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Howard M. Chaloupka
University of Nebraska Medical Center

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HYPERPARATHYROIDISM
AND ITS
RELATION TO OSSEOUS PATHOLOGY

by

Howard Michael Chaloupka
Senior Student, University of Nebraska
College of Medicine

Senior Thesis
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Hyperparathyroidism.

In the last decade advances in our knowledge of the parathyroid glands has placed them in the same category with the other endocrine glands in that the pathological physiology of hypo and hyperfunction can now be attributed to them on a fairly rational basis. Indeed, much of our knowledge rests on controversial ground but it is the purpose of this brief treatise to attempt to present in a practical manner the factors involved in the relationship of hyperparathyroidism to osseous pathology.

Historical.

The earliest recorded experiment that had any bearing on the parathyroid glands were those of Raynard (2) in 1835 when he noted that following the removal of the thyroid gland in a number of dogs, death followed in the course of a few days. Schiff (2) in 1859 removed the thyroid in a number of different species of animals and noted that some survived while others died within a few days. The superior pair of parathyroid glands were discovered by Sandström in 1880 who found the bodies at 50 autopsies and accurately described them in animals. His work was lost sight of until eleven years later when Gley rediscovered the superior pair and at this time it became apparent to him that thyroidectomy as previously practiced meant parathyroidectomy as well.

With the discovery by Kohn 1895 of the inferior pair of parathyroid bodies it was recognized that all animals

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contained two pair of parathyroids though in herbivorous the pairs were separated at some distance while in carnivorous they were in close association. Schiff's work then assumed a rational explanation for in the case of complete thyroidectomy in cats and dogs death always resulted because all of the parathyroid glandular tissue was taken while rats and rabbits lived after thyroidectomy because the anatomical separation of the two pair of glands saved half of the glandular tissue to carry on its function following operation.

Vassale and Generali (2) in 1900 removed the parathyroid glands (leaving thyroid intact) in rats and dogs and all except one died with a typical syndrome of fibrillary contractions and muscular spasm, rigid and uncertain gait, tachycardia, emaciation, fall of body temperature, convulsions and death. At post-mortem only slight congestion of the liver and kidneys were found, but nothing specific to account for death. These two men interpreted the finding by formulating the hypothesis that the parathyroids exerted an anti-toxic function.

Physiology.

Many investigators believed that the parathyroids exerted an anti-toxic influence but it was not until 1912 when Koch (3) described the presence of methyl guanidine and other bases in the urine following parathyroidectomy that the toxic theory became founded on an experimental basis. He noted the similarity of tetany and experimental guanidine intoxication. The number of believers rather than the evidence made out a

strong case for this theory which is in direct opposition to the calcium theory which will be discussed next.

MacCallum and Voegtlin (4) 1909 showed that the calcium in the blood was lowered in parathyroid tetany and that the symptoms were alleviated when the blood calcium was restored to its normal level and concluded that the parathyroids regulated the calcium level and that tetany was due to calcium deficiency. MacCallum (5) 1912 further attempted to prove this by showing the galvanic hyperexcitability of the muscles of a normal dog's leg when blood from a tetany dog was allowed to flow through it. Luckhardt and Goldberg (6) in 1922 showed that parathyroidectomized dogs could be held symptom free on calcium therapy. Salvesen (2) 1923 and Collip (2) 1925 confirmed the above results and the theory that the parathyroids exerted an influence on the blood calcium level became the most acceptable because it was founded on experimental evidence rather than circumstantial evidence as was the guanidine or toxic theory.

A number of successful parathyroid grafts to relieve post-operative tetany have been reported (2) by Schiff 1884 Eiselberg 1892 and Halsted 1909 but as soon as scar tissue repair occurred the animal died of tetany.

Maussu 1898, Vassale 1905, Vincent 1905, Berkely and Beebe 1909 and Berman 1924 from time to time reported (2) the attempted use of extracts prepared in various ways, in the treatment of post-operative parathyroid tetany, but whether their work was not accepted or whether their articles went unnoticed is not known, but it was not until Hanson (7) 1923 prepared a hydrochloric acid extract of beef parathyroid glands that

attention was directed toward the possibility of preparing an active extract.

Hanson (7) laid down no scientific proof to establish the fact that the extract contained an active substance and suggested its use in many unrelated conditions. "Many of Hanson's results are highly suggestive of the presence of an active principle in his extract. No scientific proof however, is given of the presence of the parathyroid hormone". (Collip 2)

J. B. Collip (2) in 1924 brought forward final proof that extracts prepared by weak acid hydrolysis of fresh or acetone preserved parathyroid glands of the ox contained the active principle of these glands. A brief review of his very careful work would not go amiss as an introduction to the subject of clinical hyperparathyroidism.

J. B. Collip- Parathyroidism,

Collip (2) found that the effect of a single injection of his parathyroid extract in dogs caused the blood calcium to gradually increase until a peak was reached 15 to 18 hours after injection after which it gradually returned to normal.

(2). That the increase of blood calcium attained in 15 hours is almost directly proportional to the dose administered.

(3). That because of the above two findings the extract could be physiologically standardized. "The unit of potency is defined as 1/100 of the amount of extract which produces on an average of five mgm. rise in serum calcium in 20 kilo dogs in 15 hours".

4. Repeated injections at 4 hour intervals of 25 units of parathyroid extract resulted in a typical train of symptoms and death within 48 to 72 hours. The symptoms which occur and their order of appearance are, vomiting followed by diarrhea, coma and death. During this period (24 hours) the blood calcium rose as shown in the chart below.

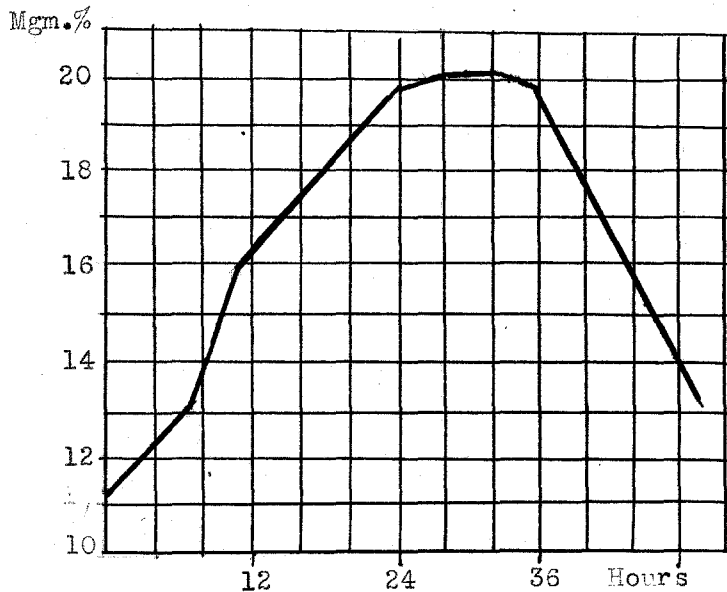


Fig. 1. The Serum Calcium as affected by repeated injections of 25 units of hormone in a normal dog. (From Collip 2)

The peak point of the blood calcium is about 20 mgm. percent. of calcium where it maintains itself for a few hours and then falls. The animal continues to vomit, has water stools, and considerable respiratory distress and death ensues. Coincident with the terminal fall of blood calcium the symptoms become more manifest and the blood phosphorous rises abruptly. Before death the coagulation time decreases and circulation fails and great difficulty is experienced in attempting to draw blood from a peripheral vein. The blood in the terminal stages presents an acidosis.

(5). The effect of single injections in parathyroidectomized dogs is in no way different from normal dogs as shown in the following chart.

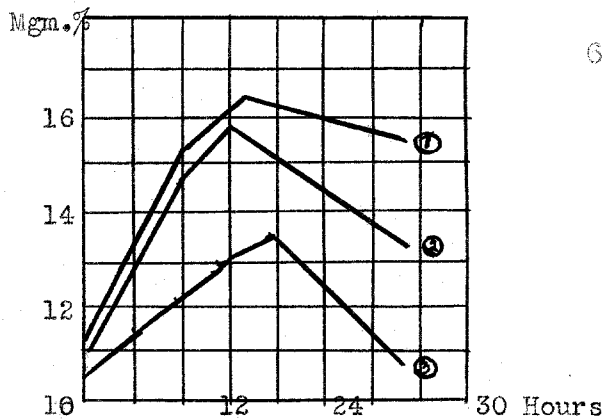
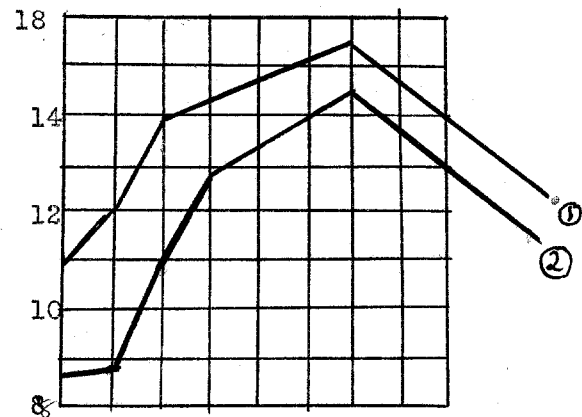


Figure 2. Showing the response of subcutaneous injection of hormone is of a quantitative nature. 1-19 kilo normal dog-100-Unit. 2. 20 kilo dog-75 Unit. 3-22 kilo dog 15 Units.

6.



Showing the response of a parathyroidectomized dog is of the same order as response of normal dog. 1-18.5 kilo normal dog. 2-19.0 kilo parathyroidectomized dog. (from Collip-2).

Further, as the thyroid was removed as well as the parathyroids Collip argues that this is one point of proof against an antagonistic relation of the thyroid and parathyroid glands as was once believed.

(6). If the parathyroidectomized dog is in tetany prior to injection of extract the symptoms are relieved on injection of the extract. In these dogs Collip noted that when the serum calcium was low following parathyroidectomy the phosphorous was high and the first injection of extract caused a lowering of the phosphorous level and an increase of the calcium level. He states that these findings tend to emphasize the importance of phosphorous in relation to the pathogenesis of tetany.

(7). Lastly, in defense of the anti-toxic guanidine theory previous investigators stated that injections of guanidine caused a decrease of the calcium level and that injections of guanidine in post-operative parathyroid tetany caused an increase in intensity of symptoms.

Collip and Clark (8) failed to confirm the accumulation of guanidine in parathyroidectomized dogs and Collip urges the dismissal of the guanidine hypothesis as being based on erroneous or circumstantial evidence.

Thus from the careful work of Collip in 1926 which has up to the present time been repeatedly confirmed and which has not been contested, it became apparent that the parathyroid glands secreted an active principle which maintains the serum calcium level.

This final proof has led to numerous investigations as to the role of calcium in the metabolism of the organism and a short review of these recent publications which are relative to boney pathology will now be discussed.

Calcium Metabolism.

The extraction by Collip of a potent hormone provided a means for accurately studying the role of these glands in calcium metabolism. Hunter and Aub (9) found in their study on lead poisoning that injections of parathyroid extract resulted in an increased excretion of calcium.

These authors concluded that since the calcium intake was controlled the excess of calcium must have been abstracted from the bones. It is interesting to note that this increase of calcium excretion is by way of the kidneys, the fecal excretion being unaffected. Under normal conditions (10, 14) 70% to 90% of the total calcium excreted is eliminated in the feces.

Under hyperparathyroidism (experimental or spontaneous) only

10 to 30% of all the calcium excreted is eliminated in the feces.

Bauer, Albright and Aub (11) in their studies of the calcium balance of normal individuals found that an appreciable amount of calcium is necessary to maintain the body in calcium equilibrium and also found a marked positive calcium balance in infancy to the extent of 300 mgm. daily.

Where then is this source or storehouse of available calcium? Bauer, Aub and Albright (13) made experimental observations on rabbits and cats by injecting parathormone in increasing doses for 91 days and then killed the animals. Roentgenograms showed diminished density compared with the controls and on examination of the bones they found that a large number of trabeculae had disappeared as compared to controls while no measurable thinning of corticalis could be demonstrable. That the diet itself affects the spongy bone is demonstrated by these men in the experiment in which five cats were placed on a high calcium diet and four on a low calcium diet. At the end of four months the left foreleg was amputated and the diet reversed and after a similar period the animals were killed. In these experiments each animal served as his own control, thus eliminating the factors as sex, age, etc. They found that trabeculae of bones were diminished on a low calcium diet and increased on a high calcium diet but no gross changes of cortical thickness were noted.

To prove further the spongiosa is a source of calcium Bauer, Aub and Albright (13) made use of the dye sodium

alizarin sulphonate. ***

After first keeping rats on a low calcium diet for 82 days (to deplete calcium) and then placing them on a high calcium diet plus this dye and after 55 days, examining the bones they found the trabeculae stained deep red while the corticalis showed no trace; further that if rats were kept in calcium equilibrium or in a negative balance by parathormone, no staining of spongiosa occurred and also while adult rats seldom showed cortical staining with this dye growing rats did.

The experiments of these men tend to show that the storehouse of available calcium lies in the spongiosa of the skeletal system. Hunter (15) in his discussion of the clinical importance states, "with this reverse supply of available calcium it would be difficult to remove abnormal calcium deposits in the body. This is proven to be the case in myositis ossificans which is unaffected by parathormone therapy and it also fails to improve acuity of hearing in otosclerosis although many grammes of calcium were eliminated from the body in both conditions by parathormone".

 *** Footnote (15)

The use of dye to stain bone was first discovered three hundred and fifty years ago by Antonius Mizaldus when he noted discoloration of bones fed with "madder". In 1736 John Belchier while eating at a calico printers home noted that the bones of pork fed on dye soaked bran (madder) he was eating were stained red. The osteogenetic function of du Hamel was demonstrated by use of this dye when he showed alternate concentric rings of red and white bone beneath periosteum. John Hunter used it in his experiments. The red dye "madder" was later found to be a glucoside of alizarin and is deposited with the calcium that is laid down in bone.***

An interesting observation which has attracted considerable attention is the relationship of hyperthyroidism and the hyper-excretion of calcium without an elevation of the blood calcium. Aub, Bauer, Heath and Ropes (16) and later Hunter (15) and confirmed by Plummer and other investigators found that in studies of exophthalmic thyroidism the excretion of calcium was greatly increased. They further found that hyper-excretion was much higher in exophthalmic than in adenomatous thyroidism.

Similar results were found in people under thyroid medication. In Aub and his workers' statistics the average basal metabolic rate was 55% above normal while the amount of calcium excreted was found to be 231% above normal.

Conversely they found the calcium excretion about 40% below normal in myxedematous patients. That this hyper-excretion was not due just to an elevated metabolic rate, but rather due to hyperparathyroidism, is shown in Aub, Bauer, Heath and Ropes (16) studies of calcium metabolism in two patients with long continued fevers, (sub acute bacterial endocarditis) in which they failed to find a negative calcium balance. All of these investigators (15--16) recognized that a state osteoporosis existed in the bones especially emphasized when the roentgenograms were taken simultaneously with the bones of an adequate control.

The state of osteoporosis of hyperthyroidism differs from osteoporosis of hyperparathyroidism in that it is evenly distributed over the entire bone while that of the latter disease, as Camp (19) states a miliary granular mottled osteoporosis. Further mention will be made in this connection elsewhere in this paper.

There is some difference of opinion as just what the normal calcium level is in man. Cantarow (14) in his book on calcium metabolism has made a collection of the data on this subject and summarized in stating that the early figures given for a normal level are exceedingly high in light of recent work. Jones found plasma calcium in infants four hours to twelve days old to average 12.3 mgm. percent. Mayer found 11.25 mgm. percent. in first two decades of life and grade ually decreasing to 10.8 mgm, per-cent. at fifty years or over. In men it fell from 11.6 mgm. percent. at age of twelve to 10 mgm. per-cent. at age of seventy eight while in women from 11.8 mgm. percent. to 9.7 mgm percent. over the same age periods. "It appears likely" states Cantarow (14) "that during infancy and in periods of active calcium storage the serum calcium is slightly above the adult level." Alterations of the blood calcium level have been noted during pregnancy. Bauer, Albright and Aub (11) confirmed Widdow's (14) observation of a slightly low calcium level during pregnancy. Mazzocco (14) observed the average serum calcium in pregnant women to be 8.77 mgm. percent as compared to 9.19 mgm. percent. in non pregnant women.

With this brief review of the action of the parathyroids on calcium metabolism we shall now pass to the subject of clinical hyperparathyroidism.

Clinical Hyperparathyroidism.

As to the historical background relative to recognition of hyperparathyroidism. Langendorf and Mommsen (20) in 1877 and

especially Virchow (20) in 1896 gave very good description of a disease later known as generalized osteitis fibrosa cystica. Virchow especially stressed the point that the condition was not neoplastic in character. Von Recklinghausen (20) in 1891 in the Jubilee Volume for Virchow described osteitis fibrosa cystica *** as a clinical entity and the disease thereafter was known by his name.

Askanazy (22) in 1904 first mentioned the association of a parathyroid tumor with osteitis fibrosa cystica. Erdheim (21) (23) in 1907 collected three cases and connected the two findings (parathyroid tumor and osteitis fibrosa cystica) etiologically and stated that the hypertrophy of the parathyroids was an inadequate attempt at compensation.

In 1915 Schlagenhauser (22) suggested the removal as a measure for cure of the disease. In 1925 Hoffheinz (21) (22) collected 45 cases of measurable enlargements of the parathyroid glands in which he found 27 cases of skeletal abnormality, 19 of which were osteitis fibrosa cystica, 8 osteomalacia and 2 rickets.

In 1925 Mandl (21) (23) of the Hochenegg Clinic of Vienna proceeded to test Erdheim's theory. If, as Erdheim

*** This condition characterized by a demineralization of the skeletal system and the replacement of the mineral elements by fibrous tissue with multiple cystic formation is known by the following names:

1. Osteitis fibrosa.
2. Osteitis fibrosa cystica.
3. Von Recklinghausen's disease.
4. Osteodystrophia cystica.
5. Osteitis fibrosa osteoplastica.
6. Osteitis fibrosa cystica generalis or diffusa.***

believed that enlargement of the parathyroid glands was an attempt at compensation then engrafting of the parathyroid glands would be beneficial. This he did by removing the parathyroids from a moribund victim of an accident and transplanted them in the abdominal wall of a 38 year old male suffering from osteitis fibrosa cystica. The transplantation was successful but the patient was not benefited and in fact became progressively worse. This fact led Mandl to believe that hypertrophy of the parathyroid might be primary and in that same patient that year though enlargement was not palpable, he exposed the neck and removed a mass which proved to be a parathyroid adenoma. Following the operation the patient which had previously been unable to lift his legs from the bed or bend his knees, regained his strength rapidly so that at the end of several months he could walk satisfactorily with a cane. Pain in the bones, which had been present, disappeared. The daily excretion of calcium which before operation had been approximately 55 mgm. was reduced to 9.6 mgm daily and roentgenograms four months later showed moderate increased density of the bones.

Two years later Gold (21) (23) in Von Eiselberger Clinic of Vienna reported an almost identical case. The blood calcium which had been 30 percent. above normal pre-operatively returned to normal and excretion of urinary calcium dropped from 100 percent. above normal to within 12 percent. of normal limits following the removal of the parathyroid tumor.

At about this time 1926 Collip (2) reported the aforementioned work of hormonal action of the parathyroids on the

calcium level in the blood. DuBois (23) (24) (30) (31) in this country knowing of Mandl operation studied a case of osteitis fibrosa cystica. The man was bed-ridden, lost 7.5 cm. in height, the blood calcium was elevated, the electric excitability of muscles was reduced and a negative calcium balance was demonstrated. At operation a tumor was not found; nevertheless two normal appearing parathyroid bodies were removed and after operation the blood calcium fell, roentgenograms showed increased density of the bones and later the man was able to work eight hours a day in an office. In this instance there was a hyper-function of the parathyroids in absence of hypertrophy.

The next case to be diagnosed and treated successfully was that of Barr, Bulger and Dixon (25) and the chief clinical features were rarefaction of bones, hypercalcemia (16 mgm. percent), a constant negative calcium balance, subnormal plasma phosphorous (1.4 mgm. percent.) hypotonicity of the musculature and a cystic tumor of the maxilla which had been previously diagnosed as a giant cell sarcoma. It is interesting to note that this patient had a further complication of urinary calculi. Which fact led J. L. Johnson (29) three years later to suggest after completing his experiments on producing chronic hyper-parathyroidism in animals and finding kidney tubule calcification microscopically that perhaps renal calculi seen clinically with parathyroidism is on a basis of metastatic calcification. A parathyroid adenoma was found in an operation on this patient of Barr, Bulger and Dixon (25) and post-

operatively the patient developed tetany which had to be controlled for some time with parathormone and calcium lactate and at the time of reporting the case the blood calcium determinations were within normal limits while the muscular weakness was approaching normal.

Wilder (21) (23) in reviewing the literature and reporting a case enumerates the symptoms found as progressive muscular weakness, loss of muscle tone, anemia, pain over shafts of long bones, decalcification of skeleton associated with increase of organic matter in bones, giant cell tumors, hypercalcemia and hypophosphatemia but suggests further in his discussions that vitamin D (21) (23) may be antagonistic to or inhibitory to the parathyroid hormonal action. He, later, retracted this statement in view of the experiments of his associate J. L. Johnson (26) (29) which were coincidental with those of Jaffe, Bodansky and Blair (32). Both of these groups came to the same conclusion. Bodansky et al state that in their experiments irradiated ergosterol did not protect guinea pigs from the demineralizing effect of experimental hyperparathyroidism, and further state quite logically however, the healing of bone lesions in experimental and clinical hyperparathyroidism would still be promoted by irradiated ergosterol after the state of hyperparathyroidism has been terminated by removal of parathormone in experimental and removal of adenoma in clinical cases. Johnson (29) in this matter takes a firmer stand for he found in his experiment in chronic hyperparathyroidism that the skeletal deformities were as great or even greater when irradiated ergosterol was used. Further he found a greater

negative calcium balance, increase of symptoms, a greater amount of renal metastatic calcification and in his discussion states, " that vitamin D then either stimulates, supplements, or intensifies the parathyroid hormonal action on the mobilization of calcium and is therefore, contraindicated." In his comment (29) he states, "where as vitamin D concentrates effectively protect against rickets and osteomalacia. It is evident from experiments that they intensify the disease produced by an excess of hormone. It is clear then that rickets and osteomalacia differ essentially from osteitis fibrosa cystica and hypertrophy of parathyroid found in rickets and osteomalacia is secondary."

Following the pioneers in the recognition of the relation of parathyroid to osteitis fibrosa cystica, many other men:

(24). Hannon, Shorr, McClelland and DuBois.

(36). Richardson, Aub, Bauer.

(22). Snapper.

(15) (19). Hunter.

(45). Boyd, Milgram, Stearns.

(18). Schnabel, have reported well worked out cases and found clinical improvement following parathyroidectomy whether it be adenoma, carcinoma, hyperplasia or simple hyperfunction.

As was shown the pathogenesis of osteitis fibrosa cystica had been suspected clinically before investigators began work on experimental animals.

The memorable recent work of Jaffe, Bodansky and Blair

(33) (34) (35) first and Johnson (27) (28) (29) later produced the final proof in which all the characteristic lesions of this condition could be produced experimentally by the prolonged administration of parathormone and are the same as those found in man in osteitis fibrosa cystica. Johnson (27) produced it in rats after Bauer, Aub and Albright (13) failed, to give sufficient parathormone and also because there was too much calcium in the diet and therefore they did not obtain a negative calcium balance in rats. ***

Jaffe, Bodansky, Blair (33) (34) (35) produced osteitis fibrosa cystica in guinea pigs and rabbits. Johnson (27) (28) (29) in rats, puppies and guinea pigs.

Before going into other pathological conditions of bone which at present are being investigated in an attempt to work out some parathyroid relationship, it would best suit the continuity of this paper to first cite from the literature several cases to illustrate the clinical syndrome of hyperparathyroidism.

*** Rats as Gollip (2) 1926 found
were relatively resistant to
the parathyroid extract. ***

Case No. 3.

Reported by Donald Hunter (15)

Hyperparathyroidism-Hyperfunction of Parathyroid Tumor in a
Case of Generalized Osteitis Fibrosa Cystica--Married Woman age 41.

Clyncal History--November 26, 1926--pain in right knee followed
by pain in lower back hips and thigh. May 1928 unable to walk with-
out crutches. Pain in lower legs. October 1928 acute attack of right
lumbar pain with a history of frequency of micturition. No history
of passing calculi. March 1929 right kidney explored. No calculi
found. Nephropexy performed. September 1929 symptoms worse, constant
pain over all bones. November 10-1929 patient twisted left ankle
causing fracture of neck of femur.

Past History-- negative- no familial history suggesting dis-
ease of bones.

Examination November 20-1929-- A thin poorly built woman. Cal-
varia normal in size and contour. Eyes, Ears and Nose negative. Neck-
no tumor or masses palpated. Heart and Lungs--negative. B.P. 140/70.
No hypotonicity of muscles. Shortening of left limb. Pressure on shafts
of all bones caused pain. In addition a firm tender swelling was observ-
ed at lower end of right ulna.

Urine--Albumen 2 plus.

Blood---Bleeding and coagulation time normal. Wasserman negative.

X-Ray--Greatly diminished densities of shadow of all bones. Pale
cystlike areas, some of them trabeculated in four or five bones. Left
femur fractured. Calvaria shows a uniform mottled appearance.

Calcium and Phosphorous Metabolism--There was a constant hypercalcemia 16.7 mgn. The corresponding figure for plasma phosphorous was very low. 1.0 mgn. On a known low calcium intake the output in urine was more than eight times normal; that in feces being approximately normal.

Operation November 29-1929-collar incision was made in the neck region and the left inferior parathyroid was replaced by a cystic adenoma which was removed as was also a piece of bone from the mass on the lower end of the right ulna.

Report of specimens by T. M. Turnbull--The appearances of the cystic adenoma indicate functional hyperactivity rather than an autonomous neoplasm. " The section from the right ulna which was excised at operation was shown to be fully calcified except in sharply defined osteoid zones. There is no histological evidence therefore of cessation of calcification characteristic of rickets or osteomalacia, nor of the removal of calcium by chemical solution. The mobilization of calcium was due to lacunar resorption by osteoclasts". The section presented a picture of osteitis fibrosa cystica.

Progress--24 hours after operation Chvostek sign appeared and has persisted since. On second day pressure on bones caused much less pain than previously. The blood chemistry 48 hours after removal of the tumor showed that the serum calcium had dropped to a level below normal 9.1 mgn. simultaneously the plasma inorganic phosphorous rose to 2.8 mgn. By the fourth day pressure upon the bones no longer produced pain. Latent tetany has persisted in the shape of a Chvostek sign but there was no manifest tetany and Trousseau's sign has never been present. The calcium and phosphorous blood levels have been persistently below normal. The calcium output estimated for four days on

the same low calcium diet as before operation is less than in the normal individual. It corresponds to that of a case of post-operative tetany.

"In this case we may say that clinical, radiological, chemical and histological evidence combined to show that the patient was by urinary excretion rapidly losing calcium salts from the skeleton."

Case No. 2.

Reported by Barr, Bulger and Dixon (25).

White female age 56. In February 1927 because of inability to walk, frequency of urination and a boney swelling on right forefinger she sought medical aid.

Past history--negative except for an ill balanced diet. At 38 years of age she was told she had "inflammation of bladder." At 47 she noticed pain on urination. Hysterectomy and oophorectomy performed that same year.

In 1918 she first experienced difficulty in walking which became progressively worse until she was unable to walk without crutches also coincident with this was muscular weakness. In 1926 with but a trifling injury clavicle was broken. She was unable to lift feet from floor at this time. Marked hypotonicity was demonstrated with a faradic current. Roentgenograms showed irregular areas of rarefaction. A moderate pyelitis existed and flat plates of the kidneys showed many stones in the pelvis of each kidney. Right forefinger was removed and diagnosed by Dr I.Y. Olch as a giant cell sarcoma.

In February 1928 while in an auto accident patient fractured left humerus. A tumor noted at this time in the maxilla and ulna. Biopsy of pieces of bone from the ulna and maxilla revealed a giant cell sarcoma exactly like that of the forefinger. Bowing of the thighs was extreme. Examination of the blood showed calcium 16 mgm. and phosphorus 1.4 mgm. Extensive metabolic studies revealed a negative calcium balance with this loss of calcium by way of the urine.

Operation for expl~~o~~ation of neck region revealed a parathyroid tumor which was removed. Microscopically it was diagnosed as a parathyroid adenoma.

Two days following operation patient developed severe tetany and large doses of parathormone and calcium chloride intervenously plus calcium lactate orally were given. From this tetany she has only partially recovered. Metabolic studies showed that she retained large amounts of calcium after the removal of the parathyroid adenoma. Post-operatively the patient's blood calcium has always been at the lower limits of normal and occasionally even below this point. The boney tumor of the jaw is becoming progressively smaller, muscular strength has increased and patient is able to perform light daily duties at the time of which these authors published this case.

Case No. 1.

Reported by R. Wilder (21-23-47)

Pathological Tissue Examined BY W. L. Wellbrock.

Married White Female age 32.

Past History-- relatively negative

Catamenia--- negative

Previous Illnesses---- childhood infectuous diseases, moderate anemia existed since childhood plus progressive weakness and nervousness. Her appetite had been capricious since childhood with overindulgence in sweets and neglect of vegetables, milk and cream which precipitated in the course of treatment of rest, sunshine and forced feeding in 1921 by G. Minot, M. D. with considerable benefit.

In 1922 a pain began in right hip associated with stiffness and later affected entire body. Standing aggravated the painⁱⁿ the hip and later produced pain in the knees.

In 1923 a small lump was noted in the thyroid glands and also in that same year a small tumor grew from the periosteum of the lower right bicuspid region. This was removed and diagnosed as a myelo-sarcoma.

In 1924 considerable swelling of the bicuspid region again occurred. Operation again performed and considerable bone was chiseled away and the remaining teeth removed (many having been removed because of decay).

Admitted to Mayo Clinic January 1925--Her complexion was sallow, her gait unusual in an effort to avoid weight on the right leg. At the lower pole of the thyroid gland a spherical mass 3 cm. in diameter was palpated and was believed to be a thryoid adenoma.

Physical Examination-- lungs and heart essentially negative, pulse 100, B. P. 120/70, abdomen held rigid making palpation difficult.

Laboratory--Blood essentially normal except for moderate anemia. Blood and spinal fluid Wasserman were negative.

Roentgenograms of pelvis showed rarefaction but no gross deformity.

B. M. R. -- plus twelve and plus two.

Symptomatic treatment advised and patient dismissed.

In March 1925 patient returned-- muscular weakness had increased to such a degree that patient was scarcely able to rise and she walked with great difficulty with crutches.

In April 1925 pain was complained of in all the bones and joints. Calcium determination slightly elevated (11.4 mgm.) while phosphorous low (1.4 mgm.). Roentgenograms of spine and pelvis revealed areas of rarefaction.

May 15 1927 weakness extreme, patient unable to walk, loss of 80 lbs. in two years. A cystic area was noted at distal end of right femur. A biopsy of a piece of bone from ilium showed that the bone was poor in mineral salts with an increase of organic material. A high vitamin diet plus ultra violet light was instituted. Some time later metabolic studies revealed a positive calcium balance.

November 16- gain of weight--high vitamin diet continued and less pain over joints. Roentgenograms showed cystic areas in the femur also boney mass palpable on anterior aspect of left axilla. Blood calcium 12.2 mgm., phosphorous 1.9 mgm., Right lower end of femur removed and a microscopic diagnosis of a giant cell tumor was made.

Attention was directed on her fifth visit to the Mayo Clinic to the similarity of her case to that of Barr, Bulger and Dixon (25).

In December 1928 a parathyroid tumor was removed and convalescence was satisfactory. The blood calcium dropped to 7.13 mgm. and continued

to slowly recede to dangerous tetany levels but actual tetany did not occur. Calcium phosphate given by mouth and a marked suppression of calcium excretion was noted.

In two weeks marked improvement in muscular strength was obvious and patient was able to walk around with crutches. In April 1929 a high calcium and vitamin D diet was continued. The patient was entirely free from pain over the shafts of the long bones and could walk quite comfortably. Roentgenograms of skull, spine, pelvis and femur compared to those before the tumor was removed showed unmistakably increased density. Blood calcium--8.33--8.16--8.14 mgm. phosphorous 1.8--1.6--1.8 mgm.

Wellbrock (47) described the parathyroid tissue removed as a malignant adenoma.

Note. For further reference to the calcium and phosphorous determination of blood, urine and bone as well as the calcium balance of the body of this patient the author refers you to Wilder's data in Endocrinology, xiii, pages 231 to 243. Also as this was the first parathyroid malignant adenoma to be described Wellbrock goes into the histopathology of it in detail in Endocrinology xiii-pages 285 to 294.

Hypoparathyroidism.

The foregoing subject matter brought forth evidence to show the effects of hyperparathyroidism, both, experimentally by injection of the hormone and spontaneously as evidenced by adenoma or hyperfunction. We are all aware of the syndrome of post-operative hypoparathyroidism following accidental removal of some of the parathyroid glandular tissue. In all endocrine glands, if a state of hyperfunction exists, it is logical to assume that a state of hypofunction can exist. Is there then such a condition as spontaneous hypoparathyroidism?

Albright and Ellsworth (51) report such a case and they made complete metabolic studies of it over a period of a number of years. The patient showed manifestations of latent tetany with occasional attacks of laryngismus, carpopedal spasms and convulsions brought on usually by exertion. The serum calcium was at the low limits of normal and occasionally fell within tetany limits, the plasma phosphorous was slightly elevated, Chvostek's and Trousseau's signs were positive, bilateral cataracts**** were present, normal density of bone existed, (in contradistinction to the picture of tetany associated with osteomalacia and rickets).

**** The association of lenticular opacities with hypoparathyroidism has long been noted (52,37) Cole reports 38 cases of post-operative tetany associated with cataracts.****

They further noted in this patient that while the serum calcium rose under parathormone therapy urinary calcium excretion which had previously been negligible changed to a very appreciable one when a critical point of about 8.5 mgm. percent. of serum calcium was noted and conversely when they discontinued parathormone the urinary calcium determination which was high became negligible when the serum calcium approached 8.5 mgm. percent., suggesting a renal threshold for calcium. The above experiments were worked out very carefully with determination of calcium and phosphorous intake and out put. They obtained excellent clinical results in this patient with parathormone therapy.

Walter Timme (53) neurologist cites three cases in which the main clinical manifestations were, lack of emotional control, anemia, fatigue and a noticable speed of mental activities. In his routine examination he found a low serum calcium (below 7.5 mgm. percent.). He treated all three with calcium and parathormone but without scientific observation and he states he noted an amelioration of patient's symptoms. It is doubtful whether any conclusions can be drawn from Timme's cases.

Rickets and Osteomalacia.

As has been previously mentioned slight enlargement of the parathyroid glands is noted not infrequently in rickets and osteomalacia. Under such conditions manifestations of hyperparathyroidism are never encountered, on the contrary there is a definite tendency in the opposite direction. In both rickets and osteomalacia any abnormality of the blood is promptly restored by the use of vitamin D concentrates or ultra violet light, and at the same time ossification begins to proceed normally.

That vitamin D concentrates do promote the storage of calcium in the bone has led to a voluminous amount of investigation and literature. The interesting experiments of Marble and Bauer (50) in which they placed 12 cats on a low calcium diet for some months (previous experiments show that this depletes the calcium and trabeculations of bone) after which one foreleg was amputated and all 12 animals were then placed on a high calcium diet, 6 having irradiated ergosterol in addition. After some months all were killed and it was demonstrated that in those having irradiated ergosterol a much greater increase of trabeculation of bone as compared to the control foreleg/ ^{than} those which did not receive the vitamin D concentrates.

To enter into a discussion of the relation of vitamin D to calcium metabolism is not in the scope of this paper.

Hunter (15-38) in reviewing the literature, states

"Morbid Anatomists are agreed that osteomalacia and rickets are essentially abnormal in the same-- namely a deficient calcification of osteoid tissue. Now, although many problems still remain unsolved as to the etiology of these two diseases, it is clear that the calcifying substance which is missing is vitamin D. In its absence the utilization of calcium and phosphorous is impaired. Studies of the blood chemistry of children with rickets show that the essential abnormality is a low inorganic phosphorous content. The serum calcium is usually normal but in a small proportion of cases it is reduced (in such cases tetany may occur). In osteomalacia low calcium is the rule and tetany common. In both diseases the abnormality in the blood, if it does exist, is promptly restored to normal by the use of cod liver oil, ultra violet light or vitamin D. Biochemistry then has therefore amply justified the view held as to the pathogenesis of these two diseases and to their essential identity."

Serum Calcium						Plasma Phosphorus					
	Osteomalacia	Hyperparathyroidism		Post-operative Tetany	Hypoparathyroidism		Osteomalacia	Hyperparathyroid		Post-operative Tetany	Hypoparathyroidism
	9.6	6.0	16.7	6.3	4.9		1.6	1.9	2.5	4.7	10.4
	8.8	7.4	16.7	5.9	5.0		2.0	1.8	1.0	5.0	10.7
	9.7	5.6	15.8	6.4	5.3	Rickets	1.2	2.3	1.5	6.5	10.6
Rickets	10.2	5.2	15.5	5.7	5.3		1.6	2.5	1.7	6.0	10.4
		7.0		3.9	5.2			2.4		6.0	10.9
		5.0			5.4			2.0			10.9

Serum calcium and plasma phosphorous as an aid to diagnosis. (Hunter .15.)

In the present state of of our knowledge the occurrence of hyperplasia of the parathyroid glands is without explanation. Since all the parathyroid glands are involved the hypothesis that the change is secondary seems attractive.

Johnson (26-29) takes a firmer stand and states that a greater negative calcium balance and an increase of symptomatology was found in experimental hyperparathyroidism when vitamin D was used, and whereas vitamin D concentrates effectively protect in rickets and osteomalacia it is clear that these two diseases differ essentially from the hyperparathyroid osteitis fibrosa cystica and hypertrophy of the parathyroid glands found in rickets and osteomalacia must be considered as secondary.

Paget's Osteitis Deformans
and Osteogenesis Imperfecta.

In Paget's osteitis deformans (37) the serum calcium and plasma phosphorous are approximately normal. Studies which have been made on the calcium balance have given conflicting results but no departure from the normal of any magnitude has been demonstrated.

In osteogenesis imperfecta (37) also no abnormality of serum calcium or plasma phosphorous or calcium balance. In the latter disease several reported cases describe enlargement of the parathyroids.

In our present state of knowledge as states Hunter (37) no inference as to the relationship of either of these diseases to parathyroid activity can be drawn.

Focal Osteitis Cystica.

While the pathogenesis of generalized osteitis fibrosa cystica is quite indisputable, the status of focal cystic areas in bones is at present controversial. In this condition Hunter (15) states that usually one bone but maybe more become slowly affected but not disabled. The focal areas resemble the cystic areas of generalized osteitis fibrosa cystica but the general skeleton is not involved and the calcium and phosphorous blood levels are normal. He states after studying eight cases that "It is of vital importance in such cases

Table from
Hunter (2) cases
of focal ostei-
tis fibrosa cys-
tica without
deviation of
Ca and P.

Sex	Age	Foci	Diagnosis	Ca	P
F.	18	Multiple	Radiological	9.9	3.5
F.	17	Single	Histological	10.5	2.3
M.	19	"	"	9.7	3.5
M.	19	"	Radiological	9.7	3.5
M.	24	"	Histological	9.9	3.8
F.	30	"	"	8.8	3.0

to realize that although many bones may be affected the condition is totally different from the generalized disease and the exploration of the neck is unjustifiable."

This view is not held by Ballin and Morse (20) and Bloom (49) who cite cases wherein the general skeleton was not demineralized and the blood calcium was within limits of normal yet operation and removal of parathyroid glandular tissue alleviated the condition and they suggest that focal fibro-cystic areas in bone or focal osteitis fibrosis cystica is the same condition as the generalized disease though probably of a lesser degree.

With these conflicting views held by competent men the relationship of the parathyroid to focal osteitis fibrosa cystica must await further investigation.

To Summarize the Features of clinical hyperparathyroidism:

Hypercalcemia-- serum calcium value ranging from 12.2 to 18 mgm. percent. Both diffusible and non-diffusible portions of blood calcium being elevated proportionately.

Increased excretion of calcium by the urine-- metabolic studies of the individual suffering from excess of parathyroid hormone reveals a negative calcium balance, being excreted mainly by way of the kidneys.

Hypophosphatemia-- Usually subnormal readings of the plasma phosphorous from 1.0 to 1.35 mgm. percent.

Increased excretion of phosphorous-- Albright, Ellsworth and Aub and their associates believe from their experiments that evidence points to the fact that the action of the parathyroid hormone acts primarily on the phosphorous.

Muscular hypotonicity-- Loss of strength and marked reduction of nerve and muscle excitability as evidenced by electrical stimulation.

Rarefaction of bones-- A milary, mottled osteoporosis as evidenced by X-Ray.

Metastatic calcifications-- Increasing evidence points to the fact that metastatic calcified deposits may be related etiologically to hyperparathyroidism.

And finally the skeletal, pathological picture of osteitis

fibrosa cystica with an occasional association in some patients of boney tumors which have been previously diagnosed as some type of sarcoma.

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