Orthopedic consideration of hyperparathyroidism

J. E. Jacobs
University of Nebraska Medical Center

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The
ORTHOPEDIC CONSIDERATION
of
HYPERPARATHYROIDISM

by
J. E. Jacobs, B. A.

A Thesis

Submitted to the Faculty of the University of
Nebraska College of Medicine in Partial
Fulfillment of the Requirements
for the Degree of Doctor
of Medicine.

1935.
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INTRODUCTION

Hyperparathyroidism is a conception less than nine years old, and there are few maladies, old or new, whose mystery has been solved so speedily. But a short time ago the parathyroid bodies were chartered only as dangerous ledges to be avoided during the surgical removal of the thyroid; now they have been carefully surveyed and are regular ports of call for the surgical navigator. As is apt to be the fate of newly discovered territory, a halo of legend and romance surrounds them and the danger of over-exploitation at the hands of traders and buccaneers is real. Even master mariners are apt to be deceived when an unexpected landfall is made and the fountain of eternal youth appears through the mist.

It is a well known fact that clinical interest in a given field is proportional to its therapeutic possibilities, and accordingly, hyperparathyroidism has been investigated for such etiological possibilities in many of our obscure clinical syndromes, especially the osseous system.

A decade ago we had no proof of the relationship between parathyroid activity and the metabolism of phosphorus and calcium, and the advance of knowledge since that time shows medical research at its happiest. The cooperation of medicine, dietetics, experimental pathology, histology, physiology, and chemistry has directed the surgeon's knife towards a tumor he could neither see nor feel. The perfection of such surgery is closely allied with the development of the knowledge concerning adenomata of the glands of internal secretion. It runs parallel with exploits of surgery in the case of tumors of the islet tissue of the pancreas, and the recognition of the basophilic adenoma of the pituitary body. The diameter of these adenomata of the endocrine glands may be measured in a
few millimeters, yet the associated constitutional disturbance frequently alters the entire aspect of the body or leads to its total destruction. The diagnosis of hyperparathyroidism is one of the most spectacular and notable achievements of the laboratories of the experimental medicine. Following closely upon the heels of the isolation of the internal secretion of the parathyroid—parathormone—experimental studies, both on animals and man, demonstrated the profound disturbance in metabolism that attends its introduction into the body in abnormally large amounts. Whereas formerly cases of these diseases of the skeleton were considered to be of only casual importance, now every case of generalized bone disease is studied for symptoms of hyperparathyroidism. It was this marked interest of the orthopedic literature in hyperparathyroidism plus my lack of knowledge of skeletal pathology of a general nature that aroused my interest in this subject.

Before starting the history of this subject I shall list some of the synonyms of hyperparathyroidism, as parathyroidism (of Max Ballin)(11), Mandl-DuBois disease (of Fuller Albright)(2), osteitis fibrosa, osteitis fibrosa cystica, osteodystrophia cystica, osteitis fibrosa osteoplastica, osteitis fibrosa cystica generalis or diffusa, osteodystrophia fibrosa cystica generalisata of von Recklinghausen, and, simply, von Recklinghausen's disease (127).
HISTORY

Classical hyperparathyroidism does not infer going back to Roman or Greek times but merely to 1926, when the bone disease known as osteitis fibrosa cystica was recognized as being due to hyperparathyroidism. Thus, the relation between the parathyroid glands, calcium metabolism, and pathological conditions of bone has been proved within the last decade. Previous to 1925, the physiology of the parathyroid tissue being obscure, medical science approached the syndrome now recognized as hyperparathyroidism by describing merely end results.

Von Langendorff and Mommesen (126) in 1877 and Virchow (125) in 1886 gave very good pictures of osteitis fibrosa cystica, mentioning shortening of the patient's skeleton and softness of the bones and the localized areas of so-called "brown cysts". Virchow especially stressed the point that these areas were not sarcomas, but areas of softening and not neoplastic in character. In the same year, 1886, Hirschberg (67) gave a vivid description of generalized osteitis fibrosa cystica although he did not recognize it as a separate entity but thought it was a form of osteomalacia. Von Recklinghausen (127) followed him five years later (1891) in the volume commemorating Virchow's seventy-first birthday. The title of his paper was "Ostitis, Osteomalacia and Osteoplastic Carcinomatosis". This paper is really the first accurate description of the disease which now bears his name. His contribution to the Festschrift is very involved, for he describes more than one bone disease. There can be now doubt, however that his cases five and seven constitute the discovery of generalized osteitis fibrosa cystica. It is important for us to notice that he went to the trouble of describing two cases of puerperal osteomalacia (cases eight and ten) in order to place on record that "so many facts differentiate case seven from true osteomalacia". He described his case seven
as "osteitis fibrosa with marked bone softening and multiple osteosarcomata". The patient was a man of forty years, thought to be suffering from osteomalacia. There was a history of eighteen months' bone pain with bowing of the bones and multiple spontaneous fractures. At necropsy the bones were soft and deformed so that with a saw they cut like rotten wood, and the shafts could be cut with a knife using moderate force. All the bones in the skeleton were affected and seemed histologically to be formed of a tough connective tissue. Brown-red projecting tumors were found in the fibula, iliac crest, and upper and lower jaws. In his earliest description von Recklinghausen regarded the disease as an inflammatory process, a chronic productive inflammation, whereby fibrous tissue was substituted for bone structure, resembling in this way fibrous myocarditis or liver cirrhosis. In his later works, however, he changed his belief and thought that he was dealing with a metaplastic condition of the existing tissue together with a calcium withdrawal. In our own subsequent knowledge of this disease there is ample clinical and pathological evidence to establish the benign nature of these giant-cell tumors. The cells themselves are similar to the osteoclasts normally present in Howship's lacunae.

In 1895, Nickulicz (94) also described the condition of osteitis fibrosa cystica as a definite type of bone tumor of some obscure inflammatory origin. Even as late as 1910, Bloodgood (24) stated that the basic cause of the osteitis fibrosa was a low-grade infection.

The earliest reference we have to tumor of the parathyroid glands are those of DeSanti (46) in 1900 and Benjamins (21) published in 1902; bone disease was not mentioned in either of these cases, however. Erdheim (48) in 1903, Julst (78) in 1904, and MacCallum (88) in 1905, also
each reported a case without associated bone disease.

Thirteen years after von Recklinghausen first described generalized osteitis fibrosa cystica, an important step was made towards solving the problem of its etiology. This was a description by Askanazy (9) in 1904 of a case of generalized osteitis fibrosa associated with a tumor of the parathyroid gland. Since its significance was scarcely suspected, the parathyroid tumor mentioned in this case passed unnoticed. However, the descriptions of such tumors with associated bone changes by Weichselbaum (129) in 1906, and by von Verebely (128) in 1907, gave Erdheim (49) a basis for his hypothesis that hypertrophy of the parathyroid gland was an inadequate attempt at compensation of an unknown function (Erdheim's hypothesis). In the same year (1907) he described three cases of osteomalacia associated with parathyroid enlargement. Thompson and Harris (122) described a similar case in 1908. Seven cases of parathyroid tumor without mention of bone changes were collected and one of his own added by DaCosta (43) in 1909. Bauer (18) in 1911 reported a case of adenoma of the parathyroid gland with a moderate degree of osteomalacia. In 1913 Molineus (95) described osteomalacia in three elderly females, two of whom had each one parathyroid tumor, while the third had two distinct tumors. Harbitz (63) in 1915 noted the "relationship between enlargement of the parathyroid glands, rickets, and other diseases affecting the bones". Tumors of the parathyroid gland have been reported as coincident findings in several diseases. Bergstrand (22) in 1921 reported tumor of the glands in nephritis, tetany, epilepsy, eclampsia and osteomalacia. In fifty cases of nephritis he found one or more enlarged parathyroid gland. Other authors, as MacCallum (88) and Dawson and Struthers (44), have reported the coincidence of parathyroid enlargement with nephritis, the latter also reporting cases of generalized osteitis fibrosa
in which areas of metastatic calcification have been found in the lungs, stomach, kidney and myocardium. In 1925, Hoffheinz (69), rejecting all cases where the parathyroid enlargement was indefinite or inadequately described, collected from the literature forty-five cases with measurable enlargement of one or more parathyroid glands. Of these, twenty-seven were associated with definite bone disease, including seventeen of generalized osteitis fibrosa, eight of osteomalacia, and two of rickets.

The concept of the related tumors of bone and the parathyroid adenomas has been changing within the last few years. Erdheim (50) in 1911 put forth the hypothesis that the enlargement of the gland was a compensatory effort to assist in replacing lost calcium to the bones. This theory held sway for many years.

In 1923, Dawson and Struthers (44) stated that the glandular hyperplasia was an effort to prevent the excessive excretion of lime salts and also to control and to prevent the development of an excess amount of guanidine, which was considered toxic.

The first intimation that hyperparathyroidism might be a cause of generalized fibrocystic disease of bones through withdrawal of calcium was in 1915, when Schlagenhauser (115) advised parathyroidectomy in two cases of generalized fibrocystic disease associated with tumor; however, it was not until 1925, when Mandl (90) of the Hochenegg Clinic of Vienna proceeded to test Erdheim's theory by transplanting parathyroid tissue into a patient with generalized fibrocystic disease. The patient's condition became worse. He then removed the transplanted parathyroid tissue and also a parathyroid tumor, and there was improvement of the fibrocystic disease. Gold (56) in the von Eiselberger Clinic of Vienna performed a parathyroidectomy in 1927, with similar improvement of the patient's bone disease. Barr and his co-workers (16) had a parallel case
in 1929. Since this time there have been reported over one hundred cases of generalized fibrocystic disease of bones associated with a parathyroid tumor, in each of which the tumor was removed, with subsequent improvement of the bone condition.

Collip in 1925 (33) described the blood calcium elevation after parathormone was injected into dogs, and also an increase in the blood phosphorus in parathyroidectomized rabbits. Greenwald and Gross (59) in 1925 and again in 1926 (60) showed that daily parathormone injections of one hundred units in animals elevated the serum calcium and caused excretion of urine calcium and phosphorus, the former to as much as six times normal. Hunter and Aub (71) also found the same hypercalcemia with increased calcium excretion in man in 1926. Albright et al. (7) have demonstrated a negative calcium balance in animals and man receiving parathormone injections. Finally, the disease picture, both gross and microscopic, of generalized fibrocystic disease of bones has been produced repeatedly by Jaffe, Bodansky, and Blair (74) and also by Byrom working with Hunter and Turnbull (72). More recently (1931) Johnson and Wilder (77) reported that repeated injections of parathyroid extract produced in puppies and young rats uniform bone lesions characteristic of generalized fibrocystic disease of the bones, and concluded that the disease observed in man was due to an oversupply of parathyroid hormone with consequent loss of bone calcium.
ETIOLOGY

The evidence to date that generalized osteitis fibrosa of von Recklinghausen is a disease of endocrine origin, with a tumor or at least a hyperfunction of the parathyroid tissue as the causative factor, has been evolved about as follows. The pioneer work of MacCallum and Voegtlin (89) demonstrated a reduction of serum calcium in dogs after parathyroidectomy. In 1922 (87) it was established that the condition of tetany was relieved by the administration of calcium salts, also that calcium injected into the blood in large doses caused relaxation of the muscles, hypotonia, weakness so that the muscles can hardly function and, finally, some of the surplus calcium brought into the circulation will settle down forming calcified areas in various organs, especially the kidney. Jaffee et al. (75) in experimenting on dogs with ammonium chloride decalcification found that when decalcification was less severe, generalized thinning of the bones without marrow fibrosis occurred (osteoporosis), but when more rapid, generalized decalcification and secondary marrow fibrosis resulted (osteo­ritis fibrosa). The theory of Koch (82) that these symptoms were due to guanidine intoxication remains unsupported by adequate evidence.

Bloodgood (24) as early as 1910 stated that osteitis fibrosa was caused by low-grade infections, but repeated cultures and animal inoculations have been uniformly negative.

Since the isolation by Hanson (62) in 1924 and Collip (32) in 1925 of the active principle of the parathyroid gland (parathormone), it has been repeatedly demonstrated that the injection of the extract causes an elevation of the serum calcium. Brehme and Gyorgy (27) in 1927 found that parathormone lowered the blood phosphorus and shifted the pH of the blood towards the acid side without affecting the carbon dioxide
combining power of the blood. Reiss (107) and Aub (10) in 1928 also found independently that parathormone lowered the level of the serum phosphorus. This appeared to be the first action, the elevation of the serum calcium following only after a long latent period, so that these men questioned whether the effect on the phosphorus was the primary effect.

The study of the influence of parathormone on the excretion of calcium and phosphorus has demonstrated less striking results than would have been expected from its effect upon the blood. In normal individuals a constant dose of parathormone causes the phosphorus excretion to rise abruptly to a maximum in the first three-day period, while the maximal increase of the calcium excretion follows more gradually. After discontinuing parathormone the phosphorus excretion falls to normal more abruptly than does the calcium (7). This early rapid excretion of phosphorus may account for the primary fall in the plasma phosphorus and is further suggestive evidence of the contention of Greenwald (58) of the primary influence of phosphorus in regard to tetany.

Parathormone raises the serum calcium in normal persons. There is a great individual variation in this response. A dose of fifty units of parathyroid extract daily is usually found to have little influence on the level of the serum calcium, yet it approximately doubles the excretion of calcium and phosphorus in the urine. When one-hundred units a day are given to normal individuals the serum calcium level is raised to an average of 12.5 mgm. %, and there is an average rise in the urinary calcium excretion to six times the normal level. The source of such large amounts of calcium salts appearing in the urine is of fundamental importance. The evidence available both in animals (59) and in man (71) points to the conclusion that these calcium salts are derived from the bones.
In 1931, Johnson and Wilder (77) not only confirmed these observations, but also demonstrated that the effects of prolonged administration of parathormone are not materially influenced by simultaneous administration of irradiated ergosterol, which indicates, or course, that the disease is not etiologically related to the vitamin D deficiency disorders, such as osteomalacia and rickets.

In contradistinction to all this confirmed experimental laboratory and physiochemical research, Lang (83) as late as 1932 still stated that osteitis fibrosa was a secondary condition of the bone, dependent on circulatory disturbances following either trauma without tearing of the periosteum or functional bending and cracking of the skeleton because of insufficient calcification (rickets, scurvy, or osteomalacia). "Occasional occurrence of osteitis fibrosa associated with tumors of the parathyroid gland does not contradict the concept which regards osteitis fibrosa as a secondary process in bone, dependent on osseous circulatory disturbances."

In the same year Semroth and McClugage (116) stated that "it remains an open question whether in the pathogenesis of osteitis fibrosa cystica, hyperparathyroidism is an indispensable etiologic factor, as suggested by experimental results, or a secondary aggravating phenomenon".

Ballin (11) states, "it is remarkable how many of the real parathyroid cases give histories of dislike of milk, thus, with the absence of the chief 'calcium-supplier' of our diets the question of primary dietary calcium deficiency, hypocaloemia, should not be disregarded".

Knowing that the endocrine hook-up is a complex one I would like to present the following deductions from the literature. Ortenberg (98) in 1933 stated that "the hormone responsible for direct excretion of cal-
Cium is the thyroid" and goes on to relate that nearly all of the reported cases of parathyroid tumors had an associated goitrous condition of one type or another. We know that the excretion of calcium in the urine is increased in thyrotoxicosis but any such condition as hypercalcemia I doubt; at least Osgood and Haskins (99) do not list thyrotoxicosis under the factors causing hypercalcemia.

The extensive literature which has accumulated in recent years on the relationship of the anterior pituitary to the other endocrine glands contains but meager clinical and experimental references to the parathyroid gland. In 1912, Cushing (38), in a monograph on the pituitary body, called attention to a group of cases showing primary hypophyseal disease with associated alteration in other members of the endocrine series. In his more recent writings on pituitary basophilism, terms such as kyphosis, lordosis, multiple fractures, marked weakness, polyuria, decrease in height, renal changes, albuminuria and gastric pains are frequently found (39); and on the pathological side, "bones soft enough to cut with a knife, osteoporosis, compression of vertebrae and healed fractures were commonly encountered". All these things are now known to be among the classic manifestations of hyperparathyroidism. In 1912, Schmorl (113) mentioned a case of typical osteitis fibrosa cystica in which he found the association of a large basophilic adenoma of the hypophysis with diffuse adenomatous hyperplasia of the parathyroid glands. He did not suspect a relationship between the two adenomatous growths, but Molineus (95), in reporting the same case in greater detail, made the suggestion of such a possible relationship. He states that "acromegaly was absent in this case because of the disease in other glands (i.e. parathyroids)". Erdheim (48)
stated that he had seen the association of osteitis fibrosa cystica and basophilic tumors of the pituitary in two necropsied cases. Lloyd (48) in 1929 reported a case from post-mortem findings with tumor-like enlargement of the parathyroid glands and islets of Langerhans in association with hypophyseal tumor. No clinical data were available in that case from which to decide whether the parathyroid or islet tissue had had excessive functional activity during life. Evans (51) in 1933 in a review of the anterior pituitary functions summarized the situation with regard to the parathyroids as follows, "there seems to be no question but that we have to do with a disturbance of calcium metabolism after hypophysectomy as reflected in the decreased calcium content in the blood; whether this is due to the correlated subnormality of the parathyroid glands remains to be established. Changes in the parathyroids as a result of hypophysectomy have not been adequately studied as yet. It is difficult to view the cessation of growth of the skeletal system after hypophysectomy as essentially due to disturbance in the inorganic salt metabolism; it is more justifiable to refer it to a singular failure in cartilage proliferation in the epiphyseal discs and, of course, the dwarfism is participated in by all the organs and tissues of the body". In 1934, Hoffmann and Anselmino (70) demonstrated in experimental dogs and rats that the calcium content of extract from the anterior lobe of the hypophysis, is thermolabile, and in parathyroprival rats the extract did not produce an increase in the calcium content of the blood. They observed that the parathyroid glands enlarged two to three times on injection of anterior pituitary substance, with the formation of clear cells more than dark cells, also oxyphil, and strong vascular reaction. Their conclusion
was that the increase in the blood calcium was affected by the extract of the anterior pituitary and due to the activation of the parathyroid gland to an increased secretion of the parathormone. Riddle and Dotti (109) in December of 1934 started on new studies to use pigeons to determine the particular anterior pituitary hormone which stimulates the parathyroid glands; so that the near future may disclose more regarding the inter-relationship of the endocrines. Collip (34), reviewing the literature up to March of 1935, showed that Hertz and Kranes (65) have obtained a fraction of beef pituitary that leads to active mitotic cell division and vacuolization of the parathyroid cells in the rabbit. Almost at the same time Anselmino, Hoffmann, and Herold (8) published their results, showing that parathyroid enlargement may be produced in the rat by the administration of a pituitary extract. The recent report by Hertz and Albright (64) that the urine of patients with hyperplasia of the parathyroids, but not of those with parathyroid adenoma, contains a substance that will produce hyperplasia in the parathyroids of normal rabbits, is of special significance. So that the present status of pituitary-parathyroid inter-relationship, and this, in turn, with osteitis fibrosa cystica seems to have some basis. In this respect the treatment may be entirely altered in the near future.
PATHOLOGICAL PHYSIOLOGY

The normal anatomy of the parathyroid glands with some of its vari-
ances will not be discussed here, only to say that a variance in number
(from two to twelve) and position (from the pharynx into the mediastinum)
(30) is common knowledge.

The histological aspect of these glands was first described by Welsh
(130) in 1898. He divided the cells of the normal gland into oxyphil
cells and principal cells and subdivided the latter into four types accon-
ding to their form and arrangement. Erdheim (48) described two kinds of
oxyphil cells, the large pale and the small dark. According to him the
oxyphil cells occur first in the tenth year, and are present in variable
number ever after. Hunter and Turnbull (72) agree with this, but only
distinguish the three types—the dark oxyphil, the pale oxyphil, and the
principal. The appearance suggests that the oxyphil cells are principal
cells in which the cytoplasm has been overcharged with oxyphil granules,
that the basophil net has been more or less completely reduced to a limit-
ing membrane. Bergstrand (22) in 1934 stated that the cells in parathyroid
tissue were only of one kind and that the cells of Welsh are degenerating
forms in the aging.

Clinical hyperparathyroidism, therefore, in the light of present
knowledge, may tentatively be divided into two types, according to Hitz-
rot and Comroe (68): the primary with benign, or rarely malignant, tumor
of the parathyroid gland, and the secondary with functional hyperactivity
and, at times, hyperplasia. In the former case, the high serum calcium,
negative calcium balance, and decalcification of bone results as the num-
ber of active parathyroid cells increase, in the latter type, the etiology
is not entirely clear. Hyperactivity is thought, however, to follow a prolonged low intake of calcium, in which the glands, to keep blood values normal, progressively remove calcium from the storehouses in the bones. The depletion of the bones may go on, as a result of this overcompensation long after the actual need for the stored calcium has passed. Barr and Bulger (15) state that hyperplasia of the parathyroid gland and clinical evidence of hyperparathyroidism have been found in many cases of general bone disease, including rickets, puerperal osteomalacia, multiple myeloma and carcinomatous metastases to bones. The parathyroid changes appear to be secondary to the changes in bone. It is a matter of common knowledge that the functional integrity of the glands of internal secretion is protected by a wide margin of safety; therefore a large portion of the gland can be removed without measurable effect on the body, also hypertrophy occurs if one removed as much as the hyperfunction demands. That tumors may occur without recognized symptoms is reported by Lloyd (86) who, in a recent review of ten thousand consecutive autopsies, found five parathyroid tumors, without recognizable clinical symptoms.

The relation of the parathyroid tumor or hyperplasia to changes in bone has been progressively depicted under History. MacCallum and Voegtlin (89) in 1909 clearly demonstrated that post-operative tetany was the result of injury or removal of the parathyroid glandules in thyroid operations. They caused convulsions of tetany to cease by intravenous injection of calcium salts. Oral and subcutaneous administration of calcium had the same effect. Thus they concluded that the function of the glands is to regulate the calcium exchange of the body and considered the symptoms following parathyroidectomy as due to calcium deficiency. Compere,
(36) in 1933 stated "that hyperplasia of the parathyroid glands may be a purely compensatory enlargement in response to a demand of the organism as a result of a deficiency of calcium absorption from the bowel." This has been demonstrated clinically in cases of deficiency diseases, such as osteomalacia and rickets and in studies of experimentally produced rickets by Pappenheimer and Hinro (100). Some of the parathyroid glands became ten times as large as normal, and the microscopic sections revealed benign hyperplasia similar to that described by Ballin and Morse (13).

Among the pathologists a difference of opinion arose as to whether the parathyroid tumor was primary or secondary in relation to the bone disease of osteitis fibrosa cystica. Erdheim (50) himself defended the view that the disease of the skeleton was the primary factor and that skeletal decalcification created such a demand for calcium that a compensatory hypertrophy of the parathyroid glands occurred. Anatomical evidence against this view was found in the fact that, in generalized osteitis fibrosa hypertrophy or tumor formation was often confined to one parathyroid gland, the others remaining apparently normal. On account of Erdheim's investigations the whole question was repeatedly discussed at scientific meetings in Vienna. Questions were raised at that time whether it was not justifiable to attempt the extirpation of such a tumor of the parathyroid gland in cases of generalized osteitis fibrosa, but it was not until Mandl (90) of the Vienna school, in 1926, first performed this operation. In view of the controversy, it is of great interest that he decided to explore the neck only after treatment by parathyroid transplants and parathyroid tablets failed to relieve the symptoms. A tumor was removed and the pains in the bones of the patient disappeared in a few days after the operation.
Let us now revert for a moment to the relationship between the three agents active in calcium metabolism. Dragstedt (46), reviewing the literature in 1927, inferred that the parathyroids served "in the transfer of calcium from the alimentary tract and its deposition in osteoid tissue during growth and repair". This is also the precise function of Vitamin D. Should the vitamins supplied, however, exceed that of the calcium intake, the additional quantity of calcium (required to fulfill the functional role of the vitamins) is withdrawn from the labile stores in the trabeculae of the bone shafts. Similar demineralization is, however, the function of excessive doses of parathormone. Clearly, then, the parathyroids act as the key-control in calcium metabolism subject to stimulation by Vitamin D. It is suggested, therefore, that the gland may also serve as a compensating mechanism when there is lack of vitamin D (and, post hoc, inadequate absorption of exogenous calcium). This compensatory overactivity of the gland will, then, release calcium from the bones for use elsewhere. Eventually, continued deficiency of the exogenous agents will result in regressive changes in the endogenous (hypoparathyroidism), or, due to some stimulus, in toxic hyperfunction (hyperparathyroidism). Osteoporosis will be manifest in both syndromes. Ortenberg (98) concluded that the normal function of the parathyroid is not in miniature that of the toxic action (decalcifier), but that it may be a positive or anabolic factor in calcium metabolism. He states that the hormone responsible for direct excretion of calcium is the thyroid gland but offers no proof. Osgood and Haskins (99) do not include thyroid disorders as a cause of hypercalcaemia, but Albright et al (7) state that in exophthalmic goiter of long standing, generalized osteoporosis occurs which persists years after thyrotoxicosis is relieved. Ortenberg gives the example in a man weighing one-hundred
and fifty pounds (his own parathyroid glands functioning normally) a corresponding daily dose would be ten thousand units for three weeks, one thousand five-hundred for six months, or eighty units daily carried over ten years. There is abundant proof that callus formation, notwithstanding a calcium-phosphorus product near the optimum (above thirty) is delayed by removal of the parathyroid glands. Collip (32) states that a patient with osteitis fibrosa cystica showing a blood calcium of thirteen and one-tenth to fifteen and three-tenths milligrams percent had a calcium excretion quite analogous to that of a normal individual who was receiving one-hundred units of parathormone every day. It is interesting to note that, in the generalized decalcification, the teeth do not take a part. They may fall out because of disease of the jaws, but they themselves remain well calcified. This is brought out by roentgenograms in which the well calcified teeth stand out sharply against the poorly calcified jaws. This failure of the teeth to become decalcified is strong evidence against their being a reserve supply of calcium (4).

The blood pathology (hypercalcemia, hypophosphatemia, and the phosphatase readings) will be taken up in the Laboratory Diagnosis section, however I want to mention here that the occasional secondary anemia and leukopenia is the result of the replacement of the marrow cavity with fibrous tissue, leading to a decrease in the hematopoietic function.

In looking through the various pathological descriptions of osteitis fibrosa it seemed that no other entity among lesions of bone have been accorded such a varied pathologic interpretation. Conceptions regarding their nature have ranged from that of simple repair or frank infection on one hand, to true neoplasm and outspoken malignancy on the other. In spite of
the differences regarding etiology there has been a growing tendency to consider both giant cell tumor and osteitis fibrosa as pathologically related, because of the number of instances in which cases combining the histological characteristics of both are encountered.

Even the Bone Registry of the American College of Surgeons in 1915 first placed osteitis fibrosa under the division of "inflammatory tumors" (31). Later (in 1931)(54) the Registry placed osteitis fibrosa under the classification of "osteogenesis with subsequent cartilagenous growth".

To the surgical generation which immediately succeeded Paget (1853) and Nelaton (1860) the myeloid sarcoma or giant cell tumor of bone appeared securely established as a clinical entity. It was sufficient merely to emphasize the distinctions between it and the true sarcoma of bone. Until the advent of von Recklinghausen's classical description of generalized osteitis fibrosa in 1891, this conception remained unchallenged. But with the ultimate widespread recognition in more recent years, that typical osteoclastomata can almost invariably be found in the varied histological pattern which characterizes the osteitis fibrosa group of lesions, the separate identity of the giant cell tumor is now by no means so obvious. For here is the seeming paradox of a histological picture shared by two lesions generically opposed--on the one hand a true tumor of bone (an osteoclastoma), which behaves in every particular as a neoplasm, and on the other hand, a dystrophy of bone, admittedly non-neoplastic, which exhibits a striking tendency toward spontaneous healing (105).

Pick (104) in his Harvey Lectures of 1931 discussed the malacic diseases of bone as follows: "osteitis fibrosa cystica is called 'metaplastic' disease associated with a complete alteration of structure, and the term
ostitis should be replaced by osteodystrophia because no inflammatory signs are present. The pathological findings of the incipient stages of von Recklinghausen's disease are known. They appear as instances of so-called 'progressive bone atrophy', a disease described by Askanazy (9). Macroscopically and by x-ray they exhibit a picture of simple osteoporosis in an otherwise quite intact skeletal system, however microscopically the connective tissue from the endosteum gives rise to a 'dissecting resorption' of the bone trabeculae." Maximow (91) in his text-book of histology states that it is almost certain that osteoclasts produce a lytic ferment, for, where they come in contact with the surfaces of the bone lamellae, the cells of the latter dissolve. The brown tumors and cysts occur in varying frequency, and reports of so-called "local osteodystrophia fibrosa" is often seen. Because the specific nature of these brown tumors and cysts was assumed a-priori, they were considered as undeveloped or abortive forms of von Recklinghausen's disease. The literature is full of instances of "localized Von Recklinghausen's disease", however recent investigations show it to be a type of granuloma (abundance of spindle cells and excessive amount of hemosiderin) also abundance of giant cells in groups, but not "giant cell sarcomata", rather reaction-and-resorption tumors. They arise upon basis of primary hemorrhage, or necrosis. They are so frequently seen in von Recklinghausen's disease because of the increased softness and poor mechanical resistance of the bone. Since the time of Nelaton (1860) it has been shown that these brown tumors require only the least amount of surgical intervention (as curettage) for cure.

According to von Recklinghausen (127) the extremely intensified pro-
cess of bone development and destruction takes place in a marrow which has previously become fibrous. This fibrosis probably represents a proliferation of the reticular cells of the bone marrow to form osteo-blasts and -clasts. The destruction occurs through the activity of mono- or multi-nucleated osteoclasts. Growth goes on, at least at first, without the participation of the osteoblasts, by an indirect metaplasia, that is, by the conversion of the proliferated connective tissue cells of the end-osteum and marrow. Because of the total irregularity in which the collagen fibrils develop about these newly formed bone cells, a totally irregular bone results. This is in marked contrast to the regular lamellation which characterizes the bone of normal adults. There is a peculiar process which plays an extensive role in the disappearance of the trabeculae of the spongy bone. Osteoclastic activity builds a pathway along which the invading connective tissue enters the solid bone trabeculae and there proliferates, excavating and finally replacing these trabeculae of the spongy bone. All the old bone structure disappears and the fatty and lymphoid marrow becomes fibrotic. The former compact or spongy bone is replaced by a totally irregular constituted bony structure. No sooner is this type of bone produced, than it disappears, only to reappear again. This indisputable coincidence of the basic histologic changes in Paget's disease as well as von Recklinghausen's disease has become the source of a fundamental misconception among many pathologists.

The two prominent clinical features which characterize late von Recklinghausen's disease are first, the marked softening of the bones, and secondly, the associated bone changes with the so-called "brown Tumors" and cysts. The bone softening goes hand-in-hand with infractions and spontaneous fracture, and often lead to astonishing snake-like warping of the bones.
These bone softenings and fractures cause very severe pains. In general the pathologic anatomic features of the disease are dominated by hypostosis, that is, by marked preponderance of the bone resorption. The small amount remains essentially as osteoid tissue. Here, too, however, as in the other diseases characterized by bone softening, calcification is by no means entirely absent. Mosaic structures, when they do occur, are of the orderly arrangement. Two additional secondary changes may occur, clefts may develop in the fibrous areas and enlarge until they form multiple cysts with fibrous walls. Secondly, the osteoclasts in certain areas may proliferate to such a degree that they form osteoclastoma (benign tumors of bone tissue with giant cells)(104).

Elmslie (47) in 1934 discussed the question of fibrocytic disease quite fully as follows.

"The name 'osteitis Fibrosa' has been applied to a miscellaneous group of cases of bone disease, in which the skeleton shows some or all of a certain group of pathological changes. These changes are:

1. Lacunar absorption of bone by osteoclasts either locally in one place or in several localities, or generally throughout the skeleton.
2. Deposit of new bone of an irregular texture (woven bone).
3. Fibrosis of the marrow, which, again may be local or general, and may simply mean that the marrow contains more fibrous tissue than normal or may mean that it is entirely replaced by masses of fibrous tissue.
4. The formation of cysts. These may lie in the bone with only a bony wall, or there may be a fibrous lining, or the cysts may lie in the masses of fibrous tissue."
5. The formation of osteocalcifications, i.e., giant-celled tumors, such as were formerly called myeloid sarcomata. They may be single or multiple.

6. Sometimes, the development of cartilage.

We must recognize that these are changes which may occur in the bone from varying causes; none of them is peculiar to any one disease. It is unfortunate, therefore, to find pathologists reporting on the histology of a specimen of bone as showing "the changes of osteitis fibrosa cystica". Even if the clinical and pathological picture leads him to arrive at this diagnosis, he should give a detailed report upon the changes shown in every case.

Since Virchow's first description of a bone-cyst in 1876 and von Recklinghausen's description of the generalized disease in 1891, an extensive literature has arisen, and a whole medley of cases of different varieties has been recorded, so that it is by no means simple to sort out the cases. Nevertheless I believe it is possible to make a series of clinical or clinico-pathological pictures classing the cases in groups and giving them definite names, as follows:

1. Bone Cysts, formed by lacunar absorption of bone by osteoclasts.

2. Osteoclastomata, classical myeloid sarcomata; related to cysts and occur in cases of hyperparathyroidism.

3. Osteoclastomatous cysts, soft tissue about margin of cysts containing giant cells.

4. Diffuse fibrosis of bone, replacement of bone and marrow by massive formation of fibrous tissue in which small fragments of bone are embedded.
5. Generalized diffuse fibrosis of bone, as in 4, but occurring in many bones; can be distinguished from cases of hyperparathyroidism by clinical history and radiological findings, as well as by the absence of general porosis of bones and the characteristic skull changes and biochemical changes found in the latter condition.

6. Hyperparathyroidism, either sex but more common in women, generalized porosis of bones, with cyst formation and osteoclastomata, and thickening and porosity of the skull, hypotonicity, and calcium metabolism disturbance; the discovery of the cause of this condition and its cure by operation constitute a triumph of biochemical research."

Jaffee (73) states that the portions of the skeleton most susceptible to decalcification are those in which formation of bone is most active, i.e., the spongy bone of the metaphysis, especially of the long tubular bones. For this reason, decalcification during the adolescent period would surely give atypical bone changes, as some of the case reports indicate.
CLINICAL SYMPTOMATOLOGY

Hyperparathyroidism may occur at any age, but usually appears between the ages of thirty-five and fifty-five years, and is more than twice as common in women as in men. The youngest case on record was thirteen years old and the oldest in a woman at sixty-nine years (72).

The symptomatology can be divided into three groups:
1. That due to the hypercalcemia per se,
2. That related to the skeletal changes, and
3. That related to the increased calcium and phosphorus in the urine.

1. Just as hypocalcemia causes increased excitability of the nerve-muscle apparatus (tetany), so hypercalcemia causes the opposite. It takes more electricity to cause a muscular contracture in such individuals than in the normal. This is the antithesis of Erb's sign for tetany. Hypotonia, lassitude, ptosis, constipation, flat feet, vasospastic phenomena, and even cardiac musculature is affected. Insomnia, hypochondriacal states, and even neurasthenia occur. It is characteristic of these vague symptoms that their having been present becomes obvious only after they have disappeared.

A few cases of parathyroidism will express themselves mainly in gastrointestinal symptoms as vague pains or attacks of acute abdominal pain with vomiting, hyperacidity, constipation, or anorexia (102). In this light, Taylor et al (121) showed that marked vascular changes occurred in the gastrointestinal tract of dogs and concluded that the effect was neurogenic, and not due to the hypercalcemia as such, affects were mitigated by full atropinisation of the dogs.

In others the muscular weakness is outstanding. The weakness of the movements of these patients resembles a pseudohypertrophy of the muscles. Fre-
falls occur on account of the hypotonia, the legs giving away. Often such patients come to the orthopedic surgeon for backache. In such cases decreased circulation of the extremities, pains in the legs and bones, and absent or diminished reflexes are common. Four methods in vogue for diagnosing the muscular hypotonia are listed as follows:

1. The determination of the milliamperes needed to provoke the muscular contraction (Oppel)(97).
2. The finer method of determining chronaxia, that is, bringing in the time factor of the muscular contraction has been of use.
3. The moving picture will show the slow and weak action of the muscles, and allow comparison pre-operatively and post-operatively (112).
4. The electrocardiogram shows that the muscular weakness does not spare even the heart muscle, this being proven by shortening of the R-T interval.

In a few cases the muscular atony is accompanied by coldness and bluish color of the limbs and this has led to ganglionectomies for suspected Raynaud's disease. Pressure on cranial nerves by the softened and deformed Paget's skull, or on the spinal root and the cord in cases of osteitis fibrosa of the cord, has led to the diagnosis of cerebral affections or spinal tumor. All the forms mentioned under this last section have been called "formes frustes" of parathyroidism.

2. The skeletal symptoms vary in severity from the cases showing absolutely no bone symptoms to one in which the skeleton becomes practically non-existent and which, in fact, may end fatally from the sheer inability to raise the thorax in respiration.

It is obvious that there must exist a stage in the osteoporosis when
just the bone demineralization is present, before the added features of
cysts, tumors and fractures have appeared. Also, a mild form of this dis-
sease may remain at this stage indefinitely and never develop true von-
Recklinghausen's disease, yet partially incapacitate the patient. Such
patients are often diagnosed flat feet, arthritis, neuritis, neurasthenia,
or ptosis.

In a pronounced case of parathyroidism the patient drags his weak legs
along slowly, a gait that Rowntree (112) thought was so characteristic that
he demonstrated it in moving pictures. The weak muscles are painful, and,
together with the weak bones, prevent the patient from finding comfort in
any posture. Some of these sufferers spend their time looking for pillows
and chairs that will support their weakened bones and muscles. Bone de-
formity is therefore a late manifestation except as regards the spine.

Bone tumor, due to an underlying cyst, may be an early manifestation
of the disease. It is especially apt to occur in the jaw and be treated
as an epulis for years before the underlying condition is recognized (4).
Spontaneous fracture is often the event that first calls attention to the
underlying disease.

More commonly, Ballin (12) states that decalcification of the bones
(osteoporosis), bone cysts, osteoclastic processes, giant-cell tumors, de-
formities and pathological fractures of the softened bones are sequelae of
increased parathyroid function. He distinguishes under this skeletal in-
volvement the following types:
1. The vertebral type usually expressed by kyphosis and compressed vertebrae;
is slow in progress.
2. The infantile type, usually more rapid.
3. The arthritic type.
4. The Paget type.
1. The vertebral type commonly begins with back-leg ache. This fact brings the disease to the attention of the orthopedic surgeon and in our experience there is hardly a case that is not first diagnosed lumbago, sciatica, or if the attending physician has orthopedic inclinations, the diagnosis may be more refined,—as sacro-iliac or intervertebral arthritis, disturbance of the nucleus pulposus in the intervertebral discs, and so forth. As the disease progresses, the pain increases and the x-ray shows the apparent kyphosis manifested by wedging of the vertebrae, loss of lime in the vertebrae, and pathological fractures of the vertebral bodies. These cases have been diagnosed metastatic malignancy (prostatic or multiple myeloma) or fractures requiring bone grafts. Any compression fracture of the spine acquired without undue violence should, in our day, be an indication for studying the blood chemistry and taking a general roentgenological survey.

There is another type of older person (between sixty and eighty years) who gets shorter and bends over; such patients are usually placed in the group of senile spondylarthritis or senile kyphosis, but their pain is so excruciating and their muscular weakness becomes so prominent that they become bedridden invalids.

2. Much more difficult is the question of the infantile skeletal lesions and their connection with parathyroidism. There is one group which usually develops very rapidly, begins with general intestinal and urinary symptoms, followed quickly by skeletal pains and deformities. The x-ray shows general decalcification, cyst formations, and osteoclasias (giant-cell tumors is the report if they are biopsied); multiple fractures occur, such as have been described by Hunter (72) and Quick and Hunsberger (105).

These cases should be operated upon early to avoid the frightful deformities which later can only be arrested but perhaps not overcome by ortho-
pedic care following parathyroidectomy. Three such cases have been ex-articulated in the hip joint, presumably for osteosarcoma (20)(57). The possibility of parathyroidism is also a reason for biopsy before amputation, in spite of warnings from eminent pathologists.

In children, if the fibrocystic process encroaches on the epiphyseal lines, it is easy to understand that we find in the bones cysts, giant cells, and chondromatous tissue arising from the epiphyseal cartilage; and, therefore, a good many of them are diagnosed chondromata. Slipping epiphysis is another name used for the disturbance.

3. The arthritic type of skeletal manifestation of hyperparathyroidism is best presented by Funsten (53) as follows: "The occurrence of arthritis is frequently responsible for the first symptoms of parathyroid disease. It may be recognized by symptoms of paroxysmal pain in the spine and abdomen, deformity of the spine, other joint involvements with secondary ankylosis." This brings up the question whether ankylosing polyarthritis should come under this heading. Oppel (97) is the proponent of this theory and has many followers, but I have included this under the discussion in Differential Diagnosis.

4. A few words about Paget's disease. I will not go into the long standing dispute as to whether osteitis fibrosa cystica (von Recklinghausen's disease) and osteitis deformans (Paget's disease) are two different entities or not. Pathologically, microscopically, and clinically we find transitory stages from one to the other, so that I have also placed the further discussion of this disease under Differential Diagnosis rather than calling it a form of parathyroidism as its primary etiological factor.
3. Where symptoms occur related to the increased calcium and phosphorus in the urine, where four times the normal amount of calcium is excreted in the urine, it is not surprising to find polyuria, and thus, necessarily, requires the polydipsia. Albright et al (5) in discussing the renal side of hyperparathyroidism found an incidence of 52% of renal stones (as evidenced by x-ray and post-mortem examination) in a series of eighty-four active cases in the literature. The urologic service at the Massachusetts General Hospital recently (1934) had been doing routine calcium and phosphorus determinations on patients with renal stones and succeeded in diagnosing hyperparathyroidism four times where diagnosis never had been suspected otherwise. Of these four two were operated and each patient had a parathyroid adenoma. It is probable that the kidney may be involved in three different ways, referred to as type I, II, and III. These are arranged in order of the severity of the hyperparathyroidism.

Type I. Pyelonephritis secondary to formation of calcium phosphate stones in the renal pelvis.

Type II. A condition midway between which simulates both chronic glomerular and vascular nephritis. It differs from type I in that the deposits are in the kidney parenchyma rather than in the pelvis, and from type III in that the kidney shows long standing changes and may be the only organs involved in the calcium deposition.

Type III. Acute parathyroid poisoning with anuria and death from undetermined cause in a few days, with calcium deposits in the kidney parenchyma as well as in other organs, but with no chronic renal changes. Is this type due to rapidly growing tumor or actual malignancy? Such a rapidly developing process would, theoretically, kill a person before actual bone involvement could have gone very far.
Several cases have erroneously been diagnosed diabetes insipidus because of the symptoms of polydipsia and polyuria (3). Renal colic and hematuria or persistent albuminuria may be the only indication of the presence of hyperparathyroidism; in fact Albright et al (4) believe that hyperparathyroidism will turn out to be a fairly common cause of urinary stone and that in the future the case in which there is a stone and no bone disease will be the commoner type to occur.

Actual tumor symptoms of the parathyroid glands themselves are rare.

Many other orthopedic diseases have been classified by some authors (13), (14), (96) as due to hyperparathyroidism but these will be considered under Differential Diagnosis.
DIAGNOSIS

The diagnosis can best be made by considering first, the symptoms, secondly, the laboratory data, and lastly confirming such diagnosis with the x-ray.

1. The diagnosis of hyperparathyroidism, therefore, has to be considered in patients presenting themselves with the most varied symptomatology. The patient with widespread skeletal disease with cysts, tumors, and fractures. The patient with an epulis or cyst of the jaw or one with generalized aches and pains and a rather thin skeleton. The old lady with a pain in the back and flat feet. The individual with renal colic. The patient with unexplained polyuria, the uremic, even, perhaps, the apparently neurasthenic individual. Once the diagnosis has been considered from the symptomatology of the patient, it is up to the chemical laboratory to rule it out; the x-ray can only add confirmatory evidence. Fuller Albright (2) states that "one must think of the diagnosis very often, but be prepared to be disappointed almost, but not quite, equally often. The rare ten-strike in the borderline case makes the effort worth while".

2. The laboratory diagnosis. Hyperparathyroidism is one of the diseases that may be diagnosed by the laboratory per se, although some men (13)(14) will perform parathyroidectomy without the characteristic hypercalcaemia and hypophosphatemia of the blood chemistry or the hypercalceunuria and hyperphosphaturia of the urinalysis.

The history of the development of the association of these abnormal findings of the laboratory have been given under that title.

Osgood and Haskins (99) give as the normal range of the blood calcium nine to eleven milligrams per cent of blood serum, and that of the
inorganic blood phosphorus as from three to four milligrams per cent.
The plasma phosphatase has a normal range from two to four units, method of Bodansky (25). It is interesting to note that this enzyme is present in largest quantities when and where calcification is taking place, i.e., is an indication of the degree of osteoblastic activity. One may deduct from this fact that often the picture may be normal in the early or arrested cases of osteitis fibrosa cystica but quite high in the active states of skeletal involvement. Phosphatase is observed to be present in unusual quantities when bone is disorganized, however it is also present in tissues which do not normally calcify, as kidney and intestinal mucosa, thus bringing up the question of pro-enzyme (80).

Albright, Aub and Bauer (4) state that "a serum phosphorus below three and five-tenths milligrams per cent and a calcium above eleven milligrams per cent should be regarded with suspicion (the serum taken fasting)". One must remember that renal insufficiency may affect the phosphorus level, raising it. Snapper (117) reported a case of hyperparathyroidism with a serum calcium as high as twenty-three and six-tenths milligrams per cent and Hannon et al (61) reported a serum phosphorus as low as one and four-tenths milligrams per cent.

It is of interest to note that under certain biological conditions hypercalcemia may occur as a normal phenomenon. It has been shown that the serum calcium of certain birds increases very considerably at the period of ovulation (110); this also occurs in the female cod in the spawning season (66). Experimentally, Hunter and Aub (71) report a case of severe hypercalcemia (nineteen and eight-tenths milligrams per cent) produced by overdosage with parathormone. The patient was a man of six-
ty years suffering from chronic lead poisoning but suffered only slight nausea and anorexia as a result of the experiment. A marked rise of the non-protein nitrogen of the blood follows the administration of large doses of parathormone. It appears that in the long standing cases there is increased absorption of calcium and phosphorus from the gastrointestinal tract and that excretion of calcium into the gastrointestinal tract is not a threshold phenomenon dependent on the level of the serum calcium. Richardson et al (108) found that the urinary output of calcium and phosphorus on a low calcium diet was six to seven times greater than was found in normal individuals under identical conditions. They found that these changes in metabolism were equivalent to those of a normal individual receiving one hundred units of parathormone daily.

Bence-Jones proteinuria can occur in von Recklinghausen's disease. Albright et al (2) reported three cases lately (1935), in which it disappeared after operation but not immediately, and he assumed that the excretion of this substance in hyperparathyroidism can occur only when there is associated von Recklinghausen's disease.

3. The x-ray diagnosis or, rather, corroboration is variable. There may be no skeletal changes in hyperparathyroidism demonstrable by x-rays. The chief roentgen evidences, when such exist, are increased radiability, deformities, cysts, tumors, and fractures; only the first of these is fundamental, the others are secondary changes. Being a metabolic disease hyperparathyroidism must exert its fundamental action, demineralization, on the entire skeleton, if at all. Such changes may be observed as diminished density of the bone compared with a control subject. Some authors consider decalcification pathognomonic of the disease, consisting
as it does of a uniform, miliary, granular mottling, best observed in the calvaria, thinning of the cortex and trabeculae, and the presence of areas of subperiosteal resorption in the long bones and phalanges. Therefore, in doubtful cases, it is essential to decide at once whether one is dealing with a generalized or a localized disease. Furthermore, a disease may be polyostotic without being generalized. It must be emphasized that at first sight the secondary bone changes—cysts, tumors, and fractures—may make one think that the skeleton is involved in a spotty manner, but a more detailed study will reveal that the decalcification is uniform and generalized. Of course, immobilization due to a fracture may enhance the decalcification in the involved part. Absence of the lamina in the tooth sockets by x-rays has been emphasized. Deformities demonstrable roentgenographically may be very extensive and obvious. Lateral roentgenograms of the lumbar vertebrae often disclose biconcave discs (fish-bone vertebrae), which occur because the softened vertebrae can no longer withstand the tendency of the nucleus pulposus of the intervertebral disk to expand. They are evidence of softened vertebrae and are not pathognomonic of hyperparathyroidism but may occur in osteomalacia, multiple myeloma and the like (4).

The cysts, if present, are usually multiple, but need not be; there may be marked expansion of the overlying bone. A cortical cyst is especially suggestive of this disease. The tumors or osteocalstomas usually occur in the jaws, at the ends of the long bones or in the ribs. In contradistinction to the cysts, they occur only where there is cancellous bone. As yet, we know of no way, roentgenographically, of differentiating these from the cysts, unless they give the definite soap bubble appearance of such tumors.
Some cases show peculiar lesions in the terminal phalanges, in that the edges of the bone everywhere are fenestrated, suggesting a complete lack of cortex. Fractures, when present, usually occur through cysts or tumors.
DIFFERENTIAL DIAGNOSIS

The differential diagnosis may best be discussed by considering the three systems which hyperparathyroidism most often attacks, namely, A. the skeletal system, B. the muscular system, and C. the renal system.

A. The skeletal system is invariably affected by hyperparathyroidism because of the osteoporotic action of the disease, but it is obvious that there may exist a stage of the disease when just the bone demineralization is present and before the added features of cyst, tumors, or fractures have appeared. Such mild forms of the disease might remain at this stage indefinitely, and never develop true von Recklinghausen's disease and yet simulate other skeletal diseases, or be evidenced by symptoms referable to the other two systems mentioned.

I have already given Ballin's classification of the skeletal manifestations of this disease under Symptoms (pages 27-29). The vertebral type usually is slowly progressive and begins with back-leg ache, and because of this symptom these cases have often been diagnosed lumbago, sciatica, or, if the attending physician has orthopaedic inclinations, the diagnosis may be more refined, such as sacro-iliac or intervertebral arthritis, disturbance of the nucleus pulposus in the intervertebral discs, and so forth. Kyphosis is a late manifestation. There is another type of older person (between the ages of 55 and 70 years) who gets shorter and bends over, such patients are usually placed in the group of senile spondylarthritis or senile kyphosis.

In considering the more common conditions that are often mistaken for hyperparathyroidism there are:
1. Osteoporosis is a condition in which the bone tissue is quantitatively decreased but qualitatively normal. It may be brought about by an underactivity of the osteoblasts in laying down bone (senile osteoporosis) or by an overactivity of the osteoclasts in resorbing the bone (osteoporotic form of hyperparathyroidism). The end result is very much the same in either case—the roentgenogram shows increased radiability. Bone pain, fractures and deformities often occur, however the serum calcium in the senile form is normal, the serum phosphorus is reduced (often about three milligrams per cent) or normal, and the plasma phosphatase is normal. Bone biopsy in the senile type would fail to show fibrosis of the marrow and the increased osteoclasts. Senile osteoporosis is perhaps the most difficult to differentiate because the resemblance in mild cases of hyperparathyroidism. A generalized osteoporosis has been observed in the experiments of Jaffee et al (74). The decalcification in their dogs showed that when the decalcification was less severe, generalized thinning of the bones without marrow fibrosis occurred (osteoporosis) but when more rapid, generalized decalcification and secondary marrow fibrosis resulted (osteitis fibrosa). Thus Moreau (96) drew his conclusion that all conditions showing decalcification and disturbed calcium metabolism are controlled by the parathyroid glands.

A generalized osteoporosis has been observed in exophthalmic goiter of very long standing, which condition has persisted for years after the thyrotoxicosis is relieved.

2. Osteitis Deformans (Paget's disease).

I will not go into the long-standing dispute as to whether osteitis fibrosa cystica (von Recklinghausen's disease) and osteitis
defor"mans (Paget's disease) are two different entities or not, but will present the summary of both sides. Pathologically, microscopi-
cally, and clinically we find transitory stages from one to the other. The incidence of sarcoma in Paget's disease is also not a distingui-
shing factor. Ballin (11) states "now the results of parathyroid-
ectomy in Paget's disease confirm the opinion that the two diseases are identical and can be controlled by parathyroidectomy. The French who have given a good deal of consideration to the question of Paget's disease have come to the conclusion that one should explore the para-
thyroid region to ascertain as to whether the case is a von Reckling-
hausen's disease or a Paget's disease".

Albright et al (4) do not agree with Ballin and Morse above, and state that the signs and symptoms of the two diseases are not the same, although they include in their "clinical types" hyperparathyroidism simulating or complicated by Paget's disease in which findings charac-
teristic of both diseases are present. The reasons of difference are given as (a) although Paget's disease is often polyostotic it is never generalized, which is almost inconceivable for a metabolic di-

sease; (b) the metabolic changes are not that of hyperparathyroidism, i.e., the serum calcium is normal or only slightly elevated (eleven milligrams per cent) and the serum phosphorus is normal or slightly elevated, and the plasma phosphatase, given a comparable degree of bone disease, is considerably higher than that observed in osteitis fibrosa cystica(80), also the calcinuria and phosphaturia are usu-
ally not present when the patients are run on a test diet; (c) the x-ray shows spotty distribution of the lesions and the presence of normal bone somewhere in the body, especially the small bones of the
hands. The involved bones, often the long bones, in most instances show a characteristic enlargement (hyperostosis), are often soft, bowed, and a thickened cortex is demonstrable on both x-ray and macroscopic examination. The skull is usually thick and gives a moth-eaten appearance. Aside from the skull, the weight-bearing bones, as the sacrum, are often involved, i.e., the apposition of new periosteal bone preponderates over the resorption of cancellous bone; (d) malignant bone tumors develop in a fair number of the cases of Paget's disease, such is rarely, if ever, observed in hyperparathyroidism. Perlman (103) thinks that osteitis fibrosa is the predisposing cause of the tumor growths of sarcoma because only those portions with very mature fibrous bone marrow show tumor formation, whereas the parts with loose bone marrow and younger bony changes, in the sense of Paget's disease, are not affected by tumor growth; (e) fractures (frequently spontaneous) occur very often in hyperparathyroidism and seldom in Paget's disease; (f) renal calculi are the exception in Paget's disease but are very often found in hyperparathyroidism. It is true that histological bone sections from these two diseases may be similar and therefore it may be difficult to diagnose on this basis alone, but the course pattern to the trabeculation of the affected bones, which in itself is almost pathognomonic of Paget's disease, contrasts with the sparse irregular trabeculae of osteitis fibrosa cystica.

Bauer (19) states that Paget's disease occurs in older people, usually males, and is regularly associated with marked arteriosclerosis, whereas hyperparathyroidism is met with in all age groups, more
commonly in females, and arteriosclerosis is not a common finding. The late Prof. Schmorl (113) in an exhaustive pathological study of the largest group of cases of Paget's disease ever reported (one-hundred and thirty-eight personally observed autopsies and seven other cases) was unable to demonstrate the presence of parathyroid tumor or histological changes, and concluded that Paget's disease was not due to hyperparathyroidism.

Directly opposed to the hyperparathyroid theory as to the etiology of Paget's disease is the theory that hypoparathyroidism is the cause. In Paget's disease the calcium metabolism as demonstrated is in a positive balance and improvement has been noted following administration of parathormone (132)(35). An article by Bassler (17) sustained this assumption and his patient showed great symptomatic relief as well as objective improvement demonstrable by the x-rays. VanHazel and Andrews (123) in extensive metabolic studies also explained the pathology of Paget's disease on the basis of hypo-secretion of the parathyroid glands and suggested treatment with parathormone. Greenwald and Gross (59) advanced the hypothesis that the calcium excretion took place faster than the calcium dissolution in the bone and thus explained the lowering of the abnormally high blood calcium by parathormone in certain cases. Compere (36) states that excision of the parathyroid glands in patients afflicted with osteitis deformans may be as serious as thyroidectomy in myxedema.

3. Osteomalacia.

Osteomalacia is the next skeletal disease often mistaken for hyperparathyroidism. In this country it is necessary to define what one means by "osteomalacia" (adult rickets) because the term is often
used very loosely. It is a condition in which bone tissue shows widened osteoid seams as a result of failure of calcium deposition in the osteoid "tissue", due to deficiency in vitamin D. The disease is practically non-existent in this country except in association with fatty diarrhea and the resulting lack of absorption of the fat-soluble vitamin D. The prevalence of the disease in women is possibly explained by the influence of pregnancy and lactation, combined with a sedentary and indoor life. The bones bend rather than fracture and show the radiographic evidence of decalcification but no cysts. A biopsy of the bone, if decalcified in such a way as to show the osteoid tissue, is pathognomonic. The blood chemistry shows a serum calcium normal or low and a corresponding phosphorus figure, and the plasma phosphatase is high. Accordingly, tetany is common although usually not severe (92). The condition responds promptly to antirachitic measures—good food, the administration of cod-liver-oil, irradiated ergosterol, and ultraviolet light. In contradistinction to this Johnson (76) showed experimentally that vitamin D concentrates intensified the disease process of hyperparathyroidism. While the hypertrophy of the parathyroid glands in conditions of vitamin D deficiencies is compensatory (49) and is certainly a secondary phenomenon, the tumors of the parathyroid glands found in association with osteitis fibrosa cystica are of primary significance.

4. Focal Osteitis Fibrosa (Solitary Cysts) (Local Osteodystrophia Fibrosa) (Localized von Recklinghausen's Disease).

Focal osteitis fibrosa, in which one or more bones may be affected with localized changes exactly similar histologically to those of the
generalized disease, must be considered in the differential diagnosis.

This localized disease is of more common occurrence and chiefly affects young individuals (ages of five to fifteen years) whose health is otherwise normal (1). The upper shaft of the metaphyses of the humerus, femur or tibia are the common sites of its localization (85), and the condition is usually not disabling until spontaneous fracture occurs. An average duration of two and one-half years occurs before these lesions are observed (54), but the tendency of these lesions to become arrested probably explains why these "healed cysts" are often discovered only incidentally. The slow progress together with the normal radiographic appearance of the remaining skeleton, the normal blood chemistry of calcium, phosphorus, and phosphatase tend to rule out such localized cysts from the category of hyperparathyroidism. D'Aunoy and Connell (42) also state "we do not agree with Virchow's original viewpoint that these cysts arise in degenerating chondromata. It is noteworthy in this respect that all case reports and pathological discussions of osteitis fibrosa stress the absence of cartilage. The attempts to correlate the localized cystic bone condition in some of their essential details with diffuse fibrocystic disease of bone (von Recklinghausen's disease), other parathyroid disturbances and disorders of calcium-phosphorus metabolism in general hardly seem plausible". Later views as Bloodgood's (24) that low-grade infections are the basic cause although possibly correct have never been definitely proved, for cultures and animal inoculations have been uniformly negative. Such "solitary Cysts" are apt to occur in the jaw and be treated as an epulis for years before the underlying condition is recognized (4).
Treatment consists in obliteration of the cavity with or without curettage, with rare recurrences and no malignant transmutation. According to Cotton (37) there is definite evidence to support the statement that giant cell tumors do degenerate to form cysts, and transitional forms are not rarely met with. Some confusion may arise here because real cysts of any origin may show in the lining membrane giant cells in some number. Giant cell tumors may be associated with cysts in the same individual, both of obvious parathyroid background (37).

5. Polycystic Osteitis Fibrosa.

Two views may be taken concerning these lesions which are considered under this heading. Geshickter and Copeland (54) state that one view is that they are an early stage of osteitis fibrosa, assuming a structure characterized by an aggregation of small cysts because a fusion of these small cavities at a later date represents the mode of origin of the large solitary cysts. The second view would be that such lesions are more progressive forms of bone cysts, and that their continued growth by the apparent budding of small cavities represents a transition between the solitary bone cysts (which is an arrested lesion) and the multiple form of osteitis fibrosa which is undoubtedly progressive. So that these lesions emphasize the relationship of the bone cyst to the giant cell tumor tissue, for in these lesions the small young cysts are found to arise in the giant cell areas, fusing together to form larger cavities (55).

6. Multiple Bone Cysts.

A review of multiple bone cysts in the literature and in the series of Geshickter and Copeland (54) emphasizes the fact that the
lesions described under this head represent a conglomeration of pathologic entities. From a histologic standpoint, the picture of many cysts frequently seen filled by hemorrhage exhibiting a predominance of osteitis fibrosa, fewer but some giant cells, and less of a polycystic structure, i.e., all the characteristics essential to the interpretation of these as a transitional form between the giant cell tumor and the solitary bone cyst.

Clinically this group is to be distinguished from multiple giant cell tumors by the higher age limits and the longer duration of the symptoms and the occurrence in the metaphyseal region, due to vascular interference or trauma. This is what would be expected if multiple bone cysts represented a later stage in the same pathologic process as multiple giant cell tumors. No Bence-Jones proteinuria occurs in this group of cysts. This condition heals without surgery, but the cysts remain a long time.

7. Giant Cell Tumors.

The tumor known under the various titles of giant cell tumor, myeloid sarcoma, or osteoclastoma is somewhat of a clinical enigma to the practical surgeon of today. There are three main reasons for this statement: (1) the tumor can no longer be regarded as a histological entity, a fact which has an important bearing on the problems of diagnosis and treatment, (2) the tumor is rare and its clinical behavior variable, and (3) in the treatment of the tumor there appears to be a tendency to substitute intervention irradiation (105). Albright et al (4) state that giant cell tumors may be completely localized or be a part of an underlying hyperparathyroidism and, if the former, the
remaining skeleton and the blood values will all be normal. Geshickter and Copeland \((54)\) state that giant cell tumors are neoplastic and not inflammatory and brought on by interference in the vascular supply, also that giant cell tumors occur in patients between the ages of fifteen to twenty, involving the epiphysis and having great tendency to expand and perforate the cortical bone asymmetrically. Bellin \((13)\) states that "breaking down of the bony tissue will cause small hemorrhages and granulation tissue with giant cells in response to the irritation in the bone; in all, a picture of the so-called 'brown tumor'. This interesting and important factor, namely, that seemingly neoplastic giant cell tissue produced by endocrine gland pathology can be cured by removal of the pathological glands may, in the future, have some influence on the teaching of the origin of some tumors". So that, in contradistinction to Geshickter and Copeland's idea that giant cell tumors are neoplastic, Bellin \((14)\) states that the term "giant cell sarcoma" is not a neoplasm, but a reaction of osseous tissue to certain factors, in some cases decalcification, and when this occurs parathyroidectomy will cure them.

Summing up the discussion on "giant cell tumors", some authorities use the term loosely to express the histological picture and consider this a disease entity, either inflammatory or neoplastic in nature; others describe such histological pictures as occurring as a process in such entities as hyperparathyroidism.

8. Osteitis Tuberculosa Multiplex Cystica.

Vastin and Bacon \((124)\) report a multiple cystic state occurring in the diaphysis of the long bones which simulates osteitis fibrosa cystica on x-ray examination, however this condition occurs in children, the blood chemistry is normal, the tuberculin reaction is strongly positive, and a biopsy is final.
9. Osteogenesis Imperfecta (Fragilitas Ossium).

The association of multiple fractures occurring rather readily in childhood and blue sclera and deafness has often been called the earmarks of this disease entity, which seems to be inherited. Kaplan (79) considers this disease as an endocrine disturbance. The pathologic changes in the bone consist in a depression of bone formation coupled with normal bone absorption. A biopsy would show, no increase in osteoclasts and no fibrosis; if anything, the osteoblasts and osteoid "tissue" would be decreased. The peculiar x-ray appearance of the bones is not unlike that found in the early cases of parathyroid disease, however, the histological picture just given and the normal calcium and phosphorus blood serum levels and the normal to slightly elevated phosphatase level plus the earlier age of onset should aid in ruling out this disease. Recently, the therapeutic response to the ovarian-gland extract in several series of cases of fragilitas ossium is interesting.

10. Xanthomatosis Generalisata Ossium.

There exists a generalized xanthomatosis of the bones without symptoms of Schüller-Christian's disease, i.e., without cranio-hypophyseal localization. The radiograms of the osteoporotic lesion of generalized xanthomatosis of the bones may easily be confused with von Recklinghausen's disease of bone (osteitis fibrosa generalisata) (119).

11. Multiple Myeloma.

This condition may very closely resemble hyperparathyroidism. The history of rheumatism, weakness, spontaneous fracture, nephritis or nephrosis often complicated by gastric disturbances, kyphosis, paralysis, with remissions, occurring in individuals past middle age is often secured in this disease. Even the x-rays may closely resemble osteitis fibrosa cystica,
and the blood chemistry of hypercalcemia are similar, however, the associated high serum phosphorus and only slightly elevated phosphatase plus the presence of Bence-Jones proteinuria (in sixty to seventy per cent of cases) is of value in the differential diagnosis. The biopsy clinches the diagnosis showing the multiple plasma cell types, the multiple endothelial cell types, the myelocytic cell and erythroblastic cell types (85).

12. Metastatic Malignancy.

Metastases from the prostate, breasts, bronchi, thyroid and from the hypernephroma should only rarely cause confusion, however hypercalcemia and hyperphosphatemia occur with this disease process and the extremely variable clinical picture caused by these various metastatic processes may cause some doubt in the clinician's mind. That such secondary deposits may be multiple or single, osteolytic or osteoplastic shows its possibilities (54). The age of the patients, the hyperphosphatemia, the other evidences of malignancy (as masses and cachexia) would aid in its elimination.

Other orthopedic conditions that have been mistaken for hyperparathyroidism have been osteosarcoma (Beck (20) reports three cases that had been exarticulated at the hip joint), chondromata, slipping epiphyses, and leontiasis ossea (29).

Other orthopedic diseases that have been stated as being due to hyperparathyroidism are melorheostosis ("candle-drip" hyperostosis of bone), hypophyseal disostosis (Schüller-Christian syndrome), hyperostotic lumbarthria, calcification of the nucleus pulposus, Kúmmell's disease, Sicard's disease, Püttri's disease, and osteosclerosis fragilis generalisata (osteo-poikilosis or "marble bone") (13) (96). Ankylosing polyarthritis has also been attributed as being caused by hyperparathyroidism and is discussed as follows:
von Oppel (97) of the University in Leningrad, where men like Bechterew had created through their work on arthritis a background for such studies, brought out the fact that the usual infectious arthritis does not lead to ankylosis, but as soon as hypercalcemia exists simultaneously, calcium deposits around the inflamed arthritic synovia will take place and lead to ankylosis. He, therefore, advised parathyroidectomy (unilateral) in cases of arthritis with symptoms of parathyroidism, but never recommended it as a cure of arthritis. In other words, if a patient with ankylosing arthritis has hypercalcemia or roentgen evidence of decalcification or muscle hypotonia, a parathyroidectomy may be of the greatest value. Oppel first reported favorable results in cases of spondylitis deformans (Strumpell-Marie type) following parathyroidectomy. Later Funsten (53) stated that various types of arthritis besides the polyarthritic ankylosing type showed improvement following parathyroidectomy, but he presented no metabolism studies on these cases showing alterations in the calcium and phosphorus blood levels.

Bauer (19) has never seen any findings in patients with either form of arthritis that would suggest the existence of hyperparathyroidism as a causal factor. It is true that many of the cases of rheumatoid arthritis show x-ray evidence of decalcification (bone atrophy), but this no more than often is seen when in association with disuse. The improvement in cases reported may have been due to anaesthesia, rest in bed, or a natural remission of the disease. These three factors are all capable of bringing about improvement, particularly in cases of rheumatoid arthritis. This disease is also characterized by remissions and relapses. Bauer also states that in the last five years at the Massachusetts General Hospital the two diseases of hyperparathyroidism and ankylosing polyarthritis have never been observed in the same patient, although seven cases of hyper-
parathyroidism had been studied. In reviewing the literature on osteitis fibrosa cystica I found no cases in which an accompanying arthritis of the ankylosing type was present, however, in many cases the earlier symptoms were often diagnosed arthritis of one sort or another before the true disease syndrome of hyperparathyroidism was discovered (see Symptoms).

There is, rather some evidence that ankylosing polyarthritis may be a deficiency disease similar to rickets or osteomalacia. The typical micro-pathology of the enlarged parathyroid glands in all three conditions is that of simple hyperplasia and may be a compensatory change. The success of Fletcher (52) in treating multiple arthritis by means of diets rich in vitamins and mineral content lends support to this theory.

Basophilic adenomas of the pituitary (Cushing's disease) are not always an orthopedic problem, yet the osteoporosis that has been one of the features of the syndrome recently described by Cushing (39) may cause confusion. It has not been decided whether or not a secondary hyperparathyroidism is present in such cases (34). In one of these cases of Cushing's the serum calcium was normal and the phosphorus low (two and seven-tenths milligrams per cent) and there was a high calcium excretion in the urine, but the obesity, hirsutism, amenorrhea and hypertension in this syndrome is rarely absent.

B. The Muscular System in Differential Diagnosis.

In considering the effect of hyperparathyroidism on the muscular system one is really considering the effect of hypercalcemia per se, i.e., hypotonia. The striated musculature may be seen to be affected by the extreme weakness of the movements of the patient and the diagnosis of pseudohypertrophy of the muscles or other muscular dystrophies must not be erroneously made.
The backache (lumbago due to myositis), flat feet (due to relaxed musculature), and diminished reflexes must be read into the picture if hyperparathyroidism is present or to be ruled out. The cardiac musculature is not spared in osteitis fibrosa cystica and any bizarre electro-cardiogram with other symptoms already mentioned must be ruled out or into the picture. The smooth musculature of the gastro-intestinal tract loses its tone giving bizarre symptoms of vague pains, constipation, nausea and vomiting, often intractible) and indigestion. The diagnosis of gastropotosis is often made on these patients because of the hypotonia and the possibility of simulating any disease complex of the gastro-intestinal tract must be kept in mind. The blood vessels show vasospastic phenomenon, such as bluish color of the limbs that has lead to ganglionectomy for suspected Raynaud's disease. Such muscular relaxation has caused pressure on the cranial and spinal nerves with diagnosis of tumor being made (12).

So that generalized muscular weakness, bizarre gastro-intestinal symptoms, and vasospastic phenomena should be carefully observed as potential hyperparathyroid symptoms.

C. The Renal System in Differential Diagnosis.

Under symptoms related to the increased calcium and phosphorus in the urine were listed polydipsia and polyuria suggesting diabetes mellitus and even insipidus. Renal colic and hematuria or persistent albuminuria often occur, so that a differential diagnosis of the various nephritides and nephroses or even a simple cystitis must be considered.
PROGNOSIS

Whereas the disease of hyperparathyroidism may produce a fatal issue, either in the form of acute parathyroid poisoning or, more commonly, through renal involvement, it probably smolders on for years in the majority of cases, crippling but not killing. Spontaneous remissions are recorded and suggest that hyperparathyroidism may sometimes show relapses and remissions analogous to those seen in acromegaly and exophthalmic goiter.

TREATMENT

1. Medical Treatment.

Albright et al (6) report a series of cases treated by ingestion of phosphates with some beneficial results, but advised it only until surgery could be performed.

Leopold (84) reported apparent recovery of some cases by administration of calcium gluconate (one and five-tenths grams a day), together with a high calcium diet, rest and massage.

As regards prophylactic therapy for prevention of renal damage in hyperparathyroidism, it is pointed out that fluids should be forced, and alkaline urine should be avoided, that ammonium chloride and, presumably other acidotic-producing salts are contra-indicated; that the high phosphate diet, prescribed above, while indicated for the demineralization process, imperils the kidneys and should be used only when the blood values can be carefully followed and that applies to the high calcium diet as well (5).

Vitamin D in the form of viosterol in large amounts was administered to patients but no appreciable effect on the calcium and phosphorus balance was noted by Albright et al (4). Johnson (76) states that "whereas vita-
min D effectively protects against rickets or osteomalacia, it is evident from the experiments that it intensifies the disease produced by excessive parathyroid hormone. However, Snapper and Boever (118) report that such treatment increased the density of the bones as judged by radiograms.

2. X-Ray Treatment.

Cutler and Owen (41) place radiation therapy in the cases of hyperparathyroidism under several circumstances:

a. when there are contraindications to operation;

b. as a post-operative method when an adenoma is only partially removed;

c. when, following removal of one parathyroid adenoma, a persistently high serum calcium suggests possibility of hyperplasia or adenoma in the glands on the opposite side.

Clinically the normal parathyroids are highly resistant to radiation, as, for example, after exposure in treatment of the thymus, thyroid, or in cases with carcinomas of the larynx, when no tetany occurs even after excessively high irradiation.

That active hyperplastic cellular tissues are more radiosensitive cannot be denied; also the rationale of radiation therapy in the control of secretory glands is sound. The informed individual no longer questions the efficacy of this form of therapy in its influence over the salivary, ovarian, pituitary, or thyroid function, and there is no reason to believe that the parathyroid glands are exception (93). Yet the radiologists report no cases of cure or even temporary aid.

Albright, Aub and Bauer (4) followed the total calcium and phosphorus metabolism for a long period of time in patients who received maximum do-
ses of x-ray over the neck region without detecting any change in the urinary excretions or blood values and subsequently a parathyroid tumor with no degeneration was removed. In this light, treating the tumors of the skeleton with x-ray should also be avoided. Whereas it will cause temporary benefit to the tumors, it will not affect the cysts and will tend to increase the fibrosis of the marrow and thus enhance the anemia.

3. Surgical Treatment.

Since Mandl's pioneer operation nine years ago, over one-hundred reported cases of cures of hyperparathyroidism by means of surgical removal of parathyroid adenomas has accumulated. The chief operative difficulty is in finding the tumor. Before undertaking this operation the surgeon should know the normal and possible aberrant situations of the parathyroid glands. He must be familiar with their reddish brown color and smooth surface (in contrast to the granular surface of the thyroid). He must be able to differentiate from lymph nodes, collections of fetal fat, and thyroid lobules, and he must be prepared to continue the search even if this leads him into the anterior mediastinum. Unlike thyroid adenomas, parathyroid tumors mold themselves surprisingly well into crevices, as between the esophagus and the trachea. This means that one can be very close to them and still not palpate them. Brewer (28) in a recent report of the occurrence of parathyroid tissue in the thymus in four cases at routine autopsy at the University of Michigan, stresses the importance of such aberrant glands.

Recent reports as those of Ballin and Morse (14) bring up the question of removing normal-appearing parathyroid gland tissue when no tumor can be found, with some evidence of clinical results, and, if thyroid history repeats itself in parathyroid history, we would remove at least one
or two bodies if there are no real adenomata present.

Actual surgical treatment of the cysts themselves is often necessary after the parathyroidectomy has quieted the pain and levelled the blood picture, as it has been shown that bone cysts formed by fibrous replacement of bone persist but tumors (osteoclastomata) disappear. Speed (120) advocated a. cystic area widely cut into, curedt and swabbed out, being left open for access of surrounding blood, or b. placing into the cavity existing after this procedure a transplant from some autogenous source, or, c. the immediately surrounding cortex is jammed down into the cavity as a sort of transplant.

POST-OPERATIVE COURSE

Starting in the first few hours after the tumor is removed from the parathyroid region, there is a marked decrease in the output of urine and in the excretion of calcium and phosphorus. The patients may become practically anuric. Tetany may develop if the blood calcium falls much below seven or even eight milligrams per cent. The sudden change from a high blood calcium to a low one may cause visual disturbances, temporary hyperacusis, and may affect the mental equilibrium. Such patients may become temporarily apprehensive. The treatment of tetany is beyond the scope of this paper, but one should mention the use of calcium and parathormone as routine post-operative treatment. The time required for the blood calcium and phosphorus to return to normal probably depends mostly on how much the skeleton has to be repaired.

The improvement in symptomatology to be noted following operation is extraordinary. Whereas the only complaint before operation may have been
related to a fracture, the patient not infrequently says after the opera-
tion that he has not felt so well in years. A gain of weight is marked, constipation disappears, lassitude is replaced by a feeling of energy, bone pain and tenderness disappear within a few days. This rapid disappearance of bone symptoms is especially surprising in view that the radiability is not changed for six months. The osteoclastomata gradually disappear, but the cysts probably remain indefinitely (4). At present I cannot state whether the genito-urinary stones are ever absorbed.

CONCLUSION

Briefly summarizing the position of hyperparathyroidism would include:
(a). hypercalcemia is definitely due to hyperparathyroidism;
(b). the relatively low phosphorus is an effect of the law of ionic dis-
sociation and is not specific to the parathormone;
(c). the high plasma phosphatase is a reaction of the osteoblasts to de-
calcification and not specific to parathormone;
(d). although the giant-celled tumors and cysts are not necessarily due
to hyperparathyroidism, this is, nevertheless definitely a condition which is likely to cause decalcification of sufficient intensity to produce these effects;
(e). although the excessive excretion of calcium and phosphorus by way of urine is also not entirely specific to parathormone, the fact of the loss being confined almost entirely to the urine is a point strongly in favor of hyperparathyroidism.

The diagnosis of hyperparathyroidism, therefore, has to be considered in patients presenting themselves with the most varied symptomatology—
the patient with widespread skeletal disease with cysts, tumors, and fractures, the patient with an epulis of the jaw or generalized aches and pains and a rather thin skeleton, the old lady with a pain in the back and flat feet, the individual with renal colic, the patient with unexplained polyuria, the uremic, even perhaps the apparently neurasthenic individual.

Once the diagnosis has been considered it is up to the chemical laboratory, to rule it out. The x-ray can only add confirmatory evidence. One must think of the diagnosis very often, but be prepared to be disappointed almost, but not quite, equally often. The rare ten-strike in the borderline case makes the effort worth while.

So much, and more, is known about hyperparathyroidism, and it seems to justify the statement that the mystery is solved. But this is less than half truth, for, if the skeletal changes are due to oversecretion from a parathyroid tumor, what then is the cause of the tumor? and, if we can not answer this question, how can we foretell the fate of the patients "cured", or say, what will happen to the glands remaining? Long-continued and careful studies are needed before these matters become clear, but, in the meantime something--very much--has been achieved, and the terrible crippling caused by generalized osteitis fibrosa will soon be a thing of the past.

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