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Parathyroid function and hyperparathyroidism

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PARATHYROID FUNCTION
and
HYPERPARATHYROIDISM

A Review of the Literature

by

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HISTORICAL DISCUSSION:

In the year 1880 Ivan Sandstrom published the discovery of a new gland in man and several animals, which he had made three years earlier. The finding was originally made upon the macroscopic preparation of the thyroid of a dog. Other species examined were the cat, rabbit, ox and horse. Only one gland was usually found in these animals and it was more or less connected with the thyroid gland. The discoverer was mainly interested in his findings in man. He examined about fifty bodies and in most cases he found two glands on each side but otherwise conditions which varied widely.

During his studies of the literature on the subject Sandstrom found a few short statements, one by Remak and the other by Virchow, which seemed to indicate that these investigators independent of one another had seen the parathyroid gland, but otherwise it was entirely unknown in the older literature. Owens in 1862 is also said to have observed the parathyroid in a rhinoceros. Sandstrom's publication was in Swedish, and was only known through references in the literature of other countries. An independent observation by Baber in 1881 was also published but likewise remained fairly unknown for a long time.

However during the following years, influenced by the studies on internal secretion, a strong interest grew up concerning the physiology of the thyroid gland. Work was done along several different lines for an explanation of the various results of thyro-

dectomy in different animals.

The importance of the parathyroid gland for the result of thyroidectomy was made clear by Gley through a series of well planned experiments. The observations made by Gley drew immediate attention to the discovery of Sandstrom. Prenant and others had already in 1893 and 1894 made observations upon the embryonic development of the parathyroid, but the correct interpretation of these findings was not possible until the anatomical conditions were further elaborated.

Sacerdotti first observed nerves following blood vessels into the gland. Andersson found that not only did such nerves end in the walls of the blood vessels, but they also showed thread or bulb-like endings intraepithelially after several dicotomic divisions.

Concerning the pathological anatomy of the parathyroid gland Sandstrom had made some observations, one of amyloid degeneration and one of cystic degeneration of the gland. The stated assumption of Sandstrom that the parathyroid could be the center of pathological growth processes has also been shown to be true by Benjamins, MacCallum, and Hulst.

The knowledge that was thus acquired about the constant occurrence and independent origin of the parathyroid glands did not support the opinion, which for a time was the usual one, that they were rudimentary thyroid glands. Moussu and Kohn early supported the opinion of their independence of the

thyroid gland. Likewise Maresch, Fusari, Aschoff, Peucker Pineles. However, experimental research gave the final justification for this opinion.

Vassali and Generali made extirpations of both the and "outer" parathyroid glands. The animals died after a few days with paralytic and convulsive symptoms. With Donaggio, Vassali showed in 1897 a peculiar degeneration of the crossed pyramidal tracts and the posterior columns of the spinal cord in the parathyroidectomized animals. Walbaum, Biedl, Leischner, and Halsted showed that transplantation of the parathyroid prevents the characteristic symptoms in parathyroidectomized animals. This finding was confirmed by Pepere and by Pfeiffer and Mayer. Pineles in 1906 and Erdheim demonstrated that tetany after struma operations occurred less often since intracapsular extirpation brought about conservation of the parathyroid region. This finding was further confirmed in an anatomical study by Landstrom in 1908.

In 1902 Jeandalize suggested that certain spasmodic in man such as convulsions in children, tetany, epilepsy, and eclampsia had their origin in an insufficiency of the parathyroid, but at the same time he warned against an exaggerated generalization of this point of view. Regarding the tetany of pregnancy, if one or one and a half of the outer parathyroid gland in the rat was extirpated there was generally none or a rapidly disappearing tetany, but if pregnancy occurs, tetany

will follow and this condition might be repeated in pregnancies of the animal. This view was further elaborated by Adler and Thaler in a clinical study of pregnancy.

Pepere in 1908 also believed that he had found microscopic signs indicating an increased activity of the parathyroid gland in pregnancy, occurring as an increase of the number of oxyphil cells and of the amount of colloid, changes which under similar conditions have been found in the anterior lobe of the hypophysis. The similarity of the clinical symptoms in the parathyroidectomized animals and those of eclampsia in women was advocated by some investigators and questioned by others. Vassale and Brun have both suggested parathyroid medication in eclampsia. Lundborg showed that the offspring of parathyroidectomized animals were more sensitive to parathyroidectomy than others. Mironesco described complete atrophy of two of the outer parathyroid glands in a case of pellagra.

Following this, certain attempts were made to associate parathyroid disfunction with certain derangements of the muscular system. This idea was brought out by Lundborg in 1904 when he tried to show, through coordination of known clinical and experimental facts that the parathyroid gland must be intimately associated with normal muscular and neuromuscular activity.

Pighini obtained promising results by parathyroid medication in three cases of dementia praecox, which caused him to consider the possibility that the catatonic symptoms of this

disease might be related to a changed or decreased parathyroid function. In a later investigation of the metabolism of the disease in question, the same investigator found in its chronic phase an increased calcium excretion, which might be mentioned in relation to the later work of MacCallum and Voegtlin.

As a working hypothesis some American investigators were of the opinion that in some way the parathyroid regulated the calcium metabolism of the body. On extirpation of the gland a condition of increased excitability occurs, similar to that which Loeb and MacCallum had earlier induced by precipitation of the calcium salts within the organism. It was this hypothesis and its subsequent confirmation that molded the direction of parathyroid research up until the present time.

PARATHYROID FUNCTION:

The fundamental nature of the hormone's action has been the subject of a considerable amount of discussion and research, but up to this time no certain conclusion can be drawn. Cameron and Morehouse thought that the hormone controlled the formation of a specific non-diffusible organic calcium compound. The calcium level in the blood was conceived to depend upon a series of interlocked equilibria between this compound and inorganic calcium ions. Increase in the concentration of the organic compound in the blood caused a corresponding increase in ionic calcium which was furnished by the bones. After parathyroidectomy conditions were reversed, a fall in concentration of the com-

pound and reduction in ionic calcium resulted. Greewald's view was that the hormone itself, or a substance formed through its action, increased the solvent power of the plasma for calcium. This substance, designated X, was supposed to unite with calcium ions to form an undissociated organic compound which was stated to resemble calcium citrate. By this action the concentration of calcium ions in the plasma was reduced and the concentration of undissociated calcium increased. Since the plasma was believed to be in equilibrium with solid tricalcium phosphate ($Ca_3(PO_4)_2$) of osseous tissue, a reduction in the calcium ion concentration of the plasma resulted in the liberation of calcium ions from the bones. The result was a rise in the total calcium of the plasma. Little direct experimental evidence can be cited in support of either of the foregoing views. They picture the liberation of calcium from the bones as a physico-chemical process. The histological studies of Selye in rats, on the other hand, suggest that the calcium is mobilized by cellular activity. During the hypercalcemia the bony trabeculae showed large numbers of osteoclasts which are believed to be responsible for the removal of calcium. When the animal became tolerant to the hormone the osteoclasts were replaced by osteoblasts and the bone density increased due to calcium deposition. However Shhour and Ham, consider the appearance of osteoclasts to be the result of the resorption of calcium from the bone rather than that these elements are active agents. They pointed out that para-

thyroid administration interferes with calcification of the dentine of the incisors of rats though osteoclasts are absent.

Aub and his associates believe that the parathyroid hormone exerts its primary action upon phosphorus metabolism, the effects upon the metabolism of calcium being secondary to the depression of the inorganic phosphorus of the blood. Ellsworth suggests that the essential action of the hormone is to lower the renal threshold for phosphate, presumably by inhibiting reabsorption of the latter. The sequence of events, according to these views are increased excretion of phosphorus, reduced inorganic phosphorus of the blood and a reciprocal rise in serum calcium. An observation which has some bearing upon this subject is the reported failure of the hormone to induce hypercalcemia in bilaterally nephrectomized animals. But the phosphate retention and the hyperphosphatemia which results from this operation might be expected to reduce or even prevent the hypercalcemic effect of the hormone, though the latter had no specific effect upon phosphorus metabolism. However, the important part played by the parathyroid hormone upon phosphorus metabolism cannot be doubted; but such action is probably separate from that upon the metabolism of calcium, for it is possible under certain circumstances to induce hypercalcemia by means of the hormone without causing a corresponding reduction in organic phosphorus as shown by Thomson and Pugsley.

A number of observations suggest a relationship between the actions of excessive dosage of vitamin D and parathyroid hormone. Hess, Weinstock and Rivkin found that in monkeys hypercalcemia is less readily induced by irradiated ergosterol after parathyroidectomy. Higgins and Sheard found that the parathyroids of chicks deprived of ultraviolet light became hyperplastic, but were restored to normal appearance by the administration of cod-liver oil. Taylor, Weld, Branion and Kay found that the toxic overdosage effects of irradiated ergosterol were less severe than is usual in completely parathyroidectomized dogs. They also showed that the overdosage effects of parathormone and irradiated ergosterol were similar. Both substances cause the same degree of hypercalcemia and hyperphosphatemia, and a rise in the non-protein nitrogen of the blood. In large doses either causes the withdrawal of calcium from the bones and increases the excretion of calcium and phosphorus in the urine. The symptoms during life and the post-mortem findings after poisoning with either material are also identical, and those species resistant to parathormone are similarly resistant to overdosage with irradiated ergosterol. It has been shown by others that either parathormone or irradiated ergosterol gives rise to metastatic calcification and to bony changes analogous to osteitis fibrosa cystica. Irradiated ergosterol, however, takes longer to show its effect upon the serum calcium than does parathyroid extract, and the hypercalcemia once established persists for some weeks.

HYPERPARATHYROIDISM

Barr defines hyperparathyroidism as a condition resulting from excessive secretion of one or more parathyroid glands or from the injection of parathyroid hormone. It is characterized by a diminished irritability of the neuromuscular system, by demineralization and deformity of the skeleton and by profound changes in the calcium and phosphorus metabolism.

History.- In 1884 Davies-Colley described to the Pathological Society of London the case of a young girl with generalized skeletal disease, a tumor of the jaw, renal stones and increased renal excretion of calcium. Detailed knowledge of osteitis fibrosa cystica started, however, with the report of von Recklinghausen, who studied two patients with decalcification, tumors and extensive deformities of the bones and attempted to differentiate the condition from the previously described cases of osteomalacia. Parathyroid tumors have been recognized since 1899, when Kocher suggested such an origin for five new growths containing glycogen which he had observed in the region of the thyroid. The first indication that there might be an association between von Recklinghausen's disease and the parathyroids came in 1904 from Askanazy, who observed a patient with generalized bone disease, multiple fractures and a tumor of a parathyroid gland.

In 1925 Hoffheinz collected the 45 cases of parathyroid

tumor which had at that time appeared in the literature and found that 27 were associated with diseases of the skeleton, most frequently with osteitis fibrosa cystica. It was not until the discovery of an active parathyroid hormone, however, that the true significance of the association could be appreciated. Some three years after the first report of such a substance, Mandl, a surgeon, recognizing in a patient the symptoms which might be expected with excessive parathyroid secretion, explored the neck and found a parathyroid tumor, the removal of which resulted in remarkable clinical improvement

The discovery that hyperparathyroidism is the cause of generalized osteitis fibrosa cystica has ledtto the assumption that hyperparathyroidism manifests itself only as a disease of bone. Because osteitis fibrosa cystica ia a great rarity, it has been assumed that hyperparathyroidism is equally rare. Both of these assumptions have been proved to be false.

In 1934 Albright and his associates reported 17 proved cases of hyperparathyroidism, most of which they had observed during a period of two years. Analysis of these cases led them to conclude that (1) hyperparathyroidism can occur without evident disease of bone, (2) involvement of the urinary tract isaa more common and more important manifestation of hyperparathyroidism than involvement of the skeleton, (3) hyperparathyroidism is relatively common and (4) it is the etiologic factor in the

formation of renal calculi in an appreciable number of cases. By 1942 Cope was able to report the remarkable total of 67 proved cases of hyperparathyroidism which had been observed at the Massachusetts General Hospital over a period of ten years. Classic osteitis fibrosa cystica had been encountered in about a third of these and minimal or atypical osseous changes had occurred in another third, while in the remainder of these cases evidence of skeletal involvement was altogether lacking. These experiences have been further substantiated by Keating and Cook in an analysis of 24 proved cases of hyperparathyroidism.

Etiology.- Hyperparathyroidism may be produced at will by the injection of parathormone. Clinically it is seen only as an accompaniment of tumors or hyperplasia of the parathyroid glands. The latter has been observed under a great variety of conditions. In animals Erdheim found it in the experimentally produced rickets of rats. Similar changes were reported by Ritter and by Pappenheimer and Minot in the rickets of children. After partial extirpation of the parathyroids, compensatory hyperplasia of the residualltissue has been noted by many observers. Marine demonstrated the overgrowth of the glands in fowls that were kept on an insufficient intake of calcium, while Higgins and Sheard noted it whenever sunlight was deficient.

Wilder has suggested that lack of sunlight may be a factor in the seemingly greater incidence of hyperplasia observed in some portions of the United States. Among the most interesting

associations is the hyperplasia which may follow prolonged renal insufficiency. This was noted at autopsy by MacCallum and by Bergstrand. The relationship has been studied more extensively by Albright, who believes that the phosphate retention of long-standing nephritis may be a cause of generalized and extensive parathyroid hyperplasia. Shelling has recently reported a case of renal rickets in which clinically there was phosphate retention and evidence of increased secretion of parathyroid hormone and at autopsy enlargement of all of the parathyroid glands.

The most striking association of parathyroid hyperplasia or tumors is with diseases of bones. This has included osteomalacia, rickets, osseous metastases from cancer, multiple myeloma, and most frequently generalized osteitis fibrosa cystica. In some of these skeletal diseases, and particularly in von Recklinghausen's disease, the change in the parathyroids must be considered primary. In others, however, there is more than a little evidence that the osseous lesions or the conditions on which they depend are responsible for overactivity and overgrowth of the parathyroids.

Most of the cases of hyperparathyroidism have occurred in middle life, although the disease has been seen at the age of two and a half and as late as seventy-four. In the 130 cases analyzed by Wilder, 99 were in womenaand 31 in men. It is not unlikely that diet and especially the previous intake of cal-

cium and phosphate may have an important bearing on the development of the condition. The possible importance of lack of sunlight as an etiologic factor has already been mentioned. In Wilder's series, 41 cases came from the North and Central states, 21 from England and Scotland, 21 from Austria and Germany, 18 from Scandinavia and the Netherlands, while only 9 were reported from France and 4 from Italy.

Symptomatology.- Generalized osteitis fibrosa cystica is the usual form of clinical hyperparathyroidism in the same sense that Grave's disease is clinical hyperthyroidism. It is characterized by multiple cysts and giant-cell tumors of the bone with decalcification and softening of the entire skeleton, and results in frequent pathologic fractures, bowing of long bones and extreme deformity and disability. There is associated hypercalcemia and hypophosphatemia with increased excretion of calcium in the urine, a negative calcium balance and at times the formation of bilateral calculi in the renal pelves. Clinically the disease displays great varability and in early cases may offer considerable difficulty in diagnosis. The symptoms presented by patients having hyperparathyroidism may be divided into three groups: those resulting from the chemical changes in the blood and urine, those resulting from secondary involvement of the urinary tract and symptoms resulting

from involvement of the skeleton.

Hyperparathyroidism is characterized by an increase of calcium and a reduction of inorganic phosphorus in the serum. As one would expect, symptoms occur which represent the antitheses of parathyroid tetany. Pronounced muscular atony is found and, with it, weakness, fatigue and constipation. Anorexia, loss of weight, nausea and vomiting also are encountered. In many of the cases of advanced hyperparathyroidism with skeletal involvement reported in the literature, such general symptoms have been very severe.

Except when they were conspicuous, the general symptoms related to hypercalcemia offered little clue to the diagnosis, largely because such symptoms are not distinctive and are frequently encountered in other conditions, particularly functional states.

The excessive excretion of calcium and phosphorus in the urine which is characteristic of hyperparathyroidism may be accompanied at times by severe polyuria and polydipsia. At times these symptoms have been conspicuous enough to lead to an erroneous diagnosis of diabetes insipidus. According to Keating and Cook, there is a persistently dilute urine in over half the cases. In 67 per cent of their cases, the specific gravity of the urine never exceeded 1.015. They regarded this

either as a result of hypercalcinuria or as evidence of impaired renal function.

The excessive excretion of calcium and phosphorus in the urine as a result of hyperparathyroidism provides conditions which favor the formation of renal calculi in the renal pelvis or even deposition of calcium in the renal tubules. Albright and his associates have shown the latter to be the probable explanation for nephrocalcinosis, or diffuse calcification of the renal parenchyma, which occurs in some instances of hyperparathyroidism. Thus urinary symptoms may be produced in hyperparathyroidism by urinary calculi, by infection of the urinary tract and pyelonephritis resulting from renal calculi or by impaired urinary function resulting from nephrocalcinosis.

Keating and Cook found symptoms attributable to renal calculi in 18 of the 24 cases. Such symptoms did not differ in any respect from those resulting from renal calculi from other causes. At first hyperparathyroidism was sought particularly in patients with a long history of renal calculi or in those found on examination to have multiple or bilateral calculi. It soon became apparent, however, that, as Albright had stated, hyperparathyroidism must be suspected in any patient having renal calculi containing calcium.

Symptoms referable to the skeleton, when present, may vary exceedingly from vague or insignificant aches and pains to the

disability and pain accompanying the pathologic fractures, cysts, tumors and deformities which occur in the classic bone disease of hyperparathyroidism. In Keating's and Cook's series pathologic fractures occurred in 5 of the 7 cases of classic bone disease. Biopsy revealed giant cell tumors in 2 of these. The absence of gross deformities, loss of height and other evidences of severe osteitis fibrosa cystica generalisata in the cases here reported attests only the fact that the skeletal disease did not happen to be far advanced in these cases. Skeletal pain, backache or vague aches and pains in the muscles were present in all of the cases in which there was classic bone disease, in 3 of the 9 cases in which there was minimal bone disease and in none of the cases without roentgenographic evidence of bone disease.

Diagnosis.-The diagnosis of hyperparathyroidism depends on the demonstration of an increased calcium in serum, of a reduction of inorganic phosphorus in serum and an increased loss of calcium in the urine.

The normal value of serum calcium is from 9.0 to 11.0 mg. per hundred cubic centimeters. Shelling and Jaffe, as well as Griffin, Osterberg and Braasch, have asserted that the serum calcium level should exceed 12.0 or 12.5 mg.% before the diagnosis of hyperparathyroidism could be made. Albright and his associates in 1937 found that this was not the case. Keating

and Cook found that in 12 of their 24 cases the serum calcium level was actually below 12.5 mg. per hundred cubic centimeters. They also found that in 17 per cent the average level of calcium fell within the normal range and that in 29 per cent the level of one or more individual determinations fell within the normal range. From this it is apparent that the elevation of serum calcium need only be very slight and repeated determinations over a period of time are often necessary to establish the significance in suspected cases.

Albright in 1941 pointed out that the concentration of calcium and consequently its diagnostic significance depend on the concentration of serum proteins. The total calcium includes two chief fractions, one of which is combined with serum protein as calcium proteinate, the other being ionic calcium. Calcium proteinate varies with alterations in the concentrations of proteins and is not primarily affected by parathyroid hormone. Persons who have a lowered level of serum protein and normal total calcium may actually have significantly elevated ionic calcium. While neither fraction can be measured directly, both can be estimated from the concentration of total calcium and total protein by the use of the nomogram prepared by McLean and Hastings. Certain conditions sometimes considered in differential diagnosis, notably multiple myeloma and sarcoidosis, are often accompanied by hyperproteinemia and by secondary hyper-

calcemia due to the elevated proteins. A sufficient reduction of serum protein to mask hypercalcemia is rarely encountered in patients having hyperparathyroidism. On the other hand, the demonstration of elevated proteins has been a relatively frequent means of avoiding an erroneous diagnosis of parathyroid disease.

The normal level of inorganic phosphorus varies from 3.0 to 4.0 mg. per hundred cubic centimeters of serum. The average depression of the serum phosphorus is small, and considerable fluctuations of the concentration of inorganic phosphorus may occur in the same patient from time to time. One or more determinations fell within the normal range in 25 per cent of Keating's and Cook's series, and the average value of inorganic phosphorus was at the lower limit of the normal range in 17 per cent of the cases. In several instances the depression of phosphorus was the best clue to the diagnosis, particularly when the value of serum calcium was equivocal.

Albright and his associates in 1937 emphasized the fact that elevation of alkaline phosphatase is a reflection of bone disease but not of hyperparathyroidism per se. This fact was further borne out by Keating and Cook, who found elevated alkaline phosphatase only in conjunction with bone changes such as generalized osteitis fibrosa cystica, but no changes where

renal calculi were found without bone changes.

The assumption that the level of alkaline phosphatase in serum reflects osteoblastic activity in bone and not parathyroid function is further supported by the fact that, after removal of a hyperfunctioning parathyroid tumor, the phosphatase remained elevated long after the serum calcium, serum phosphorus and urinary excretion of calcium had returned to normal.

The Sulkowitch test, brought into wide usage in 1937 by Albright, has proved useful as a rough measure of excessive excretion of calcium. It has been most useful in ruling out the diagnosis of hyperparathyroidism. In the absence of renal disease, a low level of excretion of calcium as indicated by the Sulkowitch test in a concentrated specimen of urine effectively rules out hyperparathyroidism.

The Sulkowitch test is simply performed by mixing an equal volume of urine and Sulkowitch reagent. The calcium present is precipitated when the test tube is inverted a few times. A minimal response or precipitate is called a grade 1 and is considered to indicate a normal concentration of calcium. More pronounced calcinuria is graded 2,3 or 4. The test was recorded in 15 cases of the Keating and Cook series. In 1 case a grade 1 response was consistently elicited in the presence of pronounced polyuria. In 5 cases the precipitate was graded 2 and in 9

cases it was graded 3.

When the diagnosis is otherwise fairly obvious, a strongly positive Sulkowitch reaction which cannot be explained on other grounds has been considered as supporting the diagnosis of hyperparathyroidism; but in most instances it is preferable to determine quantitatively the excretion of calcium under known dietetic conditions. The diet employed by Bauer and Aub contains 125 mgs. of calcium per day. Most normal persons will excrete less than 100 mg. of calcium per day on this diet. Albright regards values between 125 and 200 mg. as definitely abnormal and values in excess of 200 mg. as pathognomonic in the absence of other disease.

Camp and Ochsner in 1931 called attention to the characteristic roentgenologic appearance of the demineralized skeleton in hyperparathyroidism, the fibrous appearance of the long bones, the characteristic miliary osteoporosis of the skull and the significance of subcortical cystic regions.

Keating and Cook classified their cases according to the roentgenologic findings. Group 1 cases exhibited classic bone disease. One patient had sustained innumerable pathologic fractures resulting from a coexisting malady accompanied by uncinate fits. Cystlike areas in the long bones, the typical fibrous rearrangement of the trabecula, the characteristic changes in

the skull and the diffuse demineralization were present in all 7 cases in this group.

Group 2 cases were so classified because the roentgenologic appearance of the skeleton lacked the characteristic features described. In 2 of the patients minimal demineralization of the hands and skull together with subcortical absorption cysts was present. In both cases, however, very extensive demineralization of the spinal column was accompanied by ballooning of the intervertebral disks. This observation, together with the presence of normal alkaline phosphatase, led to the surmisal that in these cases hyperparathyroidism may have been complicated by senile osteoporosis and that the senile osteoporosis was an independent entity not related to parathyroid hyperfunction.

The remaining 7 patients comprising group 2 were reported by the roentgenologist as showing minimal osteoporosis of the skull. Changes in the remainder of the skeleton, if present, were too mild to be recognized. In several of these cases, as a matter of fact, the presence of osteoporosis even in the skull was equivocal but, in order to separate clearly those cases without any evidence of skeletal disease from those having it, any case in which there was any question of minimal bone disease was arbitrarily assigned to this group for comparison. The patients

comprising group 3 are so classified because the roentgenologic appearance of the skeleton was regarded as entirely normal in density and architecture.

The dental pathologic changes in hyperparathyroidism have been discussed by Borg, by Stafne and Austin and more recently by Strock. These writers have emphasized the fact that in a number of instances of hyperparathyroidism the presenting symptoms have been the result of changes in the oral cavity. Strock called attention to the frequency with which epulis and malocclusion occurred. He also emphasized the characteristic ground glass osteoporosis and the loss of the lamina dura which was observed in the dental roentgenogram of such patients. No increase in dental caries has been observed in patients with parathyroid disease. Albright has emphasized the usefulness of the dental roentgenogram in the diagnosis of the bone disease of hyperparathyroidism and has particularly stressed the significance of the lamina dura.

Dental roentgenograms were made in 13 of the 24 cases in the Keating and Cook series. The characteristic roentgenologic changes described by Strock were observed in all 4 of the cases in group 1, and definite, although mild, changes were present in 2 of the 3 cases in group 2. In 6 cases from group 3, however, the dental roentgenograms, like those of the rest of the skeleton, were entirely normal. The most striking change in the roentgenograms of the jaws was a pronounced and diffuse

derangement of the normal osseous pattern associated with evident diffuse demineralization. There was complete disappearance of the lamina dura in the 2 most severe cases in group 1 but only partial disappearance in the remainder. One case showed cyst formation.

Mild degrees of osteoporosis may be detected more readily in the dental roentgenograms than elsewhere because the teeth, the density of which is unaffected by hyperparathyroidism, serve as indeces of opacity. Since disappearance of the lamina dura is observed in several purely dental conditions, this criterion is significant only if associated with diffuse demineralization and obvious derangement of the bony architecture.

It has been generally assumed that renal calculi resulting from hyperparathyroidism consist of calcium and phosphorus, since both of these substances are excreted in excessive quantities. However, quantitative analysis reveals that most of these stones are made up of calcium oxalate and only a few are calcium phosphate or carbonate. This finding has been substantiated by Albright and by Keating and Cook.

Keating and Cook also found that in 4 cases out of a series of 24 the roentgenograms disclosed diffuse miliary calcification involving the parenchyma of both kidneys. Two of these had in addition discrete stones in the renal pelvis and a history of

renal colics. In the other 2 there was no definite evidence of stones and no history referable to the urinary tract. It is presumed that these cases represent nephrocalcinosis, which Albright and his associates have shown to be capable of producing serious and at times irreversible renal insufficiency. Demonstrable urinary insufficiency, as evidenced by an elevated level of urea in the blood, occurred in 2 of the 4 cases. Severe renal insufficiency was encountered in another patient without visible calcification of the kidneys; the urea clearance was 12cc. per minute. The remarkably low excretion of calcium and relatively normal blood values may perhaps be attributed to the impaired renal function, since by any other standard the parathyroid disease was most severe.

Albright and his associates have emphasized that serious renal damage, resulting from nephrocalcinosis, secondary pyelonephritis or obstruction by stones, is the most important change produced by hyperparathyroidism and the most pressing reason for early diagnosis and treatment. Churchill and Cope, as well as Downs and Scott, have reported well authenticated cases in which the urinary insufficiency resulting from hyperparathyroidism was the cause of death, and there is reason to believe that the renal damage may lead to a fatal issue either directly or

indirectly even after excision of the hyperfunctioning parathyroid lesion and correction of the metabolic disorder.

Treatment.- Because of the constant loss of calcium and phosphate in hyperparathyroidism, a diet high in these elements is theoretically indicated. The administration of vitamin D and the application of sunlight might also be considered to be logical. Although with these measures periods of positive calcium and phosphorus balance may be observed, the treatment is in general unsatisfactory and accomplishes little more than temporary arrest in the progress of the disease.

Radiation of the normal parathyroids in animals has not produced tetany in the experience of Biedl. It has seemed possible, however, that hyperplastic glands or tumors might be more sensitive than normal parenchyma. X-ray therapy has been insufficiently tested but in several instances has apparently caused remission of symptoms. In Cutler and Owen's case the serum calcium was reduced from 29.4 to 12 mg. per cent with improvement in the general condition of the patient.

For patients in whom the diagnosis of hyperparathyroidism is definitely established, operative removal of a tumor or hyperplastic tissue offers the best hope of permanent cure. Usually this must be undertaken without definite knowledge of the existence of abnormal tissue. In only 15 of the 130 cases

in Wilder's series was a tumor palpated before operation. In many instances a swelling in the region may be a nodule or adenoma of the thyroid. Usually the parathyroids are placed so deeply that even a large tumor may entirely escape the attention of the examiner. Furthermore, an adenoma of the parathyroid may develop in aberrant or abnormally placed glands. At least six have been found in the anterior mediastinum. Others have been located behind the clavicle, in the carotid triangle, in the posterior mediastinum and behind the trachea as reported by Mandl. Even when the tumor is in a normally placed gland it may not be easily found at operation. In one of Hunter's patients three operations were necessary before it was localized. The difficulties are best illustrated by the case of Charles Martel so extensively studied by DuBois, Aub, Churchill and their associates. Since a tumor was not found at the first operation, two normal parathyroid glands were removed. When this failed to accomplish permanent improvement, search was made on six separate subsequent occasions and was finally rewarded by the discovery of a large tumor in the anterior mediastinum. Another difficulty is introduced by the occasional presence of more than one tumor and the possibility of diffuse hyperplasia involving all of the parathyroid tissue.

The immediate effects of parathyroidectomy are a reduc-

tion in the concentration of serum calcium and a decrease in the excretion of calcium and phosphorus in the urine. These changes may be apparent as early as eight to twelve hours after the operation. The fall in calcium may be gradual or may occur with alarming abruptness, and severe or even fatal tetany may develop as in the experience of Beck. In the 109 operative cases studied by Wilder, 48 displayed in the post-operative period tetany or an equivalent drop in the level of serum calcium. In some patients this condition is temporary, but in some cases, according to Bulger and his associates, the condition may persist indefinitely. During the acute phase the clinical management may require all the resources which are available for the treatment of tetany.

The ultimate results of operation in hyperparathyroidism have been most gratifying. The weakness which is so characteristic of the condition gradually disappears, the apetite becomes vigorous, constipation is controlled and a gain of weight may be expected. Tumors of the bone tend to recede. X-rays of the skeleton show a gradual but definite recalcification. In patients whose bones have not become twisted and deformed and whose kidneys have not been too extensively damaged, a complete return to normal activity and health is possible.

Pathology.- Because of the great variability in the size,

shape and number of normal parathyroids, the diagnosis of hypertrophy or hyperplasia has offered unusual difficulties. Recently, however, Albright and Castleman and Mallory have described a group of cases in which the glands are greatly and diffusely enlarged and in which the histologic picture is of such a character as to leave no doubt as to the hyperplastic nature of the process. In an analysis of 174 cases of presumable hyperparathyroidism, Castleman and Mallory found 153 in which adenomata had been demonstrated and 21 in which they considered the glands hyperplastic.

Our knowledge concerning readily recognizable diffuse hyperplasia has come almost entirely from the experience of the group at the Massachusetts General Hospital in Boston. It has been seen most frequently in association with renal calculi with or without the clinical signs of osteitis fibrosa cystica. All of the parathyroid tissue is involved in the process and presents a strikingly uniform appearance. The usual type of hyperplasia involves the wasserhell cells and consists of a mass of large clear cells having an acinar arrangement. A much less common form which has been seen chiefly in cases with advanced renal involvement is characterized by a proliferation of the chief cells.

In the Keating and Cook series the tumors examined histologically contained all of the types of cells common to the

normal parathyroid gland, although one or another of these us usually predominated. No evidence of extension, invasion or distant metastasis was observed. Disagreement exists as to the histologic classification of these growths. Hyperfunctioning parathyroid tumors which show unequivocal clinical evidences of malignancy do occur but are exceedingly rare. Alexander and his associates discussed cellular changes, which in their opinion, warranted a diagnosis of adenocarcinoma in 13 of the 14 cases of parathyroid tumor in their series. Castleman and Mallory have observed similar cellular changes but do not consider them to be sufficient evidence on which to make a diagnosis of carcinoma. They classify all the tumors which they have observed as benign adenomas. Irrespective of the different interpretations given to the cellular characteristics of these growths, it is generally agreed that the great majority of them are clinically benign and lack the clinical characteristics usually associated with malignant neoplasms. They rarely recur, invade or metastasize, but there have been a very few isolated instances in which distant metastasis or local recurrences have eventually been observed. These occurrences have been recorded by Gentile, Skinner and Ashburn and by Meyer and Ragins.

Possible Associated Conditions.- The role of the parathyroids in the metabolic disturbances or rickets is somewhat mysterious. Hyperplasia of the glands has been demonstrated by Erdheim in spontaneous and experimental rickets in animals, and by Pappenheimer and Minot in the rickets of children. The symptoms and calcium disturbances of rickets are, however, far from indicative of hyperparathyroidism. Clinically, the calcium values tend to be diminished and in many instances have become so low as to permit severe tetany. The urinary excretion of calcium is not increased. Although the existence of hyperplasia of the parathyroid glands does not necessarily imply increased parathyroid function, experiments of Bengt Hamilton indicate that hyperparathyroidism may actually be an important factor, and that the blood of rachitic animals may be rich in parathormone or some other substance with an identical effect on serum calcium. It may be demonstrated in animals that doses of calcium which ordinarily cause no disturbance of serum calcium values, produce striking hypercalcemia when given after an injection of parathormone. Administration of calcium salts to rachitic rabbits usually results in death from hypercalcemia. Hamilton has shown that the injection of blood from a rachitic animal into a normal one causes a

response to calcium administration which is identical with that occurring after the administration of parathormone.

A study of the relationship between the deficiency of vitamin D and the parathyroid has been recently studied by Wilder, who found that deprivation of vitamin D insufficient to cause rickets produces hyperplasia of the parathyroid glands, which can be prevented by the administration of parathormone. With extreme deprivation, on the other hand, parathormone may restrict, but does not prevent, hyperplasia. Furthermore, it may be shown that parathyroidectomized animals are more sensitive than normal animals to an insufficient intake of vitamin D.

Although the full significance of these striking observations is not yet apparent, it seems possible that while the lack of vitamin D is the primary factor in rickets, it may not be the only one, and that the variable metabolic disturbances of the disease may depend in each individual case upon the relative influence of a lack of vitamin D on the one hand and functional hyperparathyroidism on the other.

The tumor process of multiple myeloma is accompanied by a high degree of destruction of bone. Roentgenologically it may be shown that decalcification and rarefaction occur in

those portions of the skeleton which are not actually involved in the tumor process. Pathologically there may be metastatic calcification with a deposit of calcium in the lungs, in the gastric mucosa and kidneys. Hypercalcemia has been frequently observed and in at least one case a negative calcium balance and generalized hyperplasia of the parathyroid glands were demonstrated. Apparently a similar condition may also occur in metastatic tumors of bone. Klemperer reported a case in which a tumor of the parathyroids was found associated with carcinoma of the breast and osseous metastases. Barr and Charles observed hypercalcemia and hypophosphatemia with hypernephroma metastatic to bone. The evidence, whil not complete or entirely convincing, indicates that destructive bone lesions, such as myeloma and malignant metastases, may be accompanied by a secondary hyperplasia of the parathyroid glands and that hyperparathyroidism becomes, through decalcification of the skeleton, a complicating and disabling feature.

Special mention should be made of the condition in which hyperparathyroidism may possibly be the primary cause of the pathologic change. The disease which has been called marble bones or osteosclerosis, which was described by the radiologist

Albers-Schonberg, is characterized by a great overgrowth of bone that may encroach on the marrow cavity to such an extent as to interfere with blood formation and produce anemia. Although the condition is a great rarity and has been insufficiently studied, one case in the literature has been accompanied by renal stones and questionable hyperplasia of the parathyroid gland. An additional reason for considering that it might be related to overfunction of the parathyroid arises from the work of Selye, who found that when parathormone was given to rats, there were, during a relatively short period of hypercalcemia, changes in the bones not unlike those seen in osteitis fibrosa cystica. With continued administration the serum calcium became normal and new bone was formed with a structure not unlike that encountered in the disease of Albers-Schonberg. The possibility that the condition of marble bones represents a form of hyperparathyroidism in an individual who has become partially resistant to parathormone should be considered.

The observations of Albright have indicated the importance of phosphate retention as a factor in the production of parathyroid hyperplasia, and a recent report of Shelling has shown that in renal rickets there may be generalized enlargement of the parathyroid glands. In such cases any possible hyperparathyroidism must be regarded as secondary but none

the less important in determining the character of the clinical manifestations.

Since the role of the parathyroids is so striking in some diseases of bone, it is not surprising that attempts have been made to demonstrate its importance in other skeletal conditions. Some interest has been attached to the claims of Ballin and Morse, who have attempted to show that Paget's disease, spondylitis deformans, and other forms of chronic arthritis as well as generalized decalcifications of the spine and of other bones are secondary to hyperparathyroidism. Operations have been performed on a relatively large number of cases and have consisted in most instances of removal of normal-appearing parathyroid tissue. Great improvement has been claimed, and the lead has been followed by many surgeons in other parts of the United States.

In Paget's disease, Ballin and Morse emphasize certain superficial similarities to von Recklinghausen's disease, particularly the cyst formation and the localized areas of decalcification. They also stress the improvement in pain and in the skeletal condition which has resulted in patients who have submitted to parathyroidectomy. They have not been discouraged by the fact that the serum calcium of patients with Paget's dis-

ease has been found by Snapper and others to remain within normal limits, that no parathyroid tumors or hyperplasia has been demonstrated, even in advanced cases of uncomplicated Paget's disease, nor by the fact that little improvement could be expected from partial removal of glands which are demonstrably capable of undergoing a high degree of compensatory hyperplasia.

Final Comment.- To an unparalleled degree the diagnosis of hyperparathyroidism requires that a special search be made for the condition. The early symptoms are notoriously vague and seldom pathognomonic, and in many cases without evident bone disease there may be no symptoms aside from those produced by renal calculi. In other words, until the disease manifests itself by somethingffairly spectacular, such as renal colic, there is little likelihood that it will be recognized early. When the chemical abnormalities in the blood and urine are conspicuous, the diagnosis, once suspected, can be established with ease. In many cases, however, the clinical changes are minimal and their significance cannot be ascertained without repeated analysis of the blood and urine and prolonged observation of the patient. Conversely, in many suspects who do not have the disease, it is difficult to rule out hyperpara-

thyroidism except by prolonged study.

Barney and Mintz stated in 1936 that hyperparathyroidism was the etiologic factor in 4 to 5 per cent of the cases of renal calculus which they observed. In 1938 Griffin, Osterberg and Braasch, from the routine analysis of serum calcium and phosphorus in cases of renal calculi, came to the conclusion that t he incidence of hyperparathyroidism in such cases was less than 0.2 percent. Subsequent experience indicates that this figure is too low. In retrospect it is now apparent that, using the criteria then employed, many cases would have been overlooked.

Cope has stated that between 10 and 15 per cent of the patients with renal calculi investigated personally by himself or by Albright are eventually proved to have hyperparathyroidism as the cause. Regardless of what figure is finally determined, it is apparent that hyperparathyroidism is an important and often neglected consideration in the management of patients with renal calculi. On the other hand, renal calculi have many causes and it is obvious that for every case of renal calculi found after careful study to be a consequence of hyperparathyroidism there will be many others in which this diagnosis can be excluded.

In approximately 10 per cent of all cases of renal calculi recurrent or multiple calculi eventually develop. It is reasonable to suppose that hyperparathyroidism may prove to be a factor of considerable importance in this group of cases. A persistent search for parathyroid disease will materially simplify the management of some patients seen with this difficult and serious problem.

Aside from its clinical importance, hyperparathyroidism without evident bone disease provokes speculation as to the relation of the parathyroid hormone to bone metabolism. Irrespective of other considerations it is evident that whether or not in a case of hyperparathyroidism a visibly demineralized skeleton develops depends on the calcium balance. One might suppose that a negative balance of significant degree would be most likely to occur in hyperparathyroidism of long standing. A comparison of the duration of the symptoms in the various groups throws strong doubt on the concept that patients without osteitis fibrosa cystica do not have classic bone disease because they have not been ill long enough.

Other factors being equal, the calcium balance would be most likely to be negative in patients with the greatest excess of parathyroid hormone. If the average level of the serum

calcium can be taken as a rough index of the severity of hyperparathyroidism. The observations of Keating and Cook would suggest that hyperparathyroidism is more severe in the cases in which there is classic bone disease. Comparison of the measured calcium output is a little suggestive that more calcium is lost in the urine in these cases as a group. These observations are in agreement w ith Albright's experience, although he has observed a number of instances in which hyperparathyroidism without bone disease was, by all standards, just as severe as examples of the classic type.

The quantity of calcium in the diet also affects the probable calcium balance. Persons with a high level of calcium in the diet, such as milk drinkers, are less likely to have a negative calcium balance in the presence of hyperparathyroidism than persons whose intake of calcium is low. Albright has felt that this factor accounted for the absence of bone disease in his patients. However, Keating and Cook observed a number of such patients whose previous diet contained calcium in relatively small quantities. The existence of a relatively intact skeleton in those patients implies calcium equilibrium in the presence of sustained hypercalcinuria, despite small quantities of ingested calcium. In these instances calcium equilibrium may be aided by more efficient absorption of calcium from the gastrointestinal tract. Whether such increased

efficiency of absorption is fortuitous or related to the parathyroid disease would be interesting to discover.

In conclusion, it is deemed advisable to present several case records of proven hyperparathyroidism.

The first case is that of Mrs. M.,#86465, who at the age of 42 years was first admitted to the University Hospital with several complaints. She complained of pain, tenderness, swelling, and inability to rotate the right forearm for about three weeks; of an inability to walk without crutches for six months due to weakness of legs; of several falling episodes during the six months; of weakness and tiredness, with a marked weight loss over a period of a year; of urgency, frequency, nocturia and low back pain intermittently for a period of three years; of excessive thirst for several years.

Further questioning revealed that while the patient was lifting a pan of water, she experienced a sharp pain in her right forearm, her arm rotated externally and seemed to lock in that position.

Most of the history was of no consequence as pertains to hyperparathyroidism, but the patient gave one illuminating clue, "I had to have my teeth pulled in 1941 because my jaw bone was wasting away."

Physical examination revealed no palpable abdominal masses,

or masses in the region of the parathyroids.

X-ray consultation revealed the following facts concerning this patient:

Right forearm: There is generalized decalcification of the bones with coarsening of the trabeculae of the radius. The entire central portion of the ulna shows confluent cystic areas with extreme thinning of the cortex and expansion of the shaft. There is an oblique fracture extending through this area from the mid dorsal surface obliquely upward to emerge on the ventral surface at the upper end of the shaft. There is no disturbance of alignment.

Abdomen, KUB: There are areas of flocculated calcification over both kidney areas corresponding to the distribution of the minor calices. Kidneys are normal in size and shape. There is a round area of punctate calcification in the lower abdomen just to the right of the midline, probably in a lymph node. The bones show coarsening of trabeculae and there is some collapse of vertebral bodies in the lower lumbar region. Stomach is tremendously dilated with considerable gas outlining it.

Skull: There is a granular appearance throughout with generalized thickening of the vault and several cystic areas within the thickened bone, particularly in the frontal region.

The impression of the radiologist was: Osteitis fibrosa cystica with caliceal calcification, dilatation of the stomach and mesenteric lymph node calcification. Pathological fracture through cystic area in right ulna.

A complete laboratory study was then done and the following facts revealed: Hemoglobin 9.1 Gms. %, red count three million, seven hundred sixty thousand; white count 5600 with a normal differential count; urine specific gravity, 1.010; a trace of albumin; a few epithelial cells and a urinary calcium of from 5 to 7½ mg.%.; serum calcium 15.85 mg.% ; serum inorganic phosphorus 2.55 mg.% ; serum alkaline phosphatase 12.6 units; Blood NPN 42 mg.%; Blood creatinine 1.2 mg.%; Blood urea nitrogen 19.1 mg.%; a modified Mosenthal test showed a limitation of concentrating power of the kidney with urine specific gravity varying from 1.010 to 1.014.

Following treatment for the fracture of the right forearm, the patient was transferred to the surgery service. On January 25, 1946, the neck region was explored and a tumor mass was removed from the lower pole of the left lobe of the thyroid gland. This tissue had the gross appearance of parathyroid tissue. The microscopic examination of this tissue showed polyhedral cells which varied in size from 10-25 microns and which

showed no evidence of mitoses. The microscopic report was adenoma of the parathyroid gland.

Treatment consisted of surgery followed by medical management. Postoperatively, the patient experienced hypocalcemia of a severe degree. This was combatted by injections of calcium as calcium gluconate and calcium chloride. However, these measures did not seem to be effective, so the administration of the synthetic dihydrotachysterol was begun. Following the combined use of calcium and dihydrotachysterol, the patient showed amazing recovery. A chart of pre- and post-operative blood calcium and phosphorus determinations is given in plate 1.

The second case is that of Mrs. C., # 820-886 who at the age of 50 years was admitted for the second time at Methodist Hospital, Omaha, Nebraska. She complained of weakness and fatigue for a period of nine years. This patient had previously consulted a physician in 1942, but nothing was done concerning the hyperparathyroidism which was present at that time as evidenced by a blood calcium of 19mg. %.

On x-ray examination it was noted that the bones showed irregularity and granulation of trabeculae throughout the entire skeleton.

Serum calcium on admission was 16.2 mg. % and serum phosphorus 2.8mg. %. The hemoglobin was 11.5 gms. % and the red

count was four million three hundred eighty thousand. The white count was 7400 with a normal differential. The urine showed a specific gravity of 1.007 and a trace of albumin with an occassional pus cell on microscopic examination.

The treatment consisted of parathyroidectomy two days following admission. The tumor mass was found at the lower pole of the right lobe of the thyroid gland, and was about 3 cm. in length and 2 cm. in width. It was enucleated with difficulty, and a frozen section was done to make sure that this was not a fetal adenoma.

On pathologic examination the tissue was found to be soft, very friable, yellowish brown in color and homogenous. A large cystic area was also observed and an area of calcification 0.7 cm. in greatest diameter was found to be present.

Medical management consisted of the administration of sedatives as required, calcium gluconate and dihydrotachysterol orally. The patient showed an early recovery of control of calcium metabolism. A chart of pre- and post-operative blood calcium and phosphorus determinations is given in plate 2.

In any discussion of the above cases it is important to point out that both are cases of frank hyperparathyroidism. In both cases the presenting symptom is weakness and fatigue, but

other symptoms are often elicited, such as incidental fractures, loss of the teeth or genito-urinary symptoms such as urgency, frequency and nocturia. Diagnosis depends, first of all, upon the awareness of the physician. Demonstration of hypercalcemia, hypophosphatemia and hypercalcinuria will make the diagnosis, which in many cases can be corroborated by roentgenologic findings. Oftimes it is the clue given by the x-ray appearance of the skeleton which leads the physician to suspect hyperparathyroid disease.

In both of these cases, a parathyroid tumor was found and removed. Following this, the calcium level in the blood fell to a low level and tetany was impending. It is interesting to note by a comparison of the calcium levels of the two patients that the patient given dihydrotachysterol early after operation recovered control of calcium levels more quickly and as a result her post-opprative course was more smooth. It is also interesting that the treatment of impending tetany with simple calcium salts is not sufficient to prevent actual tetany in many cases, and as a conclusion from the above cases, it is believed that dihydrotachysterol will prove a potent antidote for this serious complication of parathyroidectomy.

Summary.- Normal parathyroid function is discussed and

the experimental facts concerning the action of parathyroid hormone are elucidated.

The early history and theories of parathyroid function are given in interesting retrospect. Many of these theories have fallen into ill repute but others persist today and were obviously the result of serious consideration of the subject.

The relation of vitamin D to calcium metabolism and parathyroid function is discussed and it is pointed out that overdosage of either hormone or vitamin D causes withdrawal of calcium from the bones and hypercalcinuria.

Hyperparathyroidism is discussed from the standpoint of history, etiology, diagnosis, pathology, treatment and possible associated conditions.

In conclusion, several illustrative case reports are given in detail. The treatment of postoperative tetany with calcium salts and dihydrotachysterol is discussed.

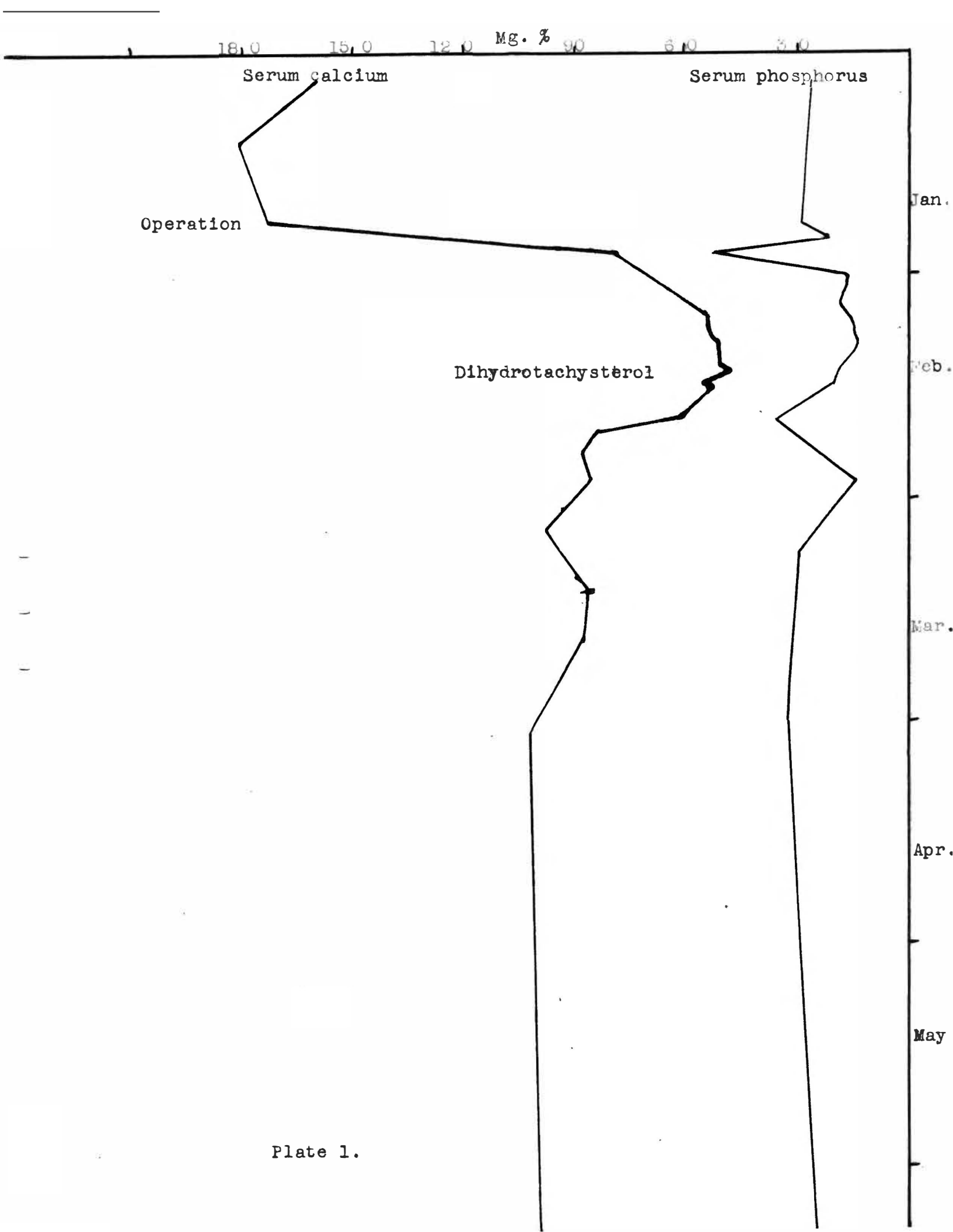
Mg. %
18.0
15.0
12.0
9.0
6.0
3.0
Serum calcium
Serum phosphorus
Operation
Dihydrotachysterol
Jan.
Feb.
Mar.
Apr.
May

Plate 1.

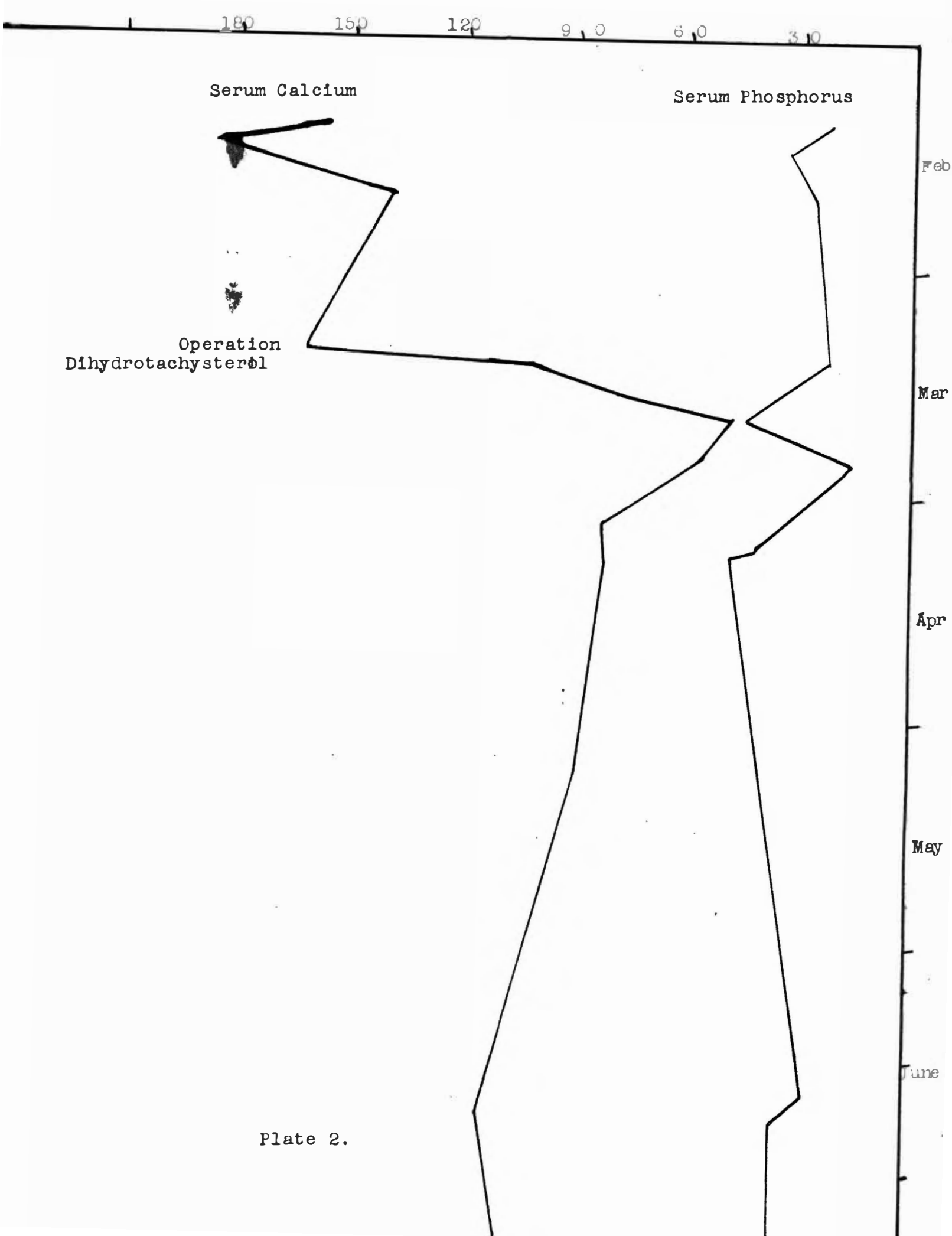
180
150
120
90
60
30
Serum Calcium
Serum Phosphorus
Operation
Dihydrotachysterol
Feb
Mar
Apr
May
June

Plate 2.

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