males. The complete curve is given below:

Modified from Castleman and Mallory (36)

No. of Cases

Age Groups in Years
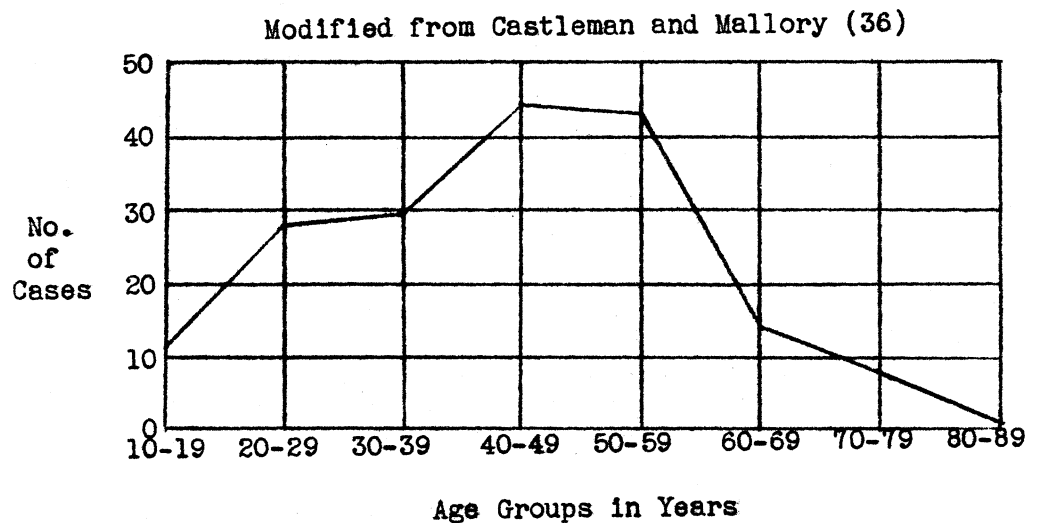
The assumption that the above forms of parathyroid growths give rise to an increased parathormone secretion was substantiated at least in part by the experimental work reported by Moolten et al (122). With the help of the E. R. Squibb and Sons laboratories these workers showed that the hormone content of a transitional oxyphil-chief cell adenoma from a patient with hyperparathyroidism was 105 units per gram of weight, or about two times the normal amount.

The first criterion, then, of hyperparathyroidism is the presence of some hyperplastic or adenomatous growth of the glands themthemselves. This feature will assist in the post-mortem diagnosis of the hyperparathyroid state, but is of little clinical aid, because the tumor is seldom palpable. It must be mentioned, however,

that some men have reported cases of hyperparathyroidism without either gross or microscopic changes in the glands (124 and 86) and conversely, others have reported cases without any other evidence of hyperparathyroidism except hyperplastic glands (75). These are definitely the exceptions to the rule.

## CLINICAL CHEMISTRY OF HYPERPARATHYROIDISM

We have already discussed the physiological and chemical effects of the parathyroid hormone in general and we are now ready to determine those features which may prove of value in diagnosing the presence of excess hormone in the body. Clinically it makes little difference whether the primary effect of the hormone is on calcium or phosphorus metabolism. The essential feature is that in the state of hyperparathyroidism the organism has a negative calcium and phosphorus balance. By this it is meant that the organism is losing more of these minerals in the excretions of the body than it is gaining in ingesta. It is generally conceded that of the two, the calcium balance is the more important.

### Hypercalcinuria.

In the normal individual 70 to 90% of the total calcium excreted is eliminated in the stool while the remaining 10 to 30% is excreted in the urine. (93). In hyperparathyroidism, however, these percentages are reversed and the great bulk of the mineral is excreted in the urine, as long as the kidney functions properly.

In addition, the total amount of calcium lost is greatly increased. In a classical case described by Mandl (111) the daily urine calcium was 54 mg.%. After parathyroidectomy this immediately dropped to 7.6 mg.%. In another case operated by Gold in 1927, the urinary calcium before operation was 412 mg. per day. It dropped to 26.4 mg. after parathyroidectomy. (112). This negative calcium balance is generally considered to be the crucial point in the diagnosis of hyperparathyroidism (17) but it is a difficult, clinical determination. It involves a very carefully regulated diet as to mineral content, careful repeated urine and stool studies and close observation over several weeks time, if accuracy is to be obtained. Consequently this method of diagnosis is not considered practical. (3).

## Hypercalcemia.

As a rule, the hypercalcinuria just discussed is associated with or is due to, a hypercalcemia. Knowing that this has been found rather regularly to follow experimental injection of parathormone, it would seem logical to assume that hypercalcemia would occur in hyperparathyroidism. This is usually true, and has been rather widely accepted as an essential criterion for the diagnosis of over-activity of the glands. Actually, however, to consider hypercalcemia as almost synonomous with hyperparathyroidism is a gross error. There are many features which affect the blood calcium level besides the presence of parathyroid hormone. Even in the face of hyperparathyroidism the blood serum calcium may be depressed to normal or below by any of the following mechanisms:

I, An absence of calcium and vitamin D in the diet so that the
total available calcium is very low (17); 2, An increased rate
of excretion of calcium (27); 3, Administration of bases by mouth
(27 and 156); 4, Increased phosphate in the blood either from ex-
cessive ingestion or retention by the kidney (32); 5, Kidney in-
sufficiency or uremia (93 and 151); and 6, In the presence of a
low plasma protein where the bound calcium value is so low that
even in the presence of a high ionized fraction, the total serum
calcium is still low (9, 74 and 116). Consequently hypercalcemia
is not a necessary feature in the diagnosis of hyperparathyroidism.
Elmslie et al (64) have reported proved cases of this type.

Conversely, the existence of a high serum calcium is not al-
ways indicative of a hyper-active parathyroid function. Hypercal-
cemia may also occur in other conditions, namely multiple myeloma,
excessive ingestion of vitamin D, polycythemia vera, excessive in-
gestion of calcium, gout, severe acne, and various bone dyscrasias.
(131). The differential diagnoses in these cases, however, are
usually not difficult.

In spite of the confusing facts presented above there should
be some method of detecting the disturbed calcium metabolism which
must follow parathyroid over-activity, from blood studies alone.
In any suspicious case we believe that the following laboratory
work is definitely indicated: total serum calcium (method Clark
and Collip, 43), total serum protein, blood non-protein nitrogen,

and serum inorganic phosphate (method of Bodansky, 26). With the
total serum calcium and protein values, recourse should be had to
the chart of McLean and Hastings on page 21 for an estimation of
the actual amount of calcium ions present. Hyperparathyroidism
may be suggested immediately. If the non-protein-nitrogen of the
blood is elevated, kidney insufficiency is apparent and the lack
of a hypercalcemia will not be considered important in ruling out
hyperparathyroidism. Likewise, in the presence of a high serum
phosphate, the diagnosis of hyperparathyroidism is still plausible
even with a normal calcium vlaue. An accurate history of the
patient's previous dietary regime may be of value in interpreting
the blood findings. As a last suggestion, it may be noted that
several investigators have stressed the point that repeated serum
calcium determinations should be made. The parathormone may appear
in "showers" in the blood, giving rise to an oscillating blood cal-
cium (9, 65 and 169).

Phosphorus Balance.

In hyperparathyroidism there is likewise a negative phosphorus
balance, but it is even more difficult to demonstrate by intake and
output studies than is the case with calcium. (93). Here again we
rely on blood studies for indications as to the state of phosphorus
metabolism in the patient. As has been previously pointed out, in
the endocrine state which we are discussing, there is usually a low
inorganic phosphate value of the blood serum. This may be present
even when the serum calcium is normal. (9). It, too, is easily

varied by the presence of kidney insufficiency and previous dietary features. Albright and others (4) have found that renal insufficiency complicating hyperparathyroidism may produce an absence of a hypophosphatemia and a reduction of the high partition of phosphorus excretion in the urine as compared to the feces. We believe the most reasonable view is that a hypophosphatemia is highly suggestive of hyperparathyroidism, but that the absence of such does not contra-indicate the diagnosis.

The following is a diagram which illustrates the sources of variation in chemical studies with reference to calcium and phosphorus. It has been modified from a diagrammatic representation by Albright (1).

### Sources of Variation
### In Calcium and Phosphorus Determinations
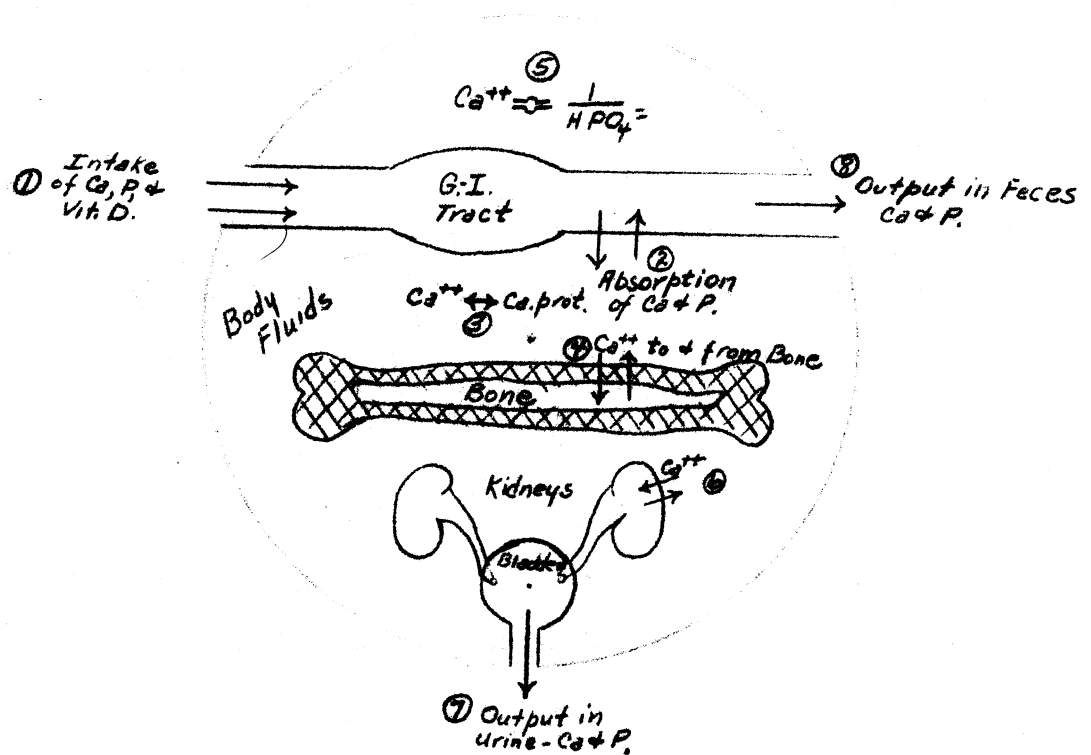
Key to diagram on preceding page:

1. Variable intake of calcium--concerned with available Ca.
   Variable intake of phosphorus-concerned with available P.

2. Variable absorption of calcium and phosphorus depending upon amount of vitamin D present and condition of bowel.

3. Variability of calcium existing in body fluids as calcium ions, depending upon activity of parathyroids, total serum protein and acid-base balance of organism.

4. Variable calcium exchange between body fluids and bone, depending upon amount of calcium available in bone and acid-base situation locally.

5. Variation of calcium and phosphorus roughly in inverse proportion.

6. Variation in excretion of calcium and phosphorus, depending upon concentration in blood, condition of kidney, and presence of polyuria or oliguria.

7. Clear fluid, gravel or stones finally secreted depending upon local conditions in tract and amount of minerals in urine.

8. Variation in fecal output depending on amount ingested, amount absorbed, and amount excreted into bowel via intestinal and accessory gland secretions.


In hyperparathyroidism the output (fecal and urinary) of calcium is greater than the intake. This is too difficult to determine directly, clinically. The blood picture is subject to so many variations, as indicated, that findings must be very carefully evaluated.

<u>"Rabbit Test."</u>

It is obvious that some method of determining the actual amount of parathyroid hormone in the blood stream should be of value in the diagnosis of hyperparathyroidism. Hamilton and Schwarz

(78) have developed the so-called "rabbit test" for this purpose.
A full grown rabbit which has been on a Steenbock-Bills stock diet
for at least three to five days and has been fasted overnight is
injected with ten cc. of the patient's fresh unclotted blood intra-
muscularly. It is also given 0.276 grams of calcium chloride in
10 cc. of water by stomach tube at zero, one, three and five hours
after injection. Blood is obtained from the rabbit for analysis of
the calcium content at zero, and fifteen minutes after each dose of
the calcium salt. Controls consist of one normal rabbit receiving
the same calcium dosage and one rabbit receiving the calcium plus
known parathormone material. The presence of hormone in the injec-
ted blood is reflected by a rise in the serum calcium of the rabbit.
The method has not been widely used and is probably too technical
and formidable for general, clinical use at the present time.
Shelling (151) believes that it will and should be used more in the
future.

Summary.

By way of summary of the diagnostic features of body chemistry
the following chart is given:

| Highly Suggestive of Hyperparathyroidism. | Compatible with Hyperparathyroidism. |
| --- | --- |
| 1. Serum calcium above 11 mg.%. | 1. Normal serum calcium with high NPN or high phosphorus. |
| 2. Normal calcium with a low serum protein. | 2. Normal serum calcium with history of diet deficient in calcium or vitamin D. |
| 3. Serum inorganic phosphate below 3.5 mg.%. (3). | |

4. Positive "rabbit test".

5. Increased urinary calcium output.

6. Total calcium excreted (urine and feces) greater than intake. (Absolute).

3. Normal serum calcium in presence of alkalosis from some extraneous source.

4. Normal or high serum phosphate with high NPN.

## MUSCLE EXCITABILITY

It is well established that the condition of hypoparathyroidism is accompanied by extreme irritability of the neuro-muscular system leading to the state which is called tetany. The reverse of this condition is seen in over-activity of the glands, where a marked atony of the muscular system may be seen. From the earliest descriptions of various hyperparathyroid cases we find constant mention of the associated muscular weakness and hypotonicity. (18 and 166). This weakness may similate Addison's disease, myasthenia gravis, or progressive muscular dystrophy. (74). Johnson (96) of the University of Chicago has done considerable experimental work on the production of hyperparathyroidism in rats, and has found that without exception, all rats injected with parathormone develop muscular weakness and hypotonia. Regardless of the nature of other accompanying symptoms, this feature must be considered as an integral part in the syndrome of hyperparathyroidism.

Skeletal Muscle.

One of the first to make actual measurements of the changes

in muscle excitability was Oppel of Leningrad (130). With a co-
worker, Dr. Schraer, he reported that 19 out of 22 patients showed
a reduction in the electro-excitation of the muscles from 5 to 10
milliamperes. Two years later Bourguignon and Sainton (29) made a
more detailed study of the same features in a case of proved hyper-
parathyroidism. They demonstrated that various motor points on the
muscles of the face and upper extremities had a chronaxie far below
the normal ranges. It is interesting to note that after parathyroid-
ectomy in this case the chronaxie of the motor points on the upper
extremity returned to normal while those of the face did not. The
reaction on the nerve points on the upper extremities also failed
to return to normal, even after treatment. They state that the
chronaxie does not vary exactly with the calcium content of the blood
but roughly so, and they suggest the use of these measurements in
the diagnosis of hyperparathyroidism.

Similar work has been done by Ballin (12) of Detroit who re-
ports that in hyperparathyroidism the chronaxie of the flexor pol-
licis may go from the normal 0.24/1000 seconds to 0.48/1000 seconds.
At the same institution Funsten (65) has developed a "chronaximeter"
which facillitates the determination of the optimum closing cathodal
contracture for the minimum time element. This instrument may
prove to be of considerable value.

### Use of Electrocardiogram.

This change in electrical excitation may also be manifest in
the heart muscle, by a shortening of the R-T interval in the electro-

cardiogram to around 0.2 seconds. (12,65 and 115). This is not invariably the case, however. Kellog and Kerr (98) made careful studies on two proved cases and found the Q-T interval to be 0.30 and 0.33 respectively which is low but still within the normal range. It is interesting to note, however, that after parathyroidectomy the same interval in both patients was raised to 0.36 seconds. In one of these cases, before operation there was a prolonged P-R interval, also. These writers conclude, however, that these changes are not of sufficient degree to be of value in the clinical diagnosis of hyperparathyroidism. After reviewing the various papers on this subject we have come to the conclusion that a shortened R-T interval must be considered confirmatory evidence of hyperparathyroidism, but a normal R-T interval does not contraindicate the diagnosis.

It must also be stated that a decreased response to stimuli (lengthened chronaxie) of the skeletal muscles must not be considered as pathognomonic of the disease, because it may be obtained in general physical debility (48), in a variety of neuromyopathies and even in normal persons when in a state of fatigue (151). It is plain, however, that we must add studies of muscle excitability to our list of tools useful in the diagnosis of hyperfunction of the parathyroids. The demonstration of a decreased muscular response, the finding of an abnormal calcium and phosphorus metabolism as indicated in the chart on page 45 and the presence of a parathyroid tumor or hyperplasia either in life or at autopsy constitute the

essential physio-pathology of hyperparathyroidism. The clinical results of these fundamental changes vary with the severity of the process, the duration of the condition and the constitution of the individual.

# PART IV

# CLINICAL TYPES OF HYPERPARATHYROIDISM

## Outline

General Remarks

Bone Disease in Hyperparathyroidism

    Generalized osteitis fibrosa
        cystica
    Rickets and Renal Rickets
    Arthritis
    Miscellaneous bone diseases

Kidney Disease and Hyperparathyroidism

    Nephrolithiasis
    Parenchymal Kidney Damage and
        Hyperparathyroidism

Miscellaneous Diseases

    Scleroderma and Raynaud's Disease
    Syndrome of Blue Sclera

Summary

# CLINICAL TYPES OF HYPERPARATHYROIDISM

## GENERAL REMARKS

The existence of parathyroid tumor growths was recognized for many years before any correlation with any definite disease entity or clinical syndrome was made. At last in 1926 through the work of Mandl (108) it was proved that the glands were very intimately associated with osteitis fibrosa cystica or Von Recklinghausen's disease of bone. There followed then a long period when clinicians believed that this was the only clinical manifestation of over-activity of the parathyroids. It has only been in the last five or six years that the profession has become keenly aware of the pleomorphism of hyperparathyroidism and the frequency of its occurrence. In this chapter we shall discuss the various clinical types of this endocrine disturbance, and correlate them with the essential physiopathology as previously outlined.

Considering all the syndromes together as one entity, there is an interesting geographical distribution of reported cases. In 1936 Wilder and Howell (169) of the Mayo clinic listed the following:

| Region | Proportion of Cases |
|---|---|
| North Atlantic States | ████████████████ |
| Scandinavia, Belgium and Holland | ██████████ |
| England and Scotland | ████████ |
| Upper Mississippi Valley | ██████ |
| Germany and Austria | █████ |
| France | ████ |
| Italy | ██ |

The cases so graphed are only those in which there is absolutely no doubt as to the diagnosis. Wilder and Howell believe that the high incidence in the north Atlantic states must be related to the lack of ultra-violet radiations (source of vitamin D) in that particular region. In the center of that region, however, local investigators point out that the rickets belt and the hyperparathyroid belt do not coincide. (9). They believe that the majority of clinics in the country are not "parathyroid conscious" and are not on the look-out for possible cases.

As we begin to divide hyperparathyroidism into several separate syndromes, we must say that the two chief organ-systems involved are the bony-skeleton and the urinary tract. In addition there is some evidence that the skin, the sympathetic nervous system and even the eyes may occasionally be damaged. For the sake of convenience we shall divide our discussion into three main sections, including bone disease in hyperparathyroidism, urinary tract disease in hyperparathyroidism and miscellaneous parathyroid syndromes. It must be borne in mind, however, that these various manifestations overlap each other and more than one may be found in the same patient.


BONE DISEASE IN HYPERPARATHYROIDISM

Generalized osteitis fibrosa cystica: Von Recklinghausen's Disease

History.

Although this disease has been recognized by the medical

profession for less than fifty years, it is by no means a new disease. Denninger (57) reports the finding of the skeleton of a prehistoric American Indian with marked deformities typical of osteitis fibrosa cystica. This skeleton is estimated to be about 1000 years old.

The clinical condition which we know as osteitis fibrosa cystica was described as early as 1877 by Langendorff and Mommsen (103) although they did not differentiate it from other forms of osteomalacia. They described patients who had intervals of bone pain with high phosphoric acid and calcium carbonate excretion in the urines. They also analyzed bone specimens and there found a low calcium and phosphorus content which they believed to account for the multiple fractures and hemorrhagic bone cysts observed. Two years later Hirschberg (85) described another rather typical case of a thirty-five year old woman with pain, weakness and lameness of the extremities, and multiple fractures. Hirschberg called attention to the need for chemical investigation of such cases. It remained for Von Recklinghausen (162), however, in the year 1891, to actually differentiate this disease from other bone dyscrasias. As a result of a comprehensive paper written on the subject, the disease still bears his name. He described a number of cases of bone disease, but his cases 5 and 7 , which he differentiated from other dyscrasias, constitute the discovery of generalized osteitis.

The relation between this bone disease and the parathyroid

glands was not even suspected, however, for many years. Erdheim
(62) described a case with associated parathyroid hyperplasia in
1903. Askanazy (10) in 1904 reported on a case with multiple frac-
tures and bones of Von Recklinghausen's disease, associated with a
neck tumor which he suggested might have been of parathyroid origin.
In 1913 Molineus (121) reported three cases of typical generalized
osteitis fibrosa cystica, in all of which he found parathyroid
tumors. Harbitz (81) followed in 1915 with the description of
another case of "osteomalacia" associated with an adenoma of a
parathyroid gland. Other investigators followed with similar re-
ports, but even as late as 1922 no agreement had been reached con-
cerning the relationship. At this time Morton (125) of Yale wrote
the first American or English paper devoted entirely to a discus-
sion of the disease and stated that although an endocrine etiology
had been suggested, nothing had been proved concerning the etiology
of the condition. In spite of this, as early as 1915 Schlagenhaufer
(145), after a study of two cases with osteomalacia-like changes
and parathyroid tumors demonstrated at autopsy, had suggested that
in such cases operative removal of the hyperplastic parathyroid gland
should be attempted. Maresch (113) agreed with this suggestion, but
no one had enough faith in the procedure to try it until ten years
later. At this time, in 1925, Mandl (111) performed the first
parathyroidectomy as treatment for osteitis fibrosa cystica. His
patient was decidedly benefited by the operation and the etiology
of the disease was established, at least in part.

The story of this pioneer surgery is of sufficient interest
to bear a more detailed discussion. Mandl had collected from the
literature some 44 cases of bone disease associated with changes
in the parathyroid glands. Erdheim (62) who first described such
a combination believed that the gland changes were secondary to
the bone disease and merely represented a compensatory mechanism.
Reasoning that if such were true, benefit should be obtained by
giving the patient more secretion, Mandl first transplanted four
parathyroid glands from a street accident victim into the pre-per-
itoneal tissue of a patient bedridden with Von Recklinghausen's
disease. There was no improvement in the patient. Consequently,
Mandl decided to try the reverse procedure, and on the 30th day of
July, 1925, with local anesthetic, he removed a large red mass ly-
ing in the position of the lower, left parathyroid gland. On
microscopic examination this proved to be parathyroid tissue. Even
at the end of the first day the patient felt better. The man had
previously been excreting enormous quantities of calcium in the
urine. Six days after operation this had ceased. By the end of
August, the pain in his extremities, which had previously been ex-
cruciating, was reduced to a minimum. By October the pain was al-
most completely gone and the patient was able to walk easily. Mandl
believed that this case proved that the parathyroid change was not
a work hypertrophy as suggested by Erdheim but was the primary cause
of the disease. Hoffheinz (87) had previously supported this same
conception.

Incidence.

From the cases reported in the literature it would seem that the disease is more frequent in the female than in the male by a ratio of three to one. (74). Jaffe (93), however, states that there is no sex factor. The age incidence varies greatly but the majority of cases reported have fallen in the middle age group, from thirty to fifty years. Attention is called agin to the age groups in which parathyroid tumors have been found, as illustrated on page 38. It has also been mentioned that the incidence seems to be greater in those regions where there is a minimal amount of ultra-violet radiation, but the significance of this fact is not well understood.

Etiology.

Since the first parathyroidectomy by Mandl, it has been well established that Von Recklinghausen's disease is primarily an over-function of the parathyroids. The experimental production of the bone changes by the administration of parathyroid hormone has been readily done by a number of investigators (28,96 and 150) and this has added the final bit of etiological evidence. In the great majority of cases one will find the presence of a parathyroid tumor or hyperplasia. The ultimate etiology of this over-growth is not clear. Wilder and Howell (169) believe that in a certain number of individuals there are regularly some groups of embryonic cells or rests in the glands, which, in the absence of vitamin D are stimula-ted to growth, with the formation of an adenoma. The adenoma, once

in the stage of multiplication, knows no restraint and the picture
of hyperparathyroidism soon follows. In those individuals who
possess no such embryonic rests of parathyroid tissue a diffuse
hyperplasia rather than an adenoma will develop. Even this may
over-compensate from the lack of vitamin D and give rise to the
same end picture. This theory has not been confirmed as yet by
experimental work or by other investigators. Goldman and Smyth
(70) have reported generalized osteitis fibrosa cystica in brother
and sister, so that the possibility of an hereditary or familial
factor is suggested.

Another point of interest surrounds the finding that all cases
of hyperparathyroidism do not show osteitis fibrosa, or any bone
changes at all. Why do some patients develop such lesions and others
escape? Davidson (53) believes that the amount of bone change in
hyperparathyroidism is proportional to the daily calcium phosphate
loss from the body multiplied by the duration of the disease. By
total loss he means that amount excreted in the urine and feces less
the quantity ingested. Thus, a short duration with a high calcium
intake would make marked bone changes unlikely.

The disease usually exists by itself, as a well defined clini-
cal entity, but Bulger and Barr (32) have suggested that the condi-
tion may also occasionally develop secondary to other bone disease
such as multiple myeloma, and metastatic bone tumors. The disturb-
ance of calcium metabolism by the neoplasms may be sufficient to

stimulate the parathyroids to compensate and finally over-compensate, so that ultimately the picture of hyperparathyroidism is superimposed on the original disease. Bulger and Barr have collected eleven such cases, all with a high blood calcium, from the literature. Klemperer (100) reports a case of bone metastasis from a breast adenocarcinoma with additional bone destruction. One hyperplastic parathyroid was found at autopsy.

The very frequent occurrence of osteitis fibrosa and kidney disease in the same patient brings up still another question concerning etiological relationships. We shall hear more of this relationship later in this paper, but it should be mentioned at this time that Albright et al (8) has recently cited 3 cases with bone changes indistinguishable from those seen in primary hyperparathyroidism where the etiological factor seemed to be fundamentally a renal insufficiency, followed by phosphate retention and consequent compensatory hypertrophy of all the parathyroids. Albright calls this "renal osteitis fibrosa cystica".

To recapitulate, Von Recklinghausen's disease is a definite clinical entity which develops as the result of over-activity of the parathyroid glands. The parathyroid changes may appear without known cause, may perhaps be related to vitamin D deficiency, or may develop as an exaggerated compensatory mechanism secondary to other bone dyscrasias or to renal insufficiency.

<u>Pathology.</u>

We have already discussed the fundamental pathology of all types of hyperparathyroidism. The osteitis fibrosa syndrome may be found associated with either an adenoma or simply a hyperplasia of the glands, and apparently any of the cells of the gland may be concerned in the process. The chief cell, the transition Wasserhelle-chief cell, the transition oxyphil-chief cell, the Wasserhelle cell and the mature oxyphil cell have all been incriminated. (36 and 163). In Albright's "renal osteitis fibrosa cystica" the hyperplasia of the parathyroids was decidedly different from the hyperplasia seen in the ordinary primary form of the disease. In the former the cells were not markedly enlarged with highly vacuolated cytoplasm as in the latter. (2). The disturbed calcium and phosphorus metabolism of the diesase is that characteristic of all hyperparathyroidism, and has been discussed previously.

We are chiefly concerned in this section with the pathological changes in the bones seen in this disease. As explained by Jaffe (92) the fundamental bone change is a decalcification or osteoporosis. This osteoporosis is unlike that of senile or disuse atrophy in that the Haversian systems are enlarged and the trabeculae of the spongy bone are thin with greatly widened intertrabecular spaces. This is the fundamental pathology, and the further changes that may occur are dependent upon the age of the patient, the duration of the disease, the intake and availability of mineral salts, the speed

and degree of decalcification and stresses and strains on the
skeleton. In the production of the osteoporosis, Cuthbertson and
Mackey (51) believe that there are two mechanisms, a diffuse and
a local. In the first, bone is changed to osteoid tissue by the
solution of its calcium phosphate complex and the osteoid tissue
in turn reverts to a more primitive state, in the form of a rather
cellular, soft, fibrous tissue. These changes may be due to a
hyperemia. The local mechanism is a focal or lacunar resorption,
dependent upon the presence of a greatly excessive number of ost-
eoclasts. The latter frequently come to form tumour masses, the
so-called osteoclastomata or myeloid sarcomata. By experiments on
hyperparathyroidism in animals, Jaffe, Bodansky and Blair (94)
found that the portions of the skeleton most susceptible to this
decalcification process are those in which bone formation is most
active. Thus the pronounced susceptibility to resorption of the
spongy bone of the metaphyses of the long tubular bones, costo-
chondral junction, cortices of the shafts, cortices of the ribs
and the bones of the skull and lowe jaw is explained. Bone resorp-
tion and bone deposition are processes that go on in all bone con-
stantly. When the rate of either of these processes is increased,
it is increased in all bone, but both processes are more rapid in
the regions of active growth, irrespective of the anatomic structure.

A more specific description of the pathology follows. (Chief-
ly from Jaffe, 92). In the medullary cavities of the long bones
there are scattered, grayish white, fibrous foci in which finely

reticulated bone may be felt. The entire cavity is traversed by
single and multilocular cystic spaces, which sometimes extend even
beneath the periosteum. In certain regions there may be old hem-
orrhage and brownish, discolored areas. The bony trabeculae of the
spongiosa are very atrophic but immediately beneath the articular
cartilage there is usually a slight amount of marrow fibrosis and
new bone formation. The articular cartilage is characteristically
entirely passive. Whatever remains of the original cortex is al-
ways thin, owing to marked resorption.

Microscopically there is some osteoblastic activity but the
great emphasis is on the osteoclasts. In addition to the new bone
there are large areas of connective tissue formation without bone.
Multinucleated giant cells and extravasated blood may appear.
Occasionally in certain regions, the deposition of new bone is main-
tained in excess of resorption so that cement lines appear, but
these are never as irregular, as numerous or as thick as those seen
in Paget's disease. Albright, Drake and Sulkowitch (8) have sum-
marized the findings as follows: evidence of rapid bone destruction
(osteoclasts), evidence of rapid bone repair (osteoblasts), evi-
dence that bone matrix which is being laid down is being calcified
(normal width of osteoid seams), and fibrosis of marrow spaces.
The condition is thus definitely different from osteomalacia in
which there are wide osteoid seams, very few osteoclasts and much
less evidence of fibrosis.

These essential changes go on in all the bones of the body.
The decalcification and fibrosis changes the consistency of the
bones, so that bowing and various deformities may take place. Thus
in the vertebral column kyphosis or scoliosis may appear. Because
of the decalcification of the bodies, the turgid, intervertebral
discs become expended and discoid with a reduction in the superior-
inferior diameter. There may be hemorrhage in the marrow of the
vertebrae. The thoracic cage becomes badly deformed with atrophic
irregular shaped ribs which may even impinge on the iliac crests.
The brim of the pelvis may become asymmetrical, distorted and re-
duced in size, while the iliac bones expand. The calvarium may be
thin, atrophic and pliable or it may become thickened. The reason
for the latter is not known. Osteoporosis of the alveolar bones
with loosening of the teeth may be a conspicuous feature. (147).

In the advanced stages of the disease, brown, tumor-like les-
ions composed of giant cell masses may appear. These are known as
giant cell tumors. They may be very small but have been known to
reach the size of a child's head. The giant cells are identical with
the osteoclasts, have phagocytic activities and often contain red
corpuscles or hemosiderin. They probably do no represent genuine
tumors or blastomas, but there is some difference of opinion as to
their pathogenesis. Goodman (71) believes that there are always
two factors in the development of these "tumors"--bone rarefaction
from hyperparathyroidism, and injury locally to the bone. The in-
jury causes a hemorrhage which later organizes and gives way to

granulation tissue.  As the latter grows it presses on the walls of the bone cavity and they expand.  As the bone is being pushed out and destroyed by pressure, the giant cells appear as they always do when there is bone destruction.  Goodman states that giant cell tumors and granulation tissue are similar microscopically and macroscopically, both respond to cauterization, the growth of both can be slowed or completely inhibited by irradiation, operative removal in both will result in cure, and both have a tendency to recur if treated indifferently.  Consequently, he believes the two are identical.  Jaffe (92) also believes that the tumors follow hemorrhage but does not insist on a traumatic origin, and prefers to believe that the reaction is of a special type in the nature of an inflammatory new bone formation.

Still another frequent finding in the advanced stages of the disease is cyst formation.  The cysts usually occur within the metaphyses or diaphyses of the long bones and in the larger areas of the fibrous marrow.  Larger cysts may be lined by a condensed layer of fibrous tissue, beneath which may be new bone.  Within the cysts may be found coagula of thin albuminous material, mixtures of red blood cells and phagocytic cells and sometimes cholesterol crystals. Jaffe lists three possibilities as to the origin of the cysts:  (1) result of edema and degeneration of the fibrous marrow, (2) hemorrhage and (3) degeneration occurring within giant cell tumor areas.

As a result of the decalcification of the bones, multiple,

pathological fractures are common in these patients. The perios-
teal reaction is sluggish but in spite of this fractures heal fair-
ly readily.

It must be emphasized that the bone changes of the disease
may be very marked or very slight, and that the complications of
giant cell tumors, cysts, and marked deformities are not necessary
to the pathological picture. Thus Albright, Aub and Bauer (3)
have listed three types of hyperparathyroidism with bone changes--
osteoporotic form, the classic form (advanced Von Recklinghausen's
disease), and a form similating or complicated by Paget's disease.
The essential pathological picture to bear in mind, however, is a
generalized porosis of the entire skeleton with cyst formation,
osteoclastomata (giant cell tumors), and thickening and porosity
of the skull, accompanied by hypotonicity of the musculature and a
negative calcium balance. (91). The cause and effect relationship
between the bone changes and the parathyroid hormone is a matter of
theories. These have been discussed under the heading "Physiology
of the Parathyroid Glands".

In addition to the parathyroid and bone pathology of Von
Recklinghausen's disease other phenomena are frequently seen.
Chief among these is metastatic calcification in practically all
the tissue of the body. Dawson and Struthers (54) described a clas-
sical case of this type in 1923. Their patient had calcareous me-
tastases in the kidney, intestines, bronchial mucosa, blood vessels,

heart wall, lungs, lymph glands, liver, spleen, striate muscles,
pituitary and pineal body. Jaffe (92) emphasizes that in the lungs
the connective tissue of the alveolar walls, the capillaries,
arteries and veins bear the brunt of the deposition. The inter-
glandular tissue of the gastric mucosa is also a frequent site.
This is especially true in the acid secreting portion of the stom-
ach. In the kidneys the tubular epithelium and the connective
tissue stroma are both involved. The importance of this renal
involvement will be mentioned more in detail later.

## Clinical picture.

The disease invariably has an insidious onset with any of a
number of varied complaints. Gutman, Swenson and Parsons (74)
state that the disease most frequently begins with pain, usually a
dull ache in the lower back, legs or arms, intensified by exercise
and often associated with stiffness in the joints. Some writers
state that oral symptoms, incident to the osteoporosis of the al-
veolar bone may precede the actual diagnosis of hyperparathyroidism
by six months to six years. (147). The symptoms mentioned most
frequently in the literature are weakness and fatigability, chronic
constipation, anorexia, bone, muscle or joint aches and pains, poly-
uria, polydipsia and gravel in the urine. (3, 20, 93, 151). The
condition becomes progressively worse, with the appearance of naus-
ea and vomiting, severe recurrent abdominal pain (especially in
younger individuals according to Jaffe, 93), bone tenderness and

finally skeletal shortening due to a kyphosis. The height of the patient may be diminished by ten inches in a few years. (151). The complete symptomotology is comprehensive and the following outline may help to give some conception of it. The symptoms are grouped according to the suggestion of Albright, Aub and Bauer (3) with additions from other authors as indicated.

### Outline of Symptomotology

Symptoms due to the hypercalcemia:

- Weakness, fatigability and lassitude.

Anorexia, nausea and vomiting, and constipation.

Weight loss.

Recurrent abdominal pain (Boyd, 31).

Anemia with leukopenia. (31).

Slow pulse rate, (Shelling, 151).

Insomnia, vasospastic phenomena, diminished or absent knee-jerks. This constitutes the essentials of the so-called "functional" type described by Leopold (104).

Note: It is emphasized by Albright and his group that in certain cases none of the above symptoms may appear, because there is no actual hypercalcemia.

Symptoms due to skeletal disease:

Bone pain and tenderness. Muscle and joint aches and pains. Bone tumors and cysts.

Kyphosis and scoliosis with skeletal shortening and possibly paraplegia. (Bauer, 20 and Dresser, 60).

Back pain.  Flat foot.

Fractures.  Hyperextensibility of joints.

Jaw stiffness and looseness of teeth.

Symptoms due to excretory factors:

Polyuria and polydipsia. (Due to excessive amount of calcium

excreted in urine, and need for a solvent.)

Nocturia and enuresis.

Urinary gravel, and urinary colic.


It is interesting to note the various diagnoses which had
been given at one time or another to 17 cases reported in 1934
from the Massachusetts Hospital. (3).  These diagnoses included
flat foot, arthritis, neurasthenia, osteomalacia, neuritis, osteo-
porosis, enchondroma, solitary cyst, giant cell tumor, rickets,
renal rickets, marble bone, rheumatism, nephrolithiasis, sarcoma
of ilium, sacroiliac disease, fractured vertebra, neurosis and
epulis of jaw.  It is apparent that osteitis fibrosa cystica may
be picked up by the orthopedist, the neurologist, pediatrician,
urologist, internist or the general surgeon.  The early and border-
line cases are those requiring the greatest diagnostic skill.
Leopold (104) believes that many so-called "neurasthenics" are in
reality victims of a functional type of Von Recklinghausen's dis-
ease.  The bone changes may be minimal or very marked.


Diagnosis:

In the presence of obscure aches and pains or any of the above

listed symptoms, the question of a possible Von Recklinghausen's disease should be raised. Probably the first laboratory procedure indicated in such patients is roentgenological study. Camp (34) of Rochester and Dresser and Hampton (60) of Boston have written excellent papers on this phase of the subject. The fundamental change in the skeleton as seen in a radiogram is a uniform, miliary, granular osteoporosis. The miliary mottling is practically pathognomonic of the disease and is best seen in the flat bones, especially those of the calvarium. In early cases, the bones have a ground glass appearance. Later, cystic changes tend to appear, particularly in the jaws, pelvis, long bones, ribs, metatarsal and metacarpal bones. More specifically the changes as seen by X-ray are as follows:

Skull: The bones of the vault show a generalized finely mottled, granular texture which is produced by closely spaced areas of diminished density alternating with bone more dense than normal. The entire calvarium is thickened from 0.5 to 1.0 cm. above the average (film taken at four feet). The inner and outer tables can not be differentiated, and the diploë are usually not visualized. There may be a flattening and dimunition in depth of the fossae posterior to the sella turcica, due to the softening, but the sella itself remains normal. Cystic areas may occur in the maxilla and mandible and these may be the first complaint of the patient. There may be loosening of the teeth, not because of any change in the dentures, but because of absorption of bone in the jaw, about

the roots.

Vertebrae: Here again there is a change in the texture of the
bone in the form of a granular osteoporosis plus coarse, perpendic-
ularly striated fibrocystic changes. The contour of the vertebral
bodies may be normal but frequently there is a narrowing of the
bodies with scoliosis or compression deformities with a dimunition
of stature.

Pelvis: There is also a granular osteoporosis of the pelvis
but this alteration is not as obvious as is the striated, fibro-
cystic change. There is extreme decalcification with replacement
of normal bone by large, trabeculated or occasionally non-trabec-
ulated cystic areas. As a result of the change in texture there is
frequently some softening with alteration in the general contour of
the pelvis, suggesting the rachitic type. The whole picture often
suggests a sacro-iliac arthritis.

Ribs: The ribs participate in the general decalcification and
frequently show cysts, particularly on the superior and inferior
margins.

Extremities: The granular osteoporosis is not so evident, but
there is a definite thinning of the trabeculae and the cortex of
the long bones. Small cysts are commonly located near the ends of
the diaphyses. In the region of such cysts the cortex may be either
markedly expanded or definitely thinned. There is no evidence of

periosteal proliferation and no associated soft tissue tumors.
Evidence of numerous previous, healed fractures is commonly present.
In young people, there may be a slipping of the epiphyses. The
same type of change is seen in the carpals, tarsals, metacarpals
and metatarsals. Here, owing to marked decalcification, the sur-
faces of joints may collapse, similating a destructive arthritis.

Abdomen: Flat plates of the abdomen may show the presence of
renal calculi, hydronephrosis, or metastatic calcification in many
regions.

It should be emphasized that all of the above mentioned
roentgenological changes are not necessary for a diagnosis. The
essential feature is a miliary, granular, generalized osteoporosis,
and this may be the only change present. The skull and pelvis are
usually listed as the two most important sites for X-ray study.
Reynolds, in a comment on Camp's paper, however, states that at
Harper hospital in Detroit they have found the earliest and easi-
est recognized changes to be in the vertebra of the lumbar region,
where there is a ground glass appearance with reduction in the size
of the vertebra.

In the presence of suggestive radiogram findings, additional
diagnostic procedures are available. A laboratory test which was
formerly stressed is the determination of the serum phosphatase
level. In well established cases of Von Recklinghausen's disease
this is always elevated, and it was though to have diagnostic value

in hyperparathyroidism. In 1932, Kay (97) made a thorough study of blood phosphatase and found that an increased amount could be demonstrated in osteitis deformans, osteomalacia, infantile rickets, adolescent rickets and renal rickets as well as in generalized osteitis fibrosa. He concluded that the rise in this enzyme in the plasma was a secondary phenomenon and not of primary significance in hyperparathyroidism. This opinion has been substantiated by subsequent investigators and it is now rather generally accepted that the plasma phosphatase represents merely the degree of osteoblastic activity and is elevated in proportion to the extent of bone disease, regardless of the etiology of that bone disease. (3 and 4). Thus, it is not of great diagnostic importance but will serve to corroborate the X-ray evidence of bone involvement.

The final diagnosis of generalized osteitis fibrosa must necessarily depend upon the demonstration of that essential physiopathology of hyperparathyroidism which we have previously discussed at length. Thus, given a patient with suggestive symptoms of Von Recklinghausen's disease with X-ray evidence of generalized osteoporosis, the diagnosis is ultimately made by a demonstration of significant changes in calcium and phosphorus metabolism and a decreased muscle excitability. The presence of a palpable tumor in the neck in about 10% (74) will facillitate such a diagnosis. Using the schema given on page 43, the essential chemistry of Von Recklinghausen's disease may be represented as follows:
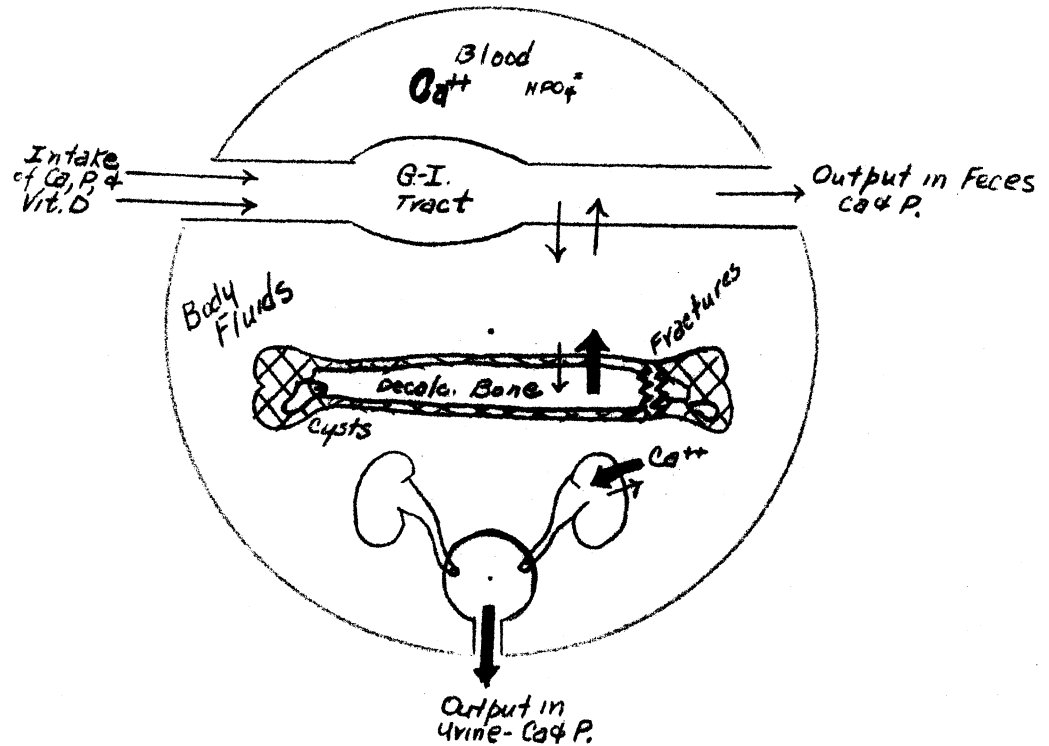
Essential Physio-pathology of Von Recklinghausen's Disease

## Differential Diagnosis.

A great many conditions which should be considered in the differential diagnosis of Von Recklinghausen's disease have been mentioned by various writers. Addison's disease, myasthenia gravis, progressive muscular dystrophy and neurasthenia may be suggested by those cases with predominate muscular and fatigue syndromes (74 and 104). With careful study, however, they should offer no great problem in diagnosis. The possibility of confusion with duodenal ulcer and appendicitis in cases with marked gastrointestinal symptoms must also be mentioned. (74). The greatest problem, however, lies in the differential diagnosis from other

bone dyscrasias. The various diseases which come under this cate-
gory are as follows:

Senile osteoporosis (3 and 93)
Paget's disease (3, 20, 92, 93 and 138)
Osteomalacia and Rickets (3, 93 and 138)
Solitary, local cysts (3, 91 and 93)
Osteogenesis imperfecta (3)
Multiple myeloma (3 and 32)
Metastatic malignancy (3, 32 and 100)
Basophilic adenoma of pituitary (3)
Fibrocystic disease of problematical origin (93)
Renal rickets (93)
Generalized diffuse fibrosis of bone (91)
Syndrome of osteitis fibrosa disseminata,
        pigmentation, etc. (7)
Arthritis of various types.

In senile osteoporosis the serum calcium is normal and will be
so on repeated examination. Paget's disease or osteitis deformans
offers greater difficulties. In the earlier literature there was
much confusion regarding the differentiation between osteitis
fibrosa and Paget's disease. Even Ballin (12 and 13) believed
the two diseases to be identical and reported good results with
parathyroidectomy in both. Schmorl (147) originally held the same
concept, but later admitted that he had been in error, and maintained
that they were separate and distinct diseases. Histologically there
is little, if an difference in the two conditions, but there are
other distinguishing features. Primarily the age incidence is
different and while Von Recklinghausen's disease is essentially
generalized with manifestations in all the bones, Paget's tends to
be mon-ostotic or at best polyostotic. The whole skeleton is never
involved. There is periosteal activity with thickened cortex in

the latter but none in the former. In Paget's there is no change in the parathyroid glands and the disturbances in calcium and phosphorus metabolism are not demonstrable. The muscular changes are likewise lacking. Careful X-ray and metabolic studies should permit accurate differentiation. Bassler (19) has reported a well developed case of Paget's disease with thickening of the bones and a filling in of the medullary canals in which he secured immediate subjective and objective improvement after the administration of parathyroid extract. Surely if the disease is caused by overactivity of the parathyroid glands, the administration of the extract should accentuate the symptoms rather than alleviate them. It is not unlikely, however, that hyperparathyroidism may occasionally be superimposed on a Paget's disease, so that the two exist simultaneously. Ballin (12) and Albright, Aub and Bauer (3) have reported such cases.

Pick (138) classifies rickets and osteomalacia as "achalicotic" diseases showing an absent or deficient calcification and ostitis fibrosa as a "metapoetic" disease which is associated with a complete alteration of structure of the bone. The term osteomalacia has been used rather loosely in the literature but we speak of it here as the adult counterpart of rickets, manifested by a failure of calcium deposition in the osteoid tissue with a resulting widening of the osteoid seams. Thus an X-ray differential diagnosis is not difficult. In addition, the lack of parathyroid metabolic changes is obvious. As a last resort, bone biopsy may be employed.

The histological pictures in the two conditions are decidedly different.

Solitary bone cysts, in the absence of other skeletal changes cannot be considered as manifestations of hyperparathyroidism.  In osteogenesis imperfecta the calcium and phosphorus metabolism is normal, and there are the accompanying conditions of blue sclera, deafness and heredity.  Although this condition, itself, has been mentioned as one manifestation of hyperparathyroidism, it is to be differentiated from true osteitis fibrosa.

It has already been mentioned that a secondary type of osteitis fibrosa may develop as an over-compensation, secondary to multiple myeloma and metastasizing malignancies. (See page 57.)  In such cases only the demonstration of the primary malignancy or disease will help in differentiating from a true, primary osteitis fibrosa.  Multiple myeloma itself may come into the differential diagnosis because there is frequently a high serum calcium in this condition.  The phosphorus of the serum is not correspondingly lowered, and there is a normal phosphatase level.  A biopsy may be necessary to make the distinction clear, however.

A basophilic pituitary adenoma, which may occasionally cause confusion is differentiated by the additional presence of obesity, hirsutism, amenorrhea and hypertension.

Renal rickets may give a bone picture identical with that of

Von Recklinghausen's disease, and is, in fact, another manifesta-
tion of hyperparathyroidism. It is a secondary type, however, and
it is very important that the two be differentiated from the stand-
point of treatment. The syndrome will be discussed and differential
points enumerated later in this paper. Jacobs and Bisgard (91)
describe a generalized diffuse fibrosis of bone with replacement of
bone and marrow by massive formations of fibrous tissue and occur-
ring in many bones, which can be distinguished from cases of hyper-
parathyroidism only by the clinical history and very careful meta-
bolic studies.

A still more confusing syndrome described by the Massachusetts
group (7) consists of bone lesions which show osteitis fibrosa on
histological examination, associated with brown, non-elevated pig-
mented areas and precocious puberty in the female. The bone lesions
and pigmentation have a marked tendency to be unilateral only. The
bony changes are disseminated rather than generalized and consequent-
ly are called "osteitis fibrosa disseminata". This syndrome is not
a manifestation of hyperparathyroidism.

The relation of various types of arthritis to hyperparathyroid-
ism is a much disputed field and deserves separate discussion. Let
it suffice to say at this time that many of the reported cases of
proved osteitis fibrosa cystica have been originally erroneously
diagnosed as arthritis. It will pay the internist to seriously con-
sider the possibility of a true hyperparathyroidism in every case of

arthritis. The differential diagnosis involves the whole regime of diagnostic aids already mentioned.

Prognosis and Treatment.

Without treatment the general prognosis in generalized oste-itis fibrosa is bad because of such complications as marasmus, cardiac, respiratory and renal failure. The disease itself cripples but does not kill (151). In the average case it is the renal mani-festations (to be discussed more in detail later) which constitutes the real menace to life. (39).

A consideration of the treatment involves at least four groups of methods--orthopedic, medical, surgical and irradiation therapy. In the pre-parathyroidectomy days the treatment was essentially symptomatic. Morton (126) in 1922 advised coal tar products for pain, splinting of fractures and osteotomy in the presence of marked deformities. For malunion and non-union he recommended treatment by freshening of the ends of the bones and use of bone grafts. After Mandl (111 and 112) demonstrated the practicability of para-thyroidectomy in 1926, this immediately became the treatment of choice. Since that time many papers have been written on the tech-nique of the operation. The principles and steps of the surgery as brought out in the papers of Hunter and Turnbull (90), Chifoliau and Ameline (38), Churchill and Cope (40) and Lahey and Haggart (102) are as follows:

1. Attempt to locate tumor before operation by flat

radiogram of neck and radiogram with barium. Calcification in the capsule of tumor, tracheal displacement and filling defect of esophagus may give a hint as to location.

- 2. General anesthetic. The operation is apt to be too long for a local anesthetic.

3. Incision--a wide collar incision with section of the pretracheal muscles at level of the isthmus of thyroid and dissection of the middle cervical fascia away from the surface of the thyroid.

4. Lift up outer border of thyroid with clamps or fine silk traction sutures, identify the carotid sheaths, locate ligate and divide the lateral thyroid veins.

5. Palpate and examine the postero-lateral aspects of the thyroid and dissect down on one side until recurrent nerve and terminal parts of inferior thyroid artery are seen. If tumor not yet located, repeat this procedure on opposite side. If there are any suspicious masses felt in the thyroid tissue, frozen sections should be made. If tumor still not located,

6. Expose trachea and esophagus and carry dissection up to larynx and down into superior mediastinum. If necessary, branches of the inferior thyroid artery may be severed individually as they enter the capsule of the thyroid, making sure that the blood supply to the normal parathyroids is left intact. It may be necessary to ligate and cut the superior thyroid artery so that the superior pole of the thyroid can be turned down for better

exposure. Still not finding tumor,

7. Make small incision in prevertebral fascia just behind esophagus and above the inferior thyroid artery and explore the prevertebral space. Still not finding tumor,

8. Palpate the mediastinum with one finger in the superior mediastinum and one finger in posterior mediastinum. If tumor is found here, deliver it into wound by gentle traction. Lahey (102) believes that removal of the manubrium of the sternum is often necessary but Churchill and Cope (40) state that it is only necessary when the region is filled with scar tissue following previous surgery.

9. When, at any of the above stages, a parathyroid tumor is identified, the following considerations must be entertained: a subtotal resection only when the tumor is large or when a normal gland has previously been removed; but with a comparatively small tumor and in the presence of three normal glands, a complete resection is probably indicated.

10. If a tumor is not found, there is a difference of opinion as to the proper procedure. Lahey and Haggart (102) advise the removal of a normal parathyroid for pathological study. Others (90) suggest that the wound be closed and medical treatment instituted. Still others advise future X-ray therapy. The decision must be up to the individual surgeon. Wilder (167) mentions a personal communication from DuBois, Aub, Bauer and Richardson in which the latter states they had removed two normal glands in a patient with osteitis

fibrosa cystica, with clinical improvement following. In later papers, however, Albright, Aub and Bauer insist that a normal gland must not be removed.

11. If extensive dissection has been done, the wound should be drained for two or three days. Otherwise it may be closed without drainage.

It has been stated that the operation is not particularly difficult and that any good thyroid surgeon can do it. The Massachusetts group (3) insist that the operator must be more than this. He must know the normal and aberrant positions and character of the glands, and he must be prepared to go on down in the mediastinum, if necessary. Churchill and Cope (40) state that the technique resembles neurosurgery rather than thyroid surgery. Very careful hemostasis is necessary so that the glands can be seen and recognized. Even the smallest vessels should be doubly ligated with fine silk before sectioning. It is emphasized that even the slightest trauma to the parathyroid glands may cause a rapid hematoma formation. The various locations of the glands and their appearances have been described under "Anatomy of the Parathyroid Glands", on pages 3 to 15.

The operation is made more difficult when there has been previous surgery in the neck. Under such circumstances an exploration of the superior mediastinum will necessitate a splitting of the sternum. Churchill and Cope (40) then advise the use of positive

pressure anesthesia and a mid-line incision which sweeps to the right at the level of the third costal cartilage. By blunt dissection at the sternal end of the third interspace a finger is inserted and the great vessels are pushed back to avoid injury to them. The sternum is then split with a Lebsche knife and the exposure obtained.

It is to be mentioned that Russian school, headed by Oppel (130) uses an entirely different technique for the operation. Oppel uses chiefly a local anesthetic and makes his incision along the anterior border of the right sternocleidomastoid muscle.

There are only two post-operative complications peculiar to parathyroidectomy. These are tetany and oliguria, and of these the first is by far the most important. Albright, Aub and Bauer (3) have stated that special treatment for tetany should be seldom be necessary but they stand practically alone in this opinion. Most surgeons prefer to give a routine prophylactic course of calcium, parathormone and vitamin D therapy. Jaffe (92) gives large doses of calcium every two to three hours by mouth or vein. To smooth over the utilization time he also adds 10 to 20 units of parathyroid extract-Collip three or four times daily. Viosterol may also be given. The whole regime may be carried over a number of weeks, gradually lowering the dosages. The best guides as to the presence of impending tetany are the serum calcium variations and the clinical signs of Chvostek and Trousseau. Bernheim and Garlock (23)

stress the importance of administering calcium pre-operatively to prevent post-operative tetany. Even the administration of the above mentioned remedies may not solve the problem of tetany, however. At times the condition is extremely difficult to handle. A case reported by McClure (115) well illustrates this contention. The patient had the typical history and findings of osteitis fibrosa cystica and a partial thyroidectomy and resection of a parathyroid adenoma was done. In four days the patient had a positive Chvostek's sign and then a carpo-pedal spasm. In spite of intensive medication she was still on the verge of tetany three months later. Parathyroid extract and vitamin D preparations were continued and finally two parathyroid glands were implanted in the rectus muscle according to the Halsted technique (76). Still the patient had more and more frequent periods of circulatory collapse and she finally died four months after operation. Although she had never had an actual tetanic convulsion, she had bordered on this state almost constantly for the entire time, in spite of strenuous efforts on the part of the surgeons. McClure believes that this patient either developed an immunity to the extract or developed an over production of some inhibitory principle. In general it may be stated that those patients with the most bone damage will have the greatest tendency to post-operative tetany. The decalcified bone draws the calcium from the blood more quickly than it can be supplied, and a very low serum calcium with resulting tetany appears. Bulger et al (33) have reported a case in which it was necessary to

administer large doses of calcium and parathormone for 18 months
in order to prevent tetany.

The second complication is urinary suppression, seen partic-
ularly in patients with polyuria before operation. After the sur-
gery, the amount of urine diminishes considerably and there may
even be complete suppression with an increase of the non-protein
nitrogen level of the blood. This is temporary, however, and dis-
appears with the partaking of normal amounts of water and food with
soluble electrolytes. If necessary, intravenous saline or glucose
will hasten the return to normal. (151 and 92).

The beneficial results of parathyroidectomy are both subject-
ive and objective. There is always complete relief of pain. (93).
The patient characteristically feels better than he has for many
years, constipation disappears, and he senses a new energy and
vitality. (3). Objectively, the serum calcium usually returns to
normal and a calcium balance is reestablished. General muscular
weakness often disappears with dramatic rapidity. (39). Some of
the pathological changes of the disease are reversible and some
are not. The decalcification in the bones is rapidly corrected,
the giant cell tumors regress and un-united fractures are repaired
by calcification of the callus. (39). The bone trabeculae become
more dense and well delineated and the margins of cystic portions
may become more sharply defined because of increased calcium content,
although the cysts may persist in some degree indefinitely. The

cortices of the bones returns to normal thickness. Changes in stature due to kyphosis, coxa vara and softening of the pelvis, however, persist. (35). Thus, orthopedic management, even after parathyroidectomy, may often be indicated. It is obvious that early diagnosis and treatment is essential if the marked deformities are to be prevented.

Although Weil (169) is said to have administered roentgen therapy to the neck in a case of osteitis fibrosa cystica in 1922, with remarkable benefit, the procedure was not generally recognized until 1932. In that year both Biedl (24) and Merritt (117) reported the successful use of X-ray therapy to the parathyroids in the disease. Biedl's case had a hypercalcemia and a "localized" osteitis fibrosa. It is unfortunate that he did not more accurately describe the pathology present, because a purely localized cystic formation of the bones is not generally considered to be a manifestation of hyperparathyroidism. At any rate he administered X-rays at two anterior and two posterior ports in the following dosage: 180 kilovolts, 4 milliamperes, 30 cm. FHD, using 0.5 mm. copper and 1 mm. aluminum as a filter. He gave 700 roentgen units per field, giving treatments at two day intervals in three separate series. With the last series, the hip joint, where the cystic development was located, was given 350 roentgens anteriorly and posteriorly also. There was remarkable improvement in the patient with a lowering of the blood calcium and disappearance of the hip

lesions. In the report of Merritt's first case, no mention was made of the calcium metabolism, but there were cyst-like areas of bone destruction in the distal end of the femur with some periosteal proliferation and an associated hyperthyroidism. Just as with Biedl's case, we can thus not be sure that this was actually a case of generalized osteitis fibrosa. It was so considered by Merritt, however, and two areas of the neck, including the thyroid and parathyroid regions were irradiated using about the same dosage factors as Biedl. Three weeks after the first treatment, there was noticeable improvement, with a gain in weight, lessened nervousness and a decrease in the pulse rate. Pain in the knee was almost gone. After later treatments the patient was able to walk comfortably and radiograms showed marked regeneration of bone in the cystic areas.

Merritt has continued to use this therapy and in 1934 he and McPeak (118) reported a total of six cases so treated with clinical cure or improvement. They recommend exposure of four areas, one over each side of the neck, one over the upper thorax anteriorly and one over the neck posteriorly. The dosage factors suggested are 140 kilovolts, 5 milliamperes of current, fields 10 by 15 cm., 6 mm. aluminum filter and an exposure of 240 roentgens (measured in air) to each field.

It is of interest to note that the Massachusetts General Hospital group administered roentgen therapy to two patients over a

long period of time without any improvement. (3). They also advise
against irradiation of the cysts locally because of the tendency
to increase the fibrosis of the marrow with enhancement of the assoc-
iated anemia.

We agree with Cutler and Owen (52) that irradiation of the
parathyroids should be resorted to only under the following con-
ditions:

1. When there are definite contra-indications to surgery.

2. As a post-operative method when an adenoma has been only
partially removed.

3. When following removal of an adenoma, a persistently high
serum calcium suggests the possibility of a hyperplasia or adenom-
atous growth on the opposite side of the neck.
These writers have also suggested the possibility of diagnosing
the position of a misbehaving parathyroid gland by use of X-ray
therapy. Since it was shown by Biedl (24) that as much as 2000
units on the parathyroids of normal, healthy dogs will cause no
change in the blood calcium, it has been assumed that only abnormal
glands are radio-sensitive. Thus, Cutler and Owen have divided the
neck region into several separate areas and given X-ray therapy
individually over a single area at a time. The blood calcium is
studied after each treatment. Until that area which contains the
tumor is irradiated there will be no change in serum calcium.
This work has not been investigated or substantiated by other workers.

It is our believe that while there is some evidence that irradiation therapy may be effective in hyperparathyroidism, the method has not been generally accepted and has not been well established.  Parathyroidectomy is to be considered as the treatment of choice, and irradiation reserved for the uses outline above.

A few medical procedures have been suggested and used from time to time in the treatment of hyperparathyroidism.  Page and Scott (132) have demonstrated that in dogs with a hypercalcemia the intravenous injection of sodium acid phosphate ($Na_2HPO_4 \cdot 12\ H_2O$) would reduce the blood calcium.  Bulger, Dixon, Barr and Schregardus (33) employed a similar treatment in two patients with clinical hyperparathyroidism by administering the phosphate solution by mouth.  One gram of sodium acid phosphate with three grams of sodium bicarbonate was given at 6:00 A.M., 10:30 A.M., 3:00 P.M. and a double dose at 10:00 P.M.  Calcium lactate was given three times a day with meals.  Under such a regime, the serum phosphate rose to normal and the serum calcium fell to a high normal (from 16 mg.% to 12.5 mg.%).  70% of the phosphorus ingested was excreted in the urine and 27% was retained in the body.  The urinary calcium excretion fell to normal while the amount in the stool increased.  The calcium lowering effect is undoubtedly not due to any change in the activity of the parathyroids but is produced by the artificial increase of phosphate in the blood.  Such management is advised for treating alarming conditions which may arise with extreme hypercalcemias, as a temporary measure.

Albright and others (3) report similar results with medical treatment and state that a high phosphorus and calcium intake will prevent decalcification but will promote kidney damage. The decrease in urinary calcium mentioned above may conceivably be due to renal damage as a result of the calcium and phosphorus therapy. Leopold (104) treats his cases of so-called "functional hyperparathyroidism" with 1.5 grams of calcium gluconate per day, gradually decreasing the dose as the blood calcium comes down. This, combined with bed rest, has given him good results. It is difficult to understand the rationale for such therapy, however.

Opinions on the use of vitamin D in the medical management of the disease are varied. We have mentioned in a previous chapter that vitamin D will tend to increase the blood calcium level. In one of Leopold's cases (104) the use of ultraviolet rays caused a jump in the blood calcium to 19 mg.%. He states that at the present time, in view of the promiscuous use of concentrates of vitamin D by the public in general, permanent damage may be done to people with mild degrees of hyperparathyroidism. This would seem to be sound reasoning, and in spite of some reports to the contrary, we believe that the vitamin is definitely contra-indicated in patients with hyperparathyroidism as a pre-operative measure. On the other hand it may be very valuable post-operatively, to assist in adequate calcium assimilation and prevention of tetany. Magnesium in the pre-operative diet is definitely contra-indicated, because it increases the calcium excretion. (158).

The above given descriptions of parathyroidectomy, irradiation therapy, etc., are all given as treatment for the primary type of osteitis fibrosa cystica. In those cases where hyperparathyroidism develops secondary to other bone dyscrasias or renal disease, the removal of the parathyroids in any way is probably contr-indicated. No therapy has been suggested for such conditions in the literature. It would seem reasonable to assume that some type of management with mild irradiation therapy to the glands might be developed which would merely keep the compensating glands from over-doing and producing additional damage in this way. Other possible therapeutic measures will be discussed in the next division of this paper.

<div align="center">Rickets and Renal Rickets</div>

### Infantile Rickets.

It is now generally accepted that infantile rickets is regularly accompanied by parathyroid hyperplasia. As early as 1920 Pappenheimer and Minor (134) demonstrated this fact in a series of 22 glands from 14 cases of rickets compared with 19 glands from 18 normal subjects as controls. They found a definite increase in the size of the glands, due to a multiplication of the individual cells. There was no constant or characteristic change in cell type, the clear cell still predominating, as normally. There was no increase in the supporting tissue or in the vascular supply. Hamilton and Schwartz (79) have demonstrated with their "rabbit test" (see page 45) that there is an increased amount of parathormone in

the blood of rachitic animals. As a result of the presence of excess hormone, the serum of rachitic blood has a very high affinity for calcium so that the rise in blood calcium level upon calcium administration is the same as is caused in normal animals only when both calcium and parathyroid extract have been given. The probable explanation for this phenomenon is that the parathyroids compensate for the lack of vitamin D. Ordinarily this hyperplasia of the glands does not overcompensate, and seldom do we get an osteitis fibrosa superimposed on an infantile rickets. The possibility of such an occurrence, however, is suggested in the case reported by Linder and Vadas (107). It was a case of late rickets with some manifestations of hyperparathyroidism--high serum calcium and very low phosphorus with excreciating bone pain, and a negative calcium balance on a restricted calcium intake. The patient was operated and an 850 mg. parathyroid gland was removed. There followed relief from the pain, but no change in the calcium and phosphorus metabolism. Under ordinary conditions, the over-activity of the parathyroids in rickets needs no special treatment.

Renal Rickets.

In recent years there has been described in children a new syndrome which similates but is not identical with infantile rickets. This condition has been described as renal infantilism, renal dwarfism and renal rickets. Clinically the height and weight of the child are retarded and there are a number of bone changes. Chiefly these are genu valgum (in 56%),enlargement of the costo-chondral junctions,

presence of Harrison's sulcus, enlarged epiphyses and bowed tib-
ias. (89). Associated with this there is constantly a polydipsia
and polyuria, and certain gastro-intestinal disturbances including
vomiting, anorexia and abdominal pain. The skin may assume a dirty
yellowish brown pigmentation and the texture may become dry, coarse
and inelastic. In Hunt's case (89), there was a definite atony of
the musculature. X-ray examination of the bones shows a decalc-
ification in all the diaphyses, giving a wooly, almost transparent
appearance. The name rickets is suggested because the epiphyseal
lines may be thickened and irregular. Finally there is the very
important observation that all of these patients show evidence of
a chronic, interstitial nephritis.

The translucency and spongy appearance of the bones is given
by Mitchell and Guest (120) as the crucial point in the differen-
tial diagnosis from true infantile rickets. Albright, Drake and
Sulkowitch (8) state that the bone changes are identical with those
previously described for osteitis fibrosa generalisata. The bone
changes, the muscular atony, and the associated gastro-intestinal
and urinary symptoms are certainly suggestive of hyperparathyroid-
ism, and a chemical study of the blood would seem warranted.

In the blood studies, however, if we expected to find a high
calcium value and low phosphorus, we should be disappointed. The
serum calcium of renal rickets is characteristically low and the
phosphorus runs characteristically very high. (89). These findings

cause us to hesitate in making a diagnosis of hyperparathyroidism.

The etiology of this condition, then, has been and still is a matter of considerable confusion and differences of opinion. The important point is that there is always a history of considerable renal damage preceding the onset of the bone symptoms. It will be recalled that we have previously mentioned the effect of renal damage on the calcium and phosphorus of the blood. Under such conditions, the calcium may be low and the phosphorus high, even with an associated hyperparathyroidism. Whether this hyperparathyroidism is primary or secondary in renal rickets is the source of considerable debate. Albright, Baird, Cope and Bloomberg (4) believe that sometimes it is one and sometimes the other, so that wrong diagnoses are made frequently on both sides. Mitchell and Guest (120) state that in the presence of renal insufficiency the phosphates are excreted by the bowel rather than by the kidney. The resulting increased concentration of phosphate in the bowel may interfere with calcium absorption through the formation of insoluble phosphates. Thus, the child suffers a true calcium starvation, and the bone manifestations may be on this basis. After careful metabolic studies on a patient with the adult counter-part of renal rickets, Albright, Drake and Sulkowitch (8) decided that the findings were consistent with this theory. It seemed entirely possible that the bone decalcification was due to the phenomenon of blocked absorption. The metabolic data do not favor the theory that the bone changes are the result directly of even a secondary

hyperparathyroidism. An excellent summary of the situation at present may be given in the words of Albright, Drake and Sulkowitch (8):

> "The bone disease is indistinguishable from that seen in hyperparathyroidism; a secondary hyperparathyroidism is present; but that the bone disease is directly due to the parathyroid hormone remains a question."

As to treatment of the condition, the suggestion of Shelling and Goodman (152) of a low phosphorus and high calcium diet is the only thing offered. Such a regime will at least help in the maintenance of conditions in the bowel suitable for calcium absorption, so that decalcification will be held at a minimum.

## Arthritis and Hyperparathyroidism

In the last decade several hundred parathyroidectomies have been performed for the treatment of various types of arthritic conditions. There are three widely separated groups which have been promoting this work with considerable enthusiasm, one in Russia, one in Detroit, Michigan and one in France. On the other hand, many competent investigators have just as enthusiasticly and vigorously condemned the entire procedure. In considering this problem, we shall attempt to present both sides of the case and draw such conclusions as seem justified.

The work started in 1926 when Dr. Belsgoradsky of Metschnikoff's clinic in Leningrad found that patients with the ankylosing arthritis syndromes had an increased blood calcium, and Dr. Schraer

noticed that such patients had a decreased electro-excitation of the skeletal muscles. In 22 patients so studied, 19 showed a reduction of from 5 to 10 milliamperes of current. (130). These findings immediately raised the possibility of a hyperparathyroid factor. The surgeons of the clinic than began a series of para- thyroidectomies in these patients.

The Russian school has confined their interests to that form of multiple joint disease which they have called chronic, ankylos- ing polyarthritis. Oppel (130) includes both Bektereff's and Strumpel-Marie's diseases in this syndrome which passes through the stages first of interference with mobility on to complete immob- ility and finally to ankylosis of the joints. Both the spine and the girdle joints are involved.

A brief summary of the results of this work on arthritis, as reported from the various investigators, is given on the following page.

| Author | Year | No. of Cases | Preoperative Remarks | No. Oper. | Post-operative Results |
|---|---|---|---|---|---|
| Ssamarin (155) | 1928 | 55 | Serum Ca range 9-11 mg.%. Average Ca 11.85 mg.%. Serum phosphate normal. | 48 | Improvement in $\frac{1}{2}$; Ca lowered in all. |
| Oppel (130) | 1929 | 55 | Serum Ca above normal in 67% | 55 | 26 hrs. after operation, sensation of stiffness gone & objective improvement. |
| Schkurov (144) | 1935 | 116 | Average duration of illness--5 yrs. 5 mon. | 116 | Patients feel "unbound", pain disappears and breathing is easier immediately. Objectively, increase of joint movement varying from 10 to 55 degrees. Late results in 40, 6 mon. to 4 yrs. later--90% continued to have subjective relief, while 55% continued to get an increase in joint mobility. |
| Funsten (65) | 1933 | 26 | Serum Ca high in "showers" Ca output averaged 3 times normal. Clinically similar to Von Recklinhausen's. Lenthened chronaxie & shortened R-T interval | 14 | Definite improvement in 93%. 12 other cases treated conservatively with cod liver oil, Ca, physio-therapy, etc., with some improvement in 67%. |
| Ballin (12) | 1932 | 13 | Sl. elevation of serum Ca. Muscular hypotonia. | 13 | Good results in 6. |
| Richet (142) | 1935 | 1 | Varying hypercalcemia. | 1 | Patient able to walk for first time in two years. |
| Jasienshi (95) | 1933 | 4 | Aver. duration of ankylosis was 14 months. | 4 | Almost instant subjective and clinical improvement which persisted. |

As nearly as can be suggested from the evidence submitted in the various papers just summarized, the compiled results are as follows: of 251 cases subjected to parathyroidectomy, 207 or 82.5% showed definite improvement, at least subjectively.

We are now ready to consider the nature of the criticisms of this work. One stumbling block is that in 8 of Ssamarin's cases and in 10 of Oppel's, microscopic study of the tissue removed showed no evidence of parathyroid tissue! These writers believe, however, that there had been sufficient interference with the blood supply of the parathyroids at the time of operation that a hypo-function had been incited. It is at this point that opponents of the procedure have aimed their strongest blows. We firmly believe however, that it would be difficult to lower the serum calcium by psychic therapy alone, as some of them have intimated.

Bauer, of the Massachusetts group says that the bone decalc-ification in these patients is simply one of disuse and that the high excretion of calcium in the urine is such as might be found in any patient who is in bed with a cast. (20). He further states that it is not like true hyperparathyroidism for the hypercalcemia to come in "showers" as Funsten described. Bauer's own co-workers, however, Albright, Sulkowitch and Bloomberg (9) in discussing borderline cases of hyperparathyroidism and the associated calcium levels make this statement:

> "In this group, furthermore, it is important to do repeated determinations as the values fluctuate from the normal range into the definitely hyper-parathyroid range (V. infra: Cases 31,32,33)."

A final argument of Bauer's is that in a series of arthritics of the hypertrophic and atrophic forms which he personally studied there was no evidence of hyperparathyroidism. None of the exponents of the principle, however, have stressed the importance of the parathyroids in simple hypertrophic and atrophic forms. The real question must be limited to ankylosing types. We can not feel that Bauer has actually invalidated the work of Funsten, Ballin and the Russian school. But Churchill and Cope (40) of Boston have also ridiculed the idea, stating that the clinical improvement in all the cases reported could be due to the anesthesia, rest in bed, change of diet or even spontaneous remissions. Nachlas (127) studied 37 cases of arthritis and found a normal blood calcium in each.

The chief thing is, that these critics can find no logical rationale for parathyroidectomy in a disease which is essentially one of soft tissues, not primarily involving the bones themselves, at all. The principle is given in a paper of Ballin and Morse (14) as one of metastatic calcification. We have already spoken of the metastatic calcium deposits often seen in generalized osteitis fibrosa. It is well accepted that these deposits may and do occur in practically every organ in the body, including the ligaments around the bodies of the vertebrae. According to Ballin and Morse, the presence of an infectious process in the synovial membranes of the joints causes certain changes which later makes a nidus for the deposition of lime. The calcification of the granulation tissue

and osteoid tissue of an arthritic joint is the exact process
which leads to ankylosis. In the presence of hyperparathyroidism,
this calcification in the soft tissues should theoretically be at
a maximum. Albright, Drake and Sulkowitch (8) have described
extensive calcification around the joints in one of their cases
of "renal osteitis fiborsa cystica". Their descriptions of the
radiograms of these regions is as follows:

> "There were masses of
> homogeneous dalcification without trabeculation surrounding
> the proximal interphalangeal joints of the right second,
> third and fourth fingers. Similar calcified areas were
> scattered along the phalanges of these fingers. Both
> elbows and acromioclavicular joints showed similar calc-
> ified masses. They were also present in the soft tissue
> proximal to the pedal phalanges."

It seems entirely probable that the so-called "ankylosing poly-
arthritis" cases of which about 90% have benefited from parathy-
roidectomy, may be victims of a similar metastatic calcification
in the arthritic joint surfaces and surrounding ligamentous struc-
tures. The exact relation of this process to the parathyroid hor-
mone cannot be settled at this time. The Russian group (144) does
not claim that parathyroidectomy will have any effect on joints
already ankylosed, but will prevent the development of more ankyl-
osis, do away with rigidity of joints and create the most favorable
conditions for subsequent methods of correction of deformities and
restoration of joint movement. Orthopedic and general measures are
a necessary adjunct to the treatment.

Still another aspect of the arthritis-parathyroid problem is

the fact that even classical cases of osteitis fibrosa cystica
may closely similate an arthritis. It will be recalled that in a
series of 17 cases reported by Albright, Aub and Bauer (3) a pre-
vious diagnosis of arthritis had been made in 4, and rheumatism
in 4. Ballin (12) has given a classification of types of osteitis
fibrosa cystica and has there listed an "arthritic type", which
is characterized by slight elevation of serum calcium, arthritic
processes, spur formation around the vertebrae and other joints,
kyphosis, moderate decalcification, some compression of vertebrae,
lime metastasis in the anterior and lateral vertebral ligaments and
muscular hypotonia. It would seem justified, at least, to consider
every patient with an arthritis or rheumatism as a potential hyper-
parathyroid until proved otherwise.

From the above listed confusing facts and opinions we have
formed the following conclusions:

1. Certain cases of ankylosing arthritis which also have other
signs and symptoms of hyperparathyroidism are benefited by simple
parathyroidectomy.

2. The percentage of patients benefited in this way is greater
than might reasonably be expected to occur from natural remissions,
simple bed rest, etc.

3. The general prognosis of this disease with any other form
of therapy is so poor that the thin ray of hope offered by parathy-
roidectomy probably justifies the operation in well chosen cases.

4. Generalized osteitis fibrosa, in its true form, may simulate various types of arthritis. Any case of the latter, then, should be investigated for evidences of the former.

## Miscellaneous Bone Diseases in Which Hyperparathyroidism has been Incriminated

### Osteogenesis Imperfecta.

This term as it is commonly used refers to any congenital disturbance that results in the formation of bones of poor quality. The discovery of an unusual vascularity with a relatively small amount of parenchymal tissue in the parathyroid glands of a newborn with such disease by Wyatt and McEachern (170) has raised the question of a parathyroid factor in some of these cases. These authors could not decide whether there was a hypersecretion of parathormone as a result of increased absorption by the rich vascular bed, or a hyposecretion from a lack of parenchymatous tissue. At best the relationship is of but academic interest at present. Some of these patients also have blue scleras, making a syndrome which will be mentioned again in a later chapter.

### Marble Bones.

As summarized by Pehu, Polecard and Dufourt (137) marble bones or osteopetrosis, is a rare disease in which the bones petrify. The compact strata of the diaphysis takes a considerable hardness and the spongiosa and medullary canal are invaded to such an extent that the latter almost completely disappears. The

epiphyses of the long bones show the greatest enlargement and deformities but all the bones of the skeleton are affected to some degree. The optic tract shows a progressive "retrecissement" with blindness. In radiograms the bones have an extraordinary density with a disappearance of the normal trabeculae. A paradox is that in spite of the apparent extreme hardness and density of the bones, one frequently observes spontaneous fractures. The blood calcium is always high. It is a very severe disease, fatal in infants.

Pehu, Polecard and Dufourt describe a personal case of a 27 months old baby, in which at autopsy a parathyroid adenoma composed of clear cells without granules was found. They believe that the dominant element of the disease is precisely a bone rarefaction with a fibrous osteitis. The increased density of the bone is interpreted to be the result of fibrosis rather than increased calcium deposition. The high blood calcium, the demonstration of a parathyroid tumor and the presence of decalcification with pathological fractures suggests a parathyroid origin of the disease. The French writers suggest parathyroidectomy as treatment.

Some substantiation of the above viewpoint has been given by the experimental work of Selye (149). When rats are given daily small doses of parathormone over long periods, the bone becomes much denser, so that it resembles the condition described above. This change is confined to the ends of the shaft, in the metaphyses.

Selye states that it is a true bone formation, however, while
Pehu, Polecard and Dufourt thought that in their case there was
decalcification with fibrosis, rather than true osteoblastic ac-
tivity.  It will be recalled that in the discussion of the physiol-
ogy of the hormone we mentioned that under certain conditions, the
hormone caused apposition of bone rather than resorption.  This
entire problem is certainly deserving of additional work.  Para-
thyroidectomy may prove to be of great value in the treatment of
this dreaded, even though rare malady.


## KIDNEY DISEASE AND HYPERPARATHYROIDISM

In the discussion of bone disease associated with hyperpara-
thyroidism we mentioned the common incidence of renal symptomotology,
urinary "gravel" and renal insufficiency.  In recent years it has
been found that in certain cases these manifestations may completely
overshadow the bone changes or even appear in the absence of bone
pathology.  Thus, we can no longer consider hyperparathyroidism as
essentially characterized by skeletal system involvement.  In a
series of 25 cases of hyperparathyroidism reported by Castleman and
Mallory (36), 20% had osteitis fibrosa alone, 44% had renal stones
alone and 36% had both together.  Urinary tract diseases associated
with this endocrine disfunction may be divided into two chief groups:
those with nephrolithiasis and those with parenchymal kidney damage.

## Nephrolithiasis

### Incidence.

It has been estimated from the various cases reported in the literature that about 70% of all cases of hyperparathyroidism have associated renal calculi. (2). Furthermore it has been stated by various workers that 5 to 10% of all cases with calculi in the urinary tract have an associated hyperparathyroidism. (2, 15 and 16). Albright and Bloomberg (6) have stated that in any case of renal stones--

> "--there is enough chance of the condition being hyperparathyroidism that the attending physician should feel obliged to rule this disease out."

### Etiology and Pathology.

There are undoubtedly many factors which influence the formation of stones,--stasis, infection, hypovitaminosis, lack of colloids, excess of crystalloids in the urine, and so forth. (2). Albright believes that the important thing is a urine of such composition that some crystalloid may precipitate out. Randall, Elman and Leberman (140) of Philadelphia have very recently published the results of some investigations with appropriate conclusions which are of interest in this connection. They have shown by a series of autopsy studies and experimental work that the formation of a calculus involves the following steps. Due to some underlying pathological process there is a deposition of calcium in the basement membrane of the collecting tubules and in the intertubular connective

tissue of the renal papillae in the minor calices. Such deposits,
or calcium plaques, while intra-papillary are innocent but when
they occur near the surface of the papillary wall, they lose their
surface covering of epithelium and, when so denuded, can and do act
as the nidus on which the salts of the caliceal urine are deposited.
Thus a tiny stone forms, attached to the original calcium plaque.
Such plaque formation, both with and without stone formation was
observed in 22.9% of 609 autopsies. A stone was found in 4.1% of
the same series. Working on this well founded conception of the
pathogenesis of calculus formation, the same workers attempted to
produce the above described calcium plaque experimentally. Using
various laboratory animals they tried vitamin-deficient diets,
staphylococcus toxoid, streptococcus hemolysin leukocidin and finally
the administration of parathyroid extract. With the latter only
were they successful. After giving the extract for six months to
dogs, they observed in one renal papilla a calcium plaque identical
to that which they had seen in man. This part of their work is of
course not in any way conclusive, but is of considerable interest
in the light of the demonstrated clinical association of hyperpara-
thyroidism and renal stones.

Even disregarding the above mentioned work on the renal papilla,
it is easy to conceive of calcium and phosphorus stones forming in
the urine of hyperparathyroid patients. In the presence of the ex-
cretion of enormous amounts of these two minerals in that urine,

the precipitation of the crystalloids seems almost inevitable. (2).
However, all hyperparathyroid patients do not develop stones, so
there must be additional factors such as deranged colloids, die-
tary factors and vitamin deficiencies concerned. (15).

Regarding the pathology of the parathyroid glands in these
cases of nephrolithiasis, a study of a series of cases reported by
Castleman and Mallory (36) is of interest. The series included
5 cases of the generalized Wasserhelle type of parathyroid hyper-
plasia in all of which there were renal stones and a minimal amount
of skeletal involvement. 4 cases of renal stones had a transition-
al Wasserhelle-chief cell type of adenoma. The only example of a
focal Wasserhelle neoplasm in the series was also associated with
renal stones. The close association between renal stones and the
Wasserhelle cell as suggested here should stimulate further in-
vestigation. No definite conclusions can be drawn at this time.

## Clinical Picture.

The clinical story of a hyperparathyroid stone is similar to
that of any renal calculus. There may be dull, aching pain, severe
colic or no pain at all. There is usually an intermittent hema-
turia, varying greatly in degree. There may or may not be a pyuria.
The differentiation between stones of parathyroid origin and other
types can in no way be made by clinical observation. The presence,
in some cases of associated bone dyscrasia and muscle atony may give
a hint as to the nature of the stone, however. Albright, Baird,

Cope and Bloomberg (4) have stated that secondary to the formation
of calcium phosphate stones in the renal pelvis, a pyelonephritis
is apt to develop.  They reviewed 83 such cases from the literature
and their own clinic.  The polyuria of hyperparathyroidism is less
marked in cases with stones. (6).

### Diagnosis and Differential Diagnosis.

The diagnosis of the presence of a renal calculus must be made
as usual by the use of flat X-ray plates, cystoscopic examination
and pyelograms, both intravenous and retrograde.  It must be men-
tioned that the hyperparathyroid stone will always be opaque to the
X-ray because of its high calcium content.

The differential diagnosis which involves the identification
of a hyperparathyroid calculus in distinction to calculi of other
origins is the feature in which we are particularly interested.
Once again we must refer back to the essential physio-pathology of
this endocrine disease.  In many of these cases of nephrolithiasis
the changes in calcium and phosphorus metabolism are only very
slight, and very careful analysis of all the data obtainable must
be made.  For purposes of comparison of the metabolic situation in
this condition with that of hyperparathyroidism with predominate
bone manifestations we submit the following diagram, again modified
from Albright (1).  We suggest that it be compared with the diagrams
given on pages 43 and 72.
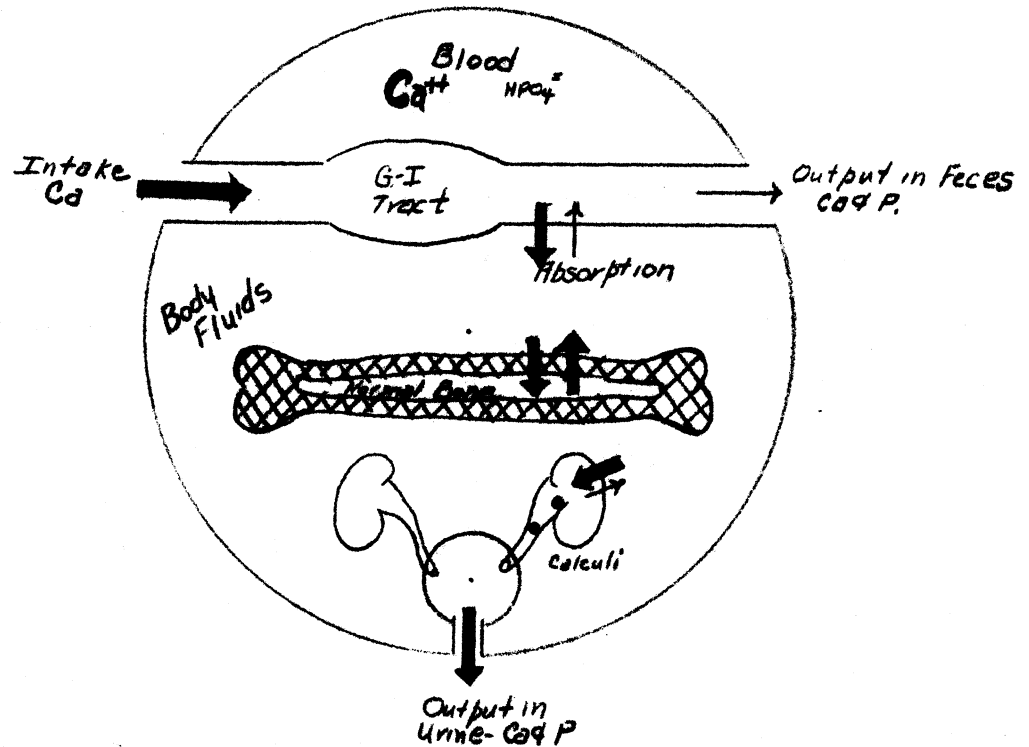
Essential Physio-pathology of Nephrolithiasis

Some evidence of the above pathological chemistry should be obtained. In regard to the demonstration of the decreased muscle excitability in these patients, it is unfortunate that no work has been done in this field. There is another diagnostic point of con-siderable importance, however. The calculi of hyperparathyroidism always contain a large amount of inorganic ash which is largely calcium and phosphorus. The stones are quite hard in consistency and are of a greyish color. (16). Although such a stone is not be considered pathognomonic of hyperparathyroidism, it is highly suggestive.

Treatment.

Since phosphates are precipitated in an alkaline urine, one
might suggest that stone formation in this disease could be preven-
ted by keeping the urine acid. Acid treatment, however, is contra-
indicated because it tremendously increases the hypercalcinuria and
hyperphosphaturia and leads to marked skeletal demineralization. (2).
Thus with such treatment we might change the situation from a hyper-
parathyroid nephrolithiasis to an osteitis fibrosa cystica.

The only real treatment of the condition is surgical, and both
the calculi and the primary parathyroid tumor must be removed. Con-
cerning the question as to which operation should be done first,
Barney and Mintz (16) believe that it depends entirely on the individ-
ual case. If the patient is in good condition and there is not much
associated renal damage, the best procedure may be to remove the
parathyroid tumor first and then the stone. On the other hand, if
one or both kidneys are badly damaged or blocked by the stones, it
is better to improve the urologic status as far as possible before
attempting a parathyroidectomy. The results of such treatment are
good and the stones do no recur after parathyroidectomy. Such per-
manent cure is the feature that makes this aspect of nephrolithiasis
so important. We know of no better way of emphasizing this fact
than to quote from Dr. Richard Chute (41):

> In conclusion, I would
> make an earnest plea to every urologist to consider the
> possibility of an underlying hyperparathyroidism in every
> case of urinary lithiasis, and I feel strongly that it is

our duty to these patients whose well-being has been
entrusted to us to give them the benefit of this newer
knowledge by a careful estimation of their fasting
blood calcium."

## Parenchymal Kidney Damage and Hyperparathyroidism

The association of damaged kidneys and hyperparathyroidism
has been observed from the time of the earliest recognition of the
latter. In 1921, Bergstrand (22) called attention to a possible
connection between parathyroid hyperplasia and nephritis, evident
in 10 of his cases. In 1925 Box and dé Wesselow (30) reported a
case of chronic nephritis with a blood calcium varying from 13.7
to 20.1 mg.% and blood phosphorus from 3.2 to 5.1 mg.% and pondered
upon a possible parathyroid dyscrasia. The matter of which of the
two features was to be considered primary and which secondary has
been the source of much argumentation and debate. The present con-
ception is, however, that both situations may exist, sometimes the
one being primary and sometimes the other.

### Primary Hyperparathyroidism with Resulting Renal Damage

We shall discuss two separate syndromes under this heading--
acute parathyroid poisoning and chronic nephro-calcinosis.

### Acute Parathyroid Poisoning.

The signs and symptoms of acute overdosage with parathyroid
hormone in experimental animals are generally attributed to renal
damage since there is usually anuria or oliguria, retention of

non-protein nitrogen in the blood, failure on the part of the kidneys to excrete phosphates and frequently lime salt deposition in the kidney substance. Shelling (151) believes that this symptom complex is due not to the primary effects of the hormone on the kidney nor to the hypercalcemia induces, per se, but to the excessive loss of water and electrolytes occurring with the diuresis. Albright, Baird, Cope and Bloomberg (4) state that the occurrence of acute parathyroid poisoning in humans is extremely rare, but they believe that the case reported by Dawson and Struthers (54) is an example of this phenomenon. The demonstration of the condition in animals is of considerable interest, however, because it lends greater credibility to the next syndrome to be discussed.

## Chronic Nephro-calcinosis.

This is a condition similating both chronic glomerular and chronic vascular nephritis, with definite, long-standing changes in the parenchyma of the kidney.

Clinical Picture and Pathology: Clinically the condition is almost indistinguishable from various forms of Brights' disease. In a manner similar to that concerned in the formation of calcium phosphate stones as described above, calcium phosphate may be precipitated out of the fluid in the renal tubules, forming concretions in the kidneys which eventually lead to inflammatory changes, sclerosis and contracted kidneys. (4). Snapper (154) adds that the

calcareous material is deposited in the form of infarcts not only in the renal tubules but also occasionally in the intertubular tissue. The whole process leads to a diminished renal function, so that uremia may follow. The same syndrome has been described and discussed by various other clinicians (110 and 122). The changes in the parathyroids may be in the nature of hyperplasia or aden-omata. No particular cell type seems to be particularly concerned. (36).

Diagnosis: The diagnosis of hyperparathyroidism in these cases must again rest on a demonstration of the fundamental chemical changes of the primary disease. In addition, the demonstration of calcium deposition in the kidney tissue and perhaps also in other organs of the body, by X-ray, may be of considerable aid. As the disease advances, however, the diagnosis becomes more and more difficult because the renal insufficiency masks the characteristic blood and urine findings of hyperparathyroidism. The situation can then be illustrated as follows:
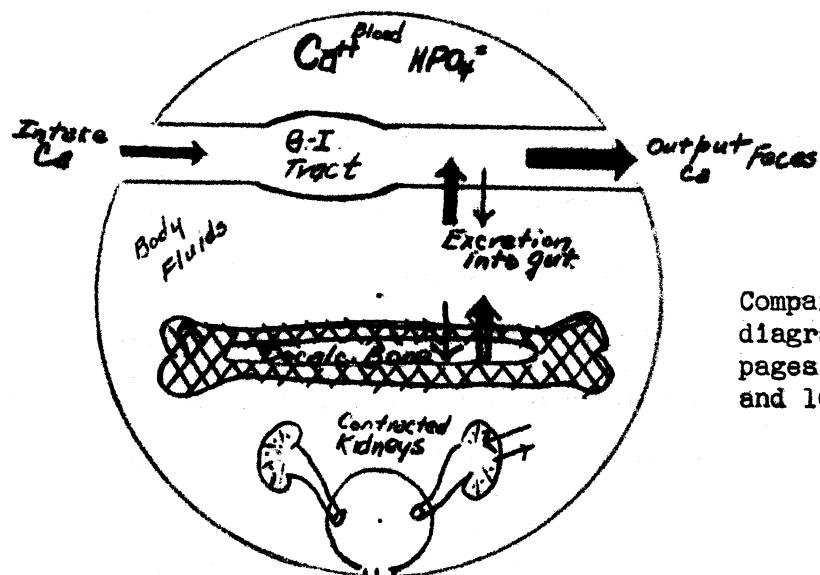


Compare with diagrams on pages 43, 72 and 107.

As suggested in the diagram, the demonstration of enormous amounts of calcium in the feces, and possibly the demonstration by X-rays of some degree of decalcification of the bones, may be of some assistance. Fine granular casts in the urine are quite common in this condition and may suggest the diagnosis. The casts are very fragile and consist of calcium phosphate depositis in a hyaline matrix. They disappear from the urine upon the addition of acid. (6).

Treatment:  In the prevention of renal damage in patients with hyperparathyroidism, Albright, Baird et al (4) have suggested the following regime:  forced fluids, avoidance of an alkaline urine, high phosphorus and high calcium diets. Acidosis producing salts are contra-indicated.

Regarding parathyroidectomy, Albright (8) has further stated that the need for this operation decreases as the renal insufficiency becomes more marked. As a patient develops more and more insufficiency eventually a point will be reached where the amount of renal damage present will require a degree of compensatory hyperparathyroidism (to keep up the blood calcium) and this may only equal the amount of primary hyperparathyroidism actually present. When this has occurred, it is probably harmful to remove any of the parathyroid tissue;  the nearer it is to occurring, the less parathyroid tissue should be removed. This principle is applicable even to outright cases of osteitis fibrosa cystica, where there is associated renal involvement. It has gained support from experience in Albright's

clinic where it has been found that the danger of post-operative
intractable tetany is considerably lessened if the principle is
kept in mind. (8 and 4). In a case reported by Moolten, Clark
and Haywood (122), however, the removal of a parathyroid adenoma
was followed by improvement of the renal function, along with the
general condition of the patient. Excellent surgical judgment is
required.

Primary Renal Damage with Resulting Hyperparathyroidism

It has been demonstrated in recent years that almost all
patients dying of chronic renal insufficiency have an associated
enlargement of the parathyroid glands. In 1935 Pappenheimer and
Wilens (135) showed that in 20 cases of nephritis studied by them
there was an increase in the combined weight of the parathyroid
glands of 50% above the normal. Their cases of severe renal in-
sufficiency showed an increase of 109% by weight. Gilmore and Mar-
tin (67) repeated this work on a larger series in 1937 and also
found that in toxic nephritis and other renal diseases, the para-
thyroids were unusually large with histological evidence of abnor-
mal activity. Nelson (127) has still more recently contributed to
the literature in this connection.

The subject of over-activity of the parathyroids in nephritis
has been approached from another angle by Highman and Hamilton (84).
Using the "rabbit test" technique they investigated the amount of
parathormone in the blood of 23 chronic nephritic patients and

demonstrated a more than normal amount in each. They could not

show any direct relation between the parathyroid activity and the

blood urea nitrogen, however, and no correlation between the para-

thormone level and the elevation of the serum phosphorus. In

spite of the latter they agree with Pappenheimer and Wilens (135)

and others that the hyperphosphatemia of renal insufficiency is

the initiating factor in the chain of events which leads to para-

thyroid hyperplasia and hyperfunction. The final bit of evidence

which proves the relationship between parathyroids and kidneys has

been supplied by Pappenheimer (133). He has found that surgical

reduction of renal tissue in young rats regularly leads to a marked

increase in the volume of the parathyroid glands. Furthermore, if

partially nephrectomized rats are maintained on a low calcium diet,

growth is stunted and skeletal lesions are produced of a far greater

severity than can be ascribed to the dietary calcium deficiency

alone. The picture closely resembles that found in cases of renal

rickets in children. Similar hyperplasia of the glands has been

produced experimentally by phosphate administration, and this may

be taken as evidence that phosphate retention is the cause of the

parathyroid changes in chronic nephritis. (58).

Thus, under the heading of primary renal damage with resulting

hyperparathyroidism we must again mention renal rickets. This sub-

ject and its adult counterpart, renal osteitis fibrosa cystica has

been discussed on page 90. These syndromes must simply represent

an over-compensation on the part of the parathyroids. Apparently

in all renal damage, some compensation by these glands is benefic-
ial in promoting phosphorus elimination and keeping the blood cal-
cium up to its normal level.

In the treatment of these secondary hyperparathyroid diseases,
parathyroidectomy would seem to be contra-indicated. We refer again
to the management of hyperparathyroidism in the presence of severe
renal disease as discussed on page 112.

## MISCELLANEOUS DISEASES

### Scleroderma and Raynaud's Disease

Working with experimental hyperparathyroidism in 1932, Selye
of Johns Hopkins (150) found that young, suckling rats, some only
receiving a single injection of 5 units of parathyroid extract in-
traperitoneally, developed within some days a specific skin disease.
This began with a symmetrical hardening of the skin on the back.
In two or three days the hair over this area fell out and the skin
became even more hard and thick. Ulceration took place in some
parts, and after healing there was left a bare, hairless, atrophic
skin. Histologically the areas showed a marked hypertrophy of the
fibrous tissue of the skin, between the epidermis and the layer of
hair follicles. There were some areas of degeneration in the fibros-
is and some amorphous deposition of calcium. Selye commented that

the entire process was very similar to human scleroderma. Leriche, Jung and Sureyya (106) repeated and confirmed this work, in 1935, with an extensive and elaborate series of experiments. They found that these lesions similating scleroderma were rather easily produced. Later, Leriche, Jung and DeBakey (105) reported some additional pathological findings--namely that the calcium content of the skin of these rats was two to three times greater than normal and that there was occasionally exfoliation of the epidermis.

Following the lead given by the above experimental work, a few investigators have attempted to find some relation between parathyroid activity and human scleroderma. This work has been done chiefly by Leriche and Jung (105) of Strasbourg, Berheim and Garlock (23 and 66) of Cornell University and DeBakey (55) of New Orleans. The latter received his introduction to this work at the Strasbourg clinic. Scleroderma is a term applied to a syndrome characterized by sclerosis, induration and pigmentation of the skin which may be localized or generalized and frequently associated with asthenia, digestive disturbances, arthritis and muscle atrophy. (105). All of the above listed workers believe that the condition is closely allied to Raynaud's disease. The latter, of course, is a neurovascular disorder in which there is a true arteriolar spasm in the fingers, toes, and occasionally the nose, ears, chin, lips and nates. It too, is usually symmetrical.

In 1929 Pautrier and Zorn and independently Naegeli found

human scleroderma to be associated with a high blood calcium. (105).
At the Strasbourg clinic 17 of 20 patients with the disease were
found to have a hypercalcemia.  In addition, in certain types of the
disease (Thibierge-Weissenbach syndrome and localized scleroderma)
there is calcium deposition in the skin.  These facts, coupled with
the demonstration of pronounced hypotonia and asthenia, as well as
definite skeletal changes of hyperparathyroidism in some of these
patients, lead Leriche and his associates to try parathyroidectomy
as a therapeutic measure. (105 and 55).  The first parathyroidectomy
at this clinic was done in January, 1931.  By the end of 1936 the
number had been increased to 13.  Of these, 38.4% showed marked
improvement, 53.8% moderate improvement, and only 7.6% no improve-
ment.  The last figure represents only 1 case, and in this patient
there was an associated Addison's disease.  Some of these cases
were followed for from 2 to 5 years, with continued improvement.
The same men had previously done sympathectomy operations in another
series of 13 cases with these results:  38.4% markedly improved,
30.7% moderate improvement and 7.5% slightly improved.  There was
apparently no improvement in 23.3%.  The French workers do not insist
that hyperparathyroidism is the cause of scleroderma, however.  They
simply recommend the use of parathyroidectomy  as a therapeutic
measure, and suggest that it may be combined with sympathectomy in
select cases.

The work and results of the Cornell group have been similar,

except that their series has included more cases with combined
scleroderma and Raynaud's disease, or simply Raynaud's disease.
For several years they have been forming the conclusion that cal-
cium metabolism is concerned in the development of Raynaud's and
other vasospastic conditions. They believe that a calcium defic-
iency in the diet may produce a negative calcium balance and may
cause in certain individuals an abnormal sensitiveness to vasospasm.
The parathyroid glands become hyperplastic to compensate for the
calcium deficiency and a vicious cycle is set up. They further
reason that the removal of two or more parathyroid glands breaks up
the cycle by curtailing the parathyroid activity by 50%. Before
a compensatory hypertrophy takes place in the remaining glands, a
high calcium intake relieves them of over-work and the whole mech-
anism returns to normal. (23). By 1936 this school had completed
13 parathyroidectomies, some in patients with generalized sclero-
derma with moderately severe Raynaud's, some in patients with sclero-
dactylia and vasospasm in the hands, and some in patients with un-
complicated Raynaud's disease. (23 and 66). They report fine
results with dramatic relief of symptoms due to vasospasm. There
is relief of the pain and a change to the normal color of the ex-
tremities practically within 24 hours of the operation. There is
rapid improvement in oscillometric determinations both as to range
of oscillation and degree of spasm. One patient had such extensive
involvement that he was unable to open his mouth widely enough to
chew solid food and had great difficulty in using his fingers.

After parathyroidectomy he was able to open his mouth sidely and eat normally. The finger mobility returned sufficiently to enable him to go back to work as a book-dealer.

Garlock and Bernheim (23) at first removed only two glands, but more recently they have been resecting two completely and doing a subtotal resection of a third. This is done only after all four glands have been exposed. They stress the importance of pre-operative calcium administration to prevent post-operative tetany, and state that a hypercalcemia and a low blood phosphorus are not necessary as indications for operation.

Although there has not yet been sufficient evidence submitted in the literature to allow of the definite conclusion that hyperparathyroidism is concerned in the etiology of scleroderma and Raynaud's disease, the results of parathyroidectomy are encouraging. The prognosis of both of these conditions is generally bad, and any procedure which promises cure, or at least arrest of the processes, should deserve careful consideration and adequate trial.

## Syndrome of Blue Sclera

Blue sclera, a condition in which the sclera of the eye is of such transparency that the retina shows through giving a blue coloration to the eye, is often associated with fragile bones and otosclerosis. In addition there may be other pathology of the eye, including varied lesions of the cornea, embryotoxon, keratocone,

and even bulbar tumor, glaucoma, strabismus or exophthalmos. In connection with the associated bone pathology, there are often pathological fractures of the long bones, ribs, clavicle and sternum. Certain deformities are also common. The long bones are often curved and the cranium becomes flattened and enlarged in all directions. This is pathognomonic of the condition. Radiograms show an abnormal permeability of the rays and a thinning of the cortex. There is a general osteoporosis in the cranium. There is laxity of the ligaments of the joints with frequent subluxations. The auditory symptoms are those of deafness, produced by the otosclerosis and a laxity of the tympanic ligament. There is an enfeeblement of muscle contraction to the faradic current and a diminution of the intensity of contraction to the galvanic current. In many cases the blood calcium is high and the phosphorus low, but this is not a constant finding. (159).

In the above description of the syndrome one may easily see certain points which are suggestive of hyperparathyroidism. The reporting of a few cases in the literature where blue scleras were found in actual, proved cases of hyperparathyroidism is of additional interest. Such cases have been reported by Cohen and Kelly (45) and Keynes and Taylor (99). A disturbance of calcium metabolism has been cited as an etiological factor in blue sclera by several investigators. Among these, Viallefont (159) lists Fonseca in 1930 and Nilus in 1931. Viallefont, himself, does not commit himself

definitely in regard to the possibility of a parathyroid factor
in the syndrome, but does suggest that surgery or irradiation of
the glands might be tried and the effect observed. He points out
that the establishment of such a relation would explain the physio-
pathology of blue sclera, and that the otosclerosis could be ex-
plained on a basis of metastatic calcium deposition. If the para-
thyroids are concerned, however, it must be early in intra-uterine
life.

Rados and Rosenberg (139) believe that in the ordinary cases
of blue sclera there are not sufficient variations in the calcium,
phosphorus and phosphatase values to warrant a supposition of an
endocrine involvement. The hereditary nature of blue sclera is in
contrast to the apparently non-hereditary nature of hyperparathyroid-
ism, as we now know it. At best, the entire problem requires fur-
ther investigation before any definite opinions can be formed.

## SUMMARY OF CLINICAL TYPES

By way of summary we have arranged the various clinical mani-
festations of hyperparathyroidism in a slightly different order than
that taken up in the text. We hope this will serve to emphasize the
differences between the various groups, and give some indication of
the treatment indicated. We repeat again that almost any of these
types may exist with one another in the same patient at the same time.

## Clinical Types of Hyperparathyroidism

| Classification | Parathyroidectomy Indicated |
|---|---|
| **Primary Hyperparathyroidism.** | |
| 1. Generalized osteitis fibrosa cystica. | Yes |
| 2. Nephrolithiasis. | Yes |
| 3. Acute parathyroid poisoning. | Probably |
| 4. Chronic nephro-calcinosis. | In early cases |
| **Secondary Hyperparathyroidism.** | |
| 1. Generalized osteitis fibrosa cystica secondary to other disease. | Probably not |
| 2. Infantile rickets. | No |
| 3. Renal rickets. | Questionable |
| 4. Chronic renal insufficiency from any cause. | No |
| **Conditions where Hyperparathyroidism may be a factor.** | |
| 1. Ankylosing polyarthritis. | In well chosen cases |
| 2. Osteogenesis imperfecta. | No |
| 3. Marble bones. | Questionable |
| 4. Scleroderma and Raynaud's disease. | Deserves a try. |
| 5. Syndrome of Blue sclera. | No |

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