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THE DIFFERENTIAL DIAGNOSIS OF SOME OF THE MORE IMPORTANT CYSTIC DISEASES OF THE BONES

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THE DIFFERENTIAL DIAGNOSIS OF SOME OF THE MORE IMPORTANT CYSTIC DISEASES OF THE BONES.

I. Introduction

A very little investigation into this topic will convince anyone of the necessity of sharply limiting the number of topics to a few of the more important diseases or syndromes showing cystic changes in the bone. It would be very easy to write an entire book on this subject. The number of disease processes having true cystic changes in the bone or simulating them on X-ray is astounding. The range encompasses embryologic malformations, infections, fungous diseases, tumors, and a number of systemic diseases with cystic changes in the bone.

As in any other diagnostic problem the final diagnosis is almost never based on one single change or finding. Always the past history, age, sex, physical deformity, blood picture, blood chemistry determinations, X-ray picture, and biopsy must be carefully weighed and correlated. Seldom, if ever, is any one change pathognomonic.

Cystic bone diseases are fascinating in much the same manner as are blood studies and blood dyscrasias in that the bony changes often reflect the disordered metabolism of the whole body. In many of the less well understood syndromes a pattern is now beginning to emerge; where formerly

three or four conditions were classified as separate entities, now it is becoming understood that they are really only different stages in the progress of the same disease.

II. Solitary Bone Cysts

The simplest type of cystic bone disease is the solitary bone cyst which is usually found in the shaft of the long bones of adolescents and young adults. The average patient is between ten and fifteen years of age. The three commonest sites are the upper shaft of the femur, humerus, and tibia. At the age period when these are prone to occur they are found in relationship to an unossified epiphyseal line. An area of new bone in a metaphyseal region is involved and the pathological process appears to be related to this new bone formation. In the older age groups, due to bone growth, the lesion has migrated to the mid-shaft region.

Clinically the patient is generally seen because of a pathologic fracture. The other clinical features include swelling, slight deformity, and a moderate degree of pain. The average duration of the symptoms is two and a half years, but it may be as long as forty years. This latter is the so-called latent bone cyst and is as a rule picked up accidentally on X-ray examination. Another variant of this lesion is the acute bone cyst of not more than six months' duration which is located on the border of the epiphyseal line and contains giant cells. This type is often

mistaken clinically for a giant cell tumor. Probably it is really a transitional lesion between benign bone cyst and giant cell tumor.

X-ray examination shows an ununited epiphysis near the lesion, which is indicative of youth, and central bone destruction located in the metaphysis with a fusiform expansion of thin cortical bone about the defect. Trabeculae extend irregularly across the cyst and when pathologic fracture occurs, the margins show an attempt at spontaneous healing by their increased density. The cortex about the cyst is rarely perforated except at the site of a fracture. The smooth, intact bone shell is an important diagnostic sign of its benign character. Roughening of the surface and radiating spicules of bone or periosteal lipping are more typical of osteogenic sarcoma. Melting away of the shell at one point without sequestration should arouse suspicion of the osteolytic form of osteogenic sarcoma. Bending in the region of the defect in the bone favors the diagnosis of benign bone cyst since it indicates a chronic disturbance to which the weakened bone has become gradually adjusted. Adjacent areas of increased density suggestive of a healing reaction also are indicative of a bone cyst.

On gross examination of such a specimen, the thickness of the cyst wall varies according to the duration of symptoms. The thicker shell in old cysts indicates that a healing reaction is taking place. On section these cysts may or may not have a connective tissue lining and may contain

serous fluid or fibrous tissue. Calcium spicules may be found on the inner side of the lining or the remains of tissue resembling a grumous giant cell tumor may be seen. In the shell of bone overlying the cavity there is frequently an indurated area extending into the fibrous lining which suggests new bone formation but the location indicates that this is proceeding from the cortical region of the shaft rather than from a central metaphyseal location. Aside from this, the gross specimen suggests a process of bone destruction rather than one of bone formation.

Microscopic examination in most instances fails to show a destructive process which could explain the cavity formation. Most of the tissue of the cyst wall is quite uniform, consisting of spindle cells and fibroblasts with a good deal of clear intercellular substance. The cysts may show areas of old hemorrhage, islands of bone or bone trabeculae or vessels in areas of fresh hemorrhage. About the cyst wall the connective tissue is condensed to form a fibrous lining. Behind the fibrous lining fibroblasts are laying down intercellular substance with the formation of osteoblasts and the direct proliferation of new bone. Occasional giant cell areas with round cells may be seen. The remnants of old hemorrhages are often found within the smaller cysts. The first row of cells around a bony spicule is an actively proliferating layer of osteoblasts gradually merging into fibroblasts toward the periphery. Beyond this there is loose fibrous tissue, almost myxomatous in appearance. The cycle

appears to be from spindle cells to fibroblasts to osteoblasts and then to new bone formation, the bone being osteoid tissue before calcification. Giant cells are associated only with new vessels and fresh hemorrhages rather than with old blood seen within the cysts.

The process seems to be one of fibrous proliferation and new bone formation and is therefore concerned with repair or healing. There is no evidence of inflammatory reaction although repair following a medullary abscess may show the same healing phases as osteitis fibrosa. Regeneration takes place independently of the periosteum. In most cases this healing reaction is found around an area of bone destruction. The reparative nature of the reaction is shown by the benign course and the tendency to undergo spontaneous healing. The persistence is the result of nature's difficulty in collapsing the walls. Often the lesion heals following a fracture which collapses the cavity.

Copeland and Geschickter[1] feel that the etiology of the solitary benign cyst is as follows: 1. The formation of giant cell areas followed by the development of new blood vessels and hemorrhage; 2. the absorption of hemorrhage with cyst formation; 3. the lining of the cyst by fibrous tissue which is gradually transformed into bone. This would indicate that they feel it is a healing giant cell tumor. McLachlin[2], on the other hand, feels that this is untenable since giant cell tumor occurs in an older age group and is on the epiphyseal rather than the metaphyseal side of the epiphyseal

line. He feels that it may be due to a single congenital defect or to a small hemorrhage resulting from minor trauma. Osmotic pressure would then produce a local increase in pressure with resultant atrophy of the adjacent bone.

In the diagnosis of benign bone cyst, the points that will be helpful in evaluating the situation are: usually a solitary lesion, the benign course, the age incidence. Laboratory studies show that phosphatase, blood and urine phosphorus and calcium are all within normal limits. The X-ray picture is of especial value and considerable diagnostic weight will be placed upon it. If it is deemed necessary for the diagnosis or if repeated fractures occur, a biopsy may be taken which will further aid in establishing the diagnosis.

Osteogenic sarcoma must be differentiated from benign bone cyst. The roentgenogram will be helpful here as described above. Occasionally gumma may be mistaken for a cyst, but perforation of the expanded cortex, periosteal involvement, and sequestration as well as blood tests should establish the differential diagnosis. Brodie's abscess is a smaller lesion, rarely expands the bone, and is commonly seen in the tibia. Giant cell tumor is seen in older age groups, uniformly involves the epiphysis, and there is a greater tendency for the cortical bone to be asymmetrically expanded and perforated. Chondromyxoma or chondroma are usually found in the small bones of the hands and feet, more rarely in the ribs and spine. Chondromata in the long bones occur rarely and when they do are more finely multiloculated.

III. Benign Giant Cell Tumor

Benign giant cell tumor is closely related to solitary cysts, but is is a disease of adults, has a shorter duration of symptoms, and a greater tendency to be progressive. Its location is invariably at the epiphysis where osteogenesis from cartilage occurs. Forty per cent of all cases of giant cell tumor occur in the third decade of life. The sites most commonly involved are the epiphysis of the lower end of the femur and radius and the upper part of the tibia. Although giant cell tumors are typically benign, recurrences following surgical treatment are not infrequently seen.

Copeland and Geschickter[1a] believe that both bone cyst and giant cell tumor have their origin in abnormal functional activity of the bone marrow. They say, "Giant cell formation, therefore, marks the beginning of bone perforation in the embryo, and in the wake of these cells new blood vessels and osteoblasts follow. More specifically and convincingly the bone destructive character of these lesions and the prevalence of giant cells or osteoclasts in them relates them to the process of resorption of temporary bone characterized by the proliferation of osteoclasts or giant cells. From this we conclude that the giant cell tumor and the related lesion of bone cyst are the result of an abnormal hyperplasia of osteoclasts preceded by a normal stage in which osteoclastic proliferation is taking place as a phase in the histiogenesis of intracartilaginous bone." However, if this is true, it is odd that it is not more common in the younger age group where

such changes are occurring more rapidly.

The usual duration of symptoms is two to fourteen months with a sequence of trauma, pain, tumor, and fracture. Trauma seems to be a more definite etiologic factor than in benign bone cyst. In cases X-rayed at the time of injury and at times thereafter, the gradual development of areas of destruction can often be traced. Pain is more severe than in bone cysts and of a more constant character. Pathologic fracture is seen to occur in about fourteen per cent of cases.

By X-ray the lesion is generally seen in an asymmetrical position in the epiphysis. From this it may be assumed that bone destruction begins subcortically and extends to a more central position at the expense of cancellous bone. The bony shell is very thin and is soon perforated in the majority of cases. Early in the course of the disease trabeculae may be seen crossing the lesion; later these disappear. The lesion may extend into the soft parts. Extension into the joint cavity is extremely rare. Even in advanced cases the periosteum shows no reaction. This is an important point in differentiating it from the osteolytic form of osteogenic sarcoma.

Grossly the tumor is hemorrhagic. It is multicolored, varying from red to black. At operation it oozes like a sponge when touched. The cyst wall shows the bone destruction observed on X-ray as well as the healing reaction about the margin. On section the tumor is seen to be very friable and the trabeculae seen by X-ray prove to be inward extensions of the capsule. Sometimes the capsule is leathery

and fibrous like that of the bone cyst. Fibro-ostosis is seen to be most pronounced on the shaft side where the cortical bone thickens and extends downward from the shaft toward the epiphysis preceded by fibrous tissue. The cancellous bone in the medullary cavity also attempts to limit the advance of the cystic growth and occasionally an attempt at capsule formation is noted on this side. However, this reaction forms a less satisfactory limitation than on the cortical side as the tumor often extends to the opposite side of the epiphysis before the cortical shell gives way. The joint cavity resists invasion by calcification of its compact substance, the calcified tissue being transformed into bone.

On microscopic examination the tumor presents large multinucleated giant cells embedded in a stroma in which there are masses of small round cells. The giant cells average around thirty per low power field, each cell containing from fifteen to two hundred nuclei. The number of giant cells is increased about hemorrhagic areas, spicules of old bone, and about walls of small cysts. Giant cells with few nuclei and sparsely distributed are not typical of the benign giant cell tumor; their presence is to be associated with osteitis fibrosa and osteogenic sarcoma. In the stroma are found spindle cells and round cells, the round cells typically far outnumbering the spindle cells. Wherever the giant cells predominate in the tumor, the round cells correspondingly predominate in the stroma.

Hemorrhage and new blood vessel formation are con-

spicuous in giant cell tumors. Scattered red blood cells in a good state of preservation are common. Spicules of bone are frequently found near the margin of the tumor or its capsule. Some of these bone spicules are undoubtedly old bone undergoing destruction as evidenced by giant cells at their periphery, condensation of calcium salts, frayed edges, and the small size of the bone cells in the matrix; other spicules with osteoblasts at their margin represent a healing reaction.

An important variant of the benign giant cell tumor is the occasional one which shows malignant change following repeated surgical curetting, chemical swabbing, and irradiation. Thus, Gershon-Cohen[3] reports two such cases in a series of twenty-nine cases. This type is characterized by persistent regrowth and more rapid growth when it becomes malignant.

Another variant of the benign giant cell tumor is that first described by Codman[4] and sometimes called "Codman's epiphyseal chondromatous calcifying giant cell tumor." In his series of nine cases all the lesions occurred in the upper end of the humerus. It has since been described in other locations. It occurs most frequently in adolescent or post-adolescent males. The lesion is benign and heals after thorough curettage. It begins in the epiphysis and later may involve the metaphysis. It is differentiated from the typical form of benign giant cell tumor mainly on a histologic basis.

Jaffe and Lichtenstein[5] believe that it should not be considered a variant of the benign giant cell tumor but as a chondroblastoma on the basis of its histologic composition.

The diagnosis of this condition is based on its location in the epiphysis, most frequently in the lower end of the femur, upper end of the tibia, and lower end of the radius. The characteristic history reveals the short duration of symptoms, the average being fourteen months, and the relation to trauma. As in the benign bone cyst, here too the blood biochemical findings are within normal limits. The typical picture by X-ray and finally a biopsy specimen should make the diagnosis relatively easy.

IV. Von Recklinghausen's Disease

In order to understand this very interesting disease it is necessary to review somewhat the physiology of the parathyroid glands which remained a mystery until the last twenty years.

In 1891 von Recklinghausen[6] described the disease which now bears his name and mentioned an analagous case described by Engel in 1864. In the autopsy report[7] of one of his early cases of osteitis fibrosa cystica, a tumor of the parathyroid was described, but it was not recognized as such by the great pathologist.

In 1903 Askanazy[8] reported a similar case of a parathyroid tumor with decalcification of the skeleton and multiple fractures.

The significance of the findings in these cases was not recognized for a number of years. Von Recklinghausen him-

self felt that the skeletal changes were of fundamental importance to the diagnosis. In fact, von Recklinghausen's disease was identified with Paget's disease.

Early in the twentieth century Erdheim[9] observed that hyperplasia of the parathyroids may be present with osteomalacia. He believed that the hyperplasia developed as a compensatory reaction so that the glands could cope with the large amounts of calcium and phosphorus liberated from the decalcified skeleton. This observation influenced medical thinking for a quarter of a century and the enlarged parathyroids found in many decalcifying bone diseases were all considered to be secondary to decalcification of the skeleton.

In 1926 the report of Mandl[10] that the removal of a parathyroid adenoma was followed by marked improvement in the signs and symptoms of generalized fibrocystic osteitis, brought about a clarification of the confused picture of parathyroid disease. It became apparent that there were two processes involving the parathyroids with associated bony changes, which were later termed "primary" and "secondary hyperparathyroidism" by Albright.[11] In primary hyperparathyroidism more parathormone is produced than is necessary because of the presence of a parathyroid adenoma or malignancy. In secondary hyperparathyroidism more parathormone than is usual is also produced but the excess is required for purposes of compensation, as in rickets, where interference with the absorption of calcium from the gut due to a lack of vitamin D, results in a low serum calcium. This stimulates the parathyroids to hypertrophy and hyperfunction.

In 1925 Collip had obtained a parathyroid extract from beef parathyroids, the use of which greatly aided in the experimental work in the physiology of these tiny glands.

Experimental removal of the parathyroids is followed by a fall in blood calcium and a rise in inorganic phosphorus. Signs of tetany appear when the serum calcium falls below 6 mgs. %. Administration of parathyroid extract to dogs results in an early rise in serum calcium to 18 to 22 mgs. within twenty-four hours accompanied by a moderate fall in serum phosphorus which is followed by a return to normal and a slight rise. There is also a slight rise in potassium and magnesium of the serum. During the rise in calcium there are loss of appetite, depression and weakness, polyuria, vomiting, diarrhea and dehydration. The urinary excretion of calcium and phosphorus is greatly increased. Later there is a reduction of 2 to 3 mgs. in the hypercalcemia with a pronounced rise in plasma inorganic phosphorus, a four-fold increase in blood NPN, a reduction in blood volume by fifteen per cent, and a concentration of the blood with a resultant increase in its viscosity. Accompanying these blood changes there is vomiting of bloody fluid and sometimes the passage of blood-stained stools, signs of renal failure, and prostration ending in death.

The excess calcium in the serum following parathormone overdosage is derived from the great storehouse for calcium and phosphorus in the body, the skeleton. This leads to decalcification of the skeleton. Since the blood level is far above

the renal threshold, there is a deposition of calcium in the tissues of the body, principally in the kidney with the formation of renal calculi, the arterial tree, the myocardium, lungs, and mucosa of the stomach and bronchi. This in turn leads to an impairment of the function of these organs.

In man the physiologic changes and symptoms produced experimentally in animals take place to a large extent when there is excessive production of parathormone due to the presence of an adenoma or malignancy of the parathyroid glands. When a malignant tumor is removed followed by cessation of symptoms with later recurrence of the same symptoms, it is generally ascribed to the development of metastases in the adjacent lymph nodes.

Phosphorus and calcium in the blood maintain a reciprocal relationship; a fall in calcium is accompanied by a rise in phosphorus and vice versa. The normal calcium level in the blood is 10.5 mgs. $\pm$ 1 mg. This calcium is present in two forms--ionic calcium which normally makes up 5 mgs. of the total blood calcium, and 4 to 6 mgs. which is bound to the serum protein as calcium proteinate and is controlled by the level of total protein. The renal threshold for calcium is 7.0 mgs. % so that there is a continuous loss of calcium with a normal blood level. The normal amount of calcium in a twenty-four hour specimen of urine is 0.1 to 0.3 gms. and the phosphate content is 2.5 to 3.5 gms. The ionic calcium is the fraction that controls the development of tetany. A shift of the acid base balance of the blood toward

the alkaline side causes a reduction in the ionic calcium fraction without altering the concentration of the total calcium of the serum.[12] The following equation illustrates the possible relationship between the concentrations of calcium, bicarbonate, phosphate and hydrogen ions:

$$\frac{(Ca^{++})(HCO_3^{-})(HPO_4^{--})}{(H^{+})} = K$$

According to this equation an increase in the concentration of the bicarbonate ions or of phosphate ions or a fall in the concentration of hydrogen ions would cause a reduction in the concentration of ionized calcium without a change in the total calcium level of the serum necessarily resulting.

In 1927 St. György showed that parathormone lowers plasma phosphorus and causes a shift of the blood pH to the acid side, but does not affect the CO_2 combining power of the blood.

In 1927 also Albright and Ellsworth[13] advanced the theory that the changes in calcium metabolism, including changes in bone were dependent upon preceding changes in the phosphorus metabolism. They believed that the lowering of the serum phosphorus level was the result of an increased phosphate excretion in the urine.[14] Collip, Pugsley, Selye, and Thomson, however, after a study of the long bones of eight nephrectomized rats that had been injected with parathyroid extract, concluded that the action of the parathyroid hormone on bone tissue was not dependent upon a preceding phosphorus diuresis. Likewise, McJunkin, Tweedy, and McNamara[15] found that the administration

of large doses of parathyroid extract to nephrectomized rats produced a pronounced resorption of bone although it did not produce a characteristic rise in serum calcium. These experiments showed that parathyroid extract has a decalcifying effect on bones even in the absence of the kidneys. This effect is not due to the acidity of the extract. However, nephrectomy alone leads to bone resorption although not so great and qualitatively different from that which occurs following the administration of parathyroid extract.

In further pursuance of this problem Ingalls, Donaldson, and Albright[16] reported additional experimental work in 1943. They were able to produce osteitis fibrosa in rats in sixty hours with parathyroid extract. The lesions were the same whether or not the rats were first nephrectomized. The lesions produced in nephrectomized rats by parathyroid extract were already present in twenty hours, whereas lesions produced by nephrectomy had not yet appeared at that time.

Thus, it can be seen that the physiology of the parathyroids is not yet fully established and that research is still being done on this problem.

An understanding, at least in part, of the physiology of the parathyroids makes it possible to explain many of the patient's symptoms. Weakness and malaise are to be expected from the altered body metabolism and the hypotonia of the muscles due to the high concentration of calcium, which raises the threshold of stimulation for muscles and nerves. Dull aching of the bones or pain on motion are common symptoms.

Fractures and bone deformities, as might be anticipated, are frequently encountered. Deposition of calcium salts in the pyramids may lead to renal insufficiency. Renal calculi with hematuria and kdieny colic may be the presenting symptom. These calculi are usually calcium phosphate but may have a large admixture of calcium oxalate. The presence of bilateral renal stones, often complicated by peylitis, leads more frequently to impairment of renal function than calcification of the parenchyma, however. Polyuria and polydipsia are often constant features of this condition; where these two symptoms are marked there is less tendency to develop calculi. The polyuria in part is due to the high content of calcium in the urine which holds a large amount of water with it, thereby preventing resorption of the water. This in turn causes thirst. This is not the whole explanation of the polyuria since it is known that the parathyroid hormone stimulates the kidney directly.

Nausea and vomiting, even uncontrollable vomiting, are seen and may be explained by the hypotonia and in some cases by the calcinosis of the gastro-intestinal mucosa. Muscle cramps are caused by the hypercalcemia. Cough and dyspnea may result from hypercalcinosis of the bronchi. When loss of calcium is especially marked in the terminal phalanges of the fingers, clubbing develops.

The biochemical findings in this disease typically include:

1. Hypercalcemia.
2. Hypophosphatemia.
3. Hypercalcinuria.
4. Hyperphosphaturia.
5. Increased blood phsphatase.

The blood calcium may reach as high as 30 mgs.%. The blood phosphorus usually averages around 1.5 to 3.0 mgs. Where the disease is complicated by uremia due to renal stones or calcification of the parenchyma, the blood phosphorus may be increased above normal levels. In cases of Recklinghausen's disease where the inorganic phosphorus is elevated because of renal insufficiency, the prognosis is unfavorable.

The operative shock following removal of the tumor often results in severe uremia. This is particularly true because this operation is always followed by a few days of oliguria due to the sudden decrease in stimulation to the kidney because of the fall of parathyroid hormone in the blood.

Phosphatase liberates inorganic phosphorus from the organic compounds of the blood, and is present in all cases where there is rapid proliferation of new bone. It varies according to the extent of this activity.

In normal people seventy to ninety per cent of the calcium excreted goes through the stools and only ten to thirty per cent through the urine; in osteitis fibrosa cystica this relationship is reversed. The amount of calcium in the urine varies with the blood level and with the kidney function.

X-ray shows a generalized decalcification and fibrous osteitis which may be more marked in some bones. There is widening of the marrow space with thinning of the cortex. Small scalloped areas in the cortex are seen where the bony changes are most extensive. Fibrous tissue proliferation in the Haversian canals causes dilatation of these tubules which is

seen as diffuse widening on the roentgenograms. Angular malformations are caused by spontaneous fractures of thinned bones. In the terminal stages the decalcification may become so extreme that it is well nigh impossible to obtain satisfactory X-ray pictures. Marked reduction in body length results from softening of the spine. Compression of the vertebral bodies by the elastic intervertebral discs leads to the formation of biconcave vertebrae. The finding of cysts or giant cell tumors is of great aid in diagnosis, but in many cases of even extensive von Recklinghausen's disease these may be absent. The finding of honeycombed giant cell tumors in the skull bones, upper or lower jaw or zygomatic bones is highly significant and may occur when the general decalcification is only in the initial stage. The skull may show gross-meshed trabeculation and miliary areas of osteoporosis. Decalcification of the hands and fingers is usually seen.

Biopsy of the diseased bone shows a generalized osteoclastic bone resorption with the formation of multiple Howship's lacunae. This lacunar resorption is accompanied by an increase of marrow and cortical fibrosis. In this proliferating fibrous tissue the formation of new bone may take place accounting for the presence of osteoblasts and osteoid seams surrounding the remnants of the bone trabeculae. The osteoclastic activity and accumulations often result in the formation of typical giant cell tumors. There is decalcification of the remnants of bone trabeculae. The thinned bone trabeculae are often perforated by the proliferating fibrous tissue.

It must not be thought that all cases of Recklinghausen's disease fit neatly into this picture, as in all diseases there are many exceptions. Royde[17] reports a case of a hyperplastic adenoma of the parathyroid accompanied by a generalized decalcification of the skeleton with two pathologic fractures. However, the blood chemistry was normal except for an increase of plasma phosphatase. Snapper[18] also reports a case of parathyroid tumor with generalized decalcification of the bones and giant cell tumors with a blood calcium of 16.3 mgs. and an inorganic phosphorus of 2.0 mgs., but the urine calcium was far below the normal average on a test diet. This and other atypical cases he believes may be explained on the basis of a secondary hypovitaminosis D superimposed on Recklinghausen's disease. This may be on the basis of an inadequate diet, anorexia, poor absorption or an increased need for vitamin D in the presence of bone changes and spontaneous fractures. It has been suggested that spontaneous lowering of the original hypercalcemia to normal, as occasionally reported in cases of Recklinghausen's disease, may be related to a superimposed hypovitaminosis D.

In considering the differential diagnosis of von Recklinghausen's disease, the characteristic biochemical syndrome is of great help. Every case of Recklinghausen's disease depends on hyperparathyroidism and in other diseases with bone changes simulating it such hyperfunction of the parathyroids is not present. It is not usually permissible to diagnose Recklinghausen's disease in a patient with extensive decalci-

fication of the skeleton without the biochemical findings. Conversely, where the typical biochemical findings are present with minimal decalcification, hyperparathyroidism should be diagnosed. Other important points to be considered in entertaining this diagnosis are the severe aching in the bones, generalized osteitis fibrosa cystica with its characteristic X-ray picture, frequently the presence of bilateral stones and diminution of renal function, fatigue, polyuria, and occasionally muscular hypotonia.

Generalized decalcifying diseases of the bone which must be considered in the differential diagnosis of osteitis fibrosa cystica include: Paget's disease, multiple myeloma, decalcification of the bones in hyperthyroidism, metastatic carcinoma, lipoid granulomatosis of the bones, chronic renal insufficiency, and osteomalacia. These disease processes, with the exception of chronic renal insufficiency and metastatic carcinoma, are going to be discussed in some detail and it will be seen how the clinical picture, past history, X-ray, blood chemistry, and biopsy aid in making the differential diagnosis.

Chronic renal failure may be ruled out by kidney function tests and by finding no renal stones or calcinosis of the kidney by X-ray.

In metastatic bone carcinoma the differential diagnosis is usually easy as the primary site is often known. Difficulties may arise when there is an accompanying decalcification of the skeleton. Then there is an increased phosphatase and calcium, but the phosphorus level seldom falls below normal. In difficult

cases a biopsy is advisable. Rarely the diagnosis may be most difficult when there is secondary hyperplasia of the parathyroids with the extensive malignant metastases.

V. Hyperplasia of the Parathyroids Secondary to Other Diseases

The second type of parathyroid disease which is associated with bone changes and was for many years inextricably bound up and confused with Recklinghausen's disease is the result of parathyroid hyperplasia. As previously mentioned Erdheim[9] was the first to believe that hyperplasia of the parathyroids resulted from the decalcification of the skeleton.

In contrast to Recklinghausen's disease all the parathyroids are hypertrophied in this type of parathyroid disease and also in contrast to von Recklinghausen's disease there are many instead of few mechanisms by which it is brought about. The hyperplasia of the parathyroids and the increased parathormone production result in a decalcification of the adult skeleton. (This is the converse of Erdheim's original hypothesis) In the child the hyperplasia interferes with calcification of the growing bone principally although there is some decalcification of the formed bone. In the adult, on the other hand, the picture is that of straightforward decalcification. When there is a retention of phosphorus, there is often a deposition of calcium phosphate in the soft tissues.

Hypocalcemia appears to be the mechanism through which this parathyroid hyperplasia is brought about although Albright

thinks that the stimulus is hyperphosphatemia.

Experimentally chickens kept away from ultraviolet rays or with avitaminosis D develop decalcification of the bones and hyperplasia of the parathyroids. Oberling and Guerin[19] noted skeletal lesions and hyperplasia of the parathyroids in chickens deprived of sunlight and calcium.

In patients with complete biliary fistula, impaired intestinal absorption of fat and therefore failure of vitamin D absorption results in the elimination of great quantities of fats and fatty acids in the form of calcium salts. This loss of calcium may lead to ultimate decalcification of the skeleton and spontaneous fractures. The daily loss of alkali with the bile may result in acidosis which is another etiologic factor for osteoporosis. There is experimental evidence that the rapidity of decalcification may determine whether osteoporosis or osteitis fibrosa cystica develops.

In children and young adults suffering from chronic uremia there are extensive bone changes. Most of these patients are suffering from congenital bilateral dilatation of the ureter and renal pelvis or congenital hypoplasia of the kidneys. This condition is known as renal osteodystrophy or renal hyperparathyroidism. In this condition there is marked renal failure with increase of nonprotein nitrogen and acidosis, often accompanying hyperphosphatemia. Calcification of the arterial walls is common, but hypertension and retinal changes do not occur.

The bone lesions of these juvenile cases may result

in stunted growth, sometimes in true infantilism. The bone lesions seen on X-ray and biopsy vary from those of rickets to osteoporosis, which is a localized area of decalcification, to osteitis fibrosa, which is a more generalized but patchy decalcification with fibrosis. The similarity to rickets is often striking since there is generalized decalcification with swelling of the epiphyseal discs (hence the name renal rickets). The epiphyseal lines tend to remain open even to adult age. The X-ray picture of the skull in these cases is usually woolly or motheaten and may ultimately resemble the picture of Paget's disease.

There is reason to believe that different diets have an important bearing on which type of lesion will develop. Thus, Pappenheimer[20] produced chronic uremia in young rats by removing one kidney and cauterizing the other kidney. The animals were given a low protein diet with adequate phosphorus. Different calcium intakes were given various groups. In animals with a very low calcium diet the bones showed changes corresponding to renal rickets. When slightly greater calcium was given, there was a combination of rickets and osteitis fibrosa.

There have been a few cases reported in adults similar to renal rickets in children, but it must be remembered that the bone changes develop more easily in the growing skeleton of children.

Today it is believed that renal failure must be of long duration and that it must cause acidosis before there will be hyperplasia of the parathyroids.

Jacobs[21] has reported the interesting occurrence of two cases of juvenile hyperthyroidism showing osteodystrophia fibrosa cystica with diffuse osteoporosis complicated by pathologic fractures. One case was operated on with a diagnosis of nodular parenchymatous hyperplasia of the thyroid gland and is well three years after thyroidectomy, whereas the other was unoperated and is still toxic showing osteoporosis and pathologic fractures from time to time.

Hyperthyroidism is rare in the adolescent. The relationship between thyrotoxicosis and osteoporosis was first recorded by von Recklinghausen in 1891.[6] In 1928 Plummer and Dunlap[22] recorded that "the rate of calcium excretion was directly proportional to the height of the basal metabolic rate."

In evaluating the condition of a patient with parathyroid hyperplasia clinically, an understanding and analysis of the various complicated mechanism by which this condition is brought about is essential.

The biochemical picture is of great importance. In this condition the serum calcium may be depressed, normal, or slightly elevated, but it will never show the high level found in Recklinghausen's disease. On an adequate diet the serum phosphorus will be elevated; on a markedly deficient diet it may be normal. There are often acidosis and hyperphosphatemia with hyperplasia of the parathyroids. Urine phosphorus and calcium are low. The excretion of calcium and phosphates in the feces is greatly increased.

The presence of congenital renal anomalies, especially

in children, is indicative of this condition. The past history is not of much help in differentiating between von Recklinghausen's disease and hyerplasia of the parathyroids. These patients do not respond to the administration of vitamin D. Vitamin D is unable to stem the loss of phosphates and calcium through the intestinal tract. In children failure of closure of the epiphyseal lines with proliferation of cartilage in the epiphyseal discs is found.

VI. Osteomalacia and Fetal Rickets

Osteomalacia and fetal rickets have the same etiology--lack of calcium or hypovitaminosis D. The latter may be due to dietary insufficiency or lack of exposure to the sun's rays which converts the provitamin (7 dehydrocholesterol) in the skin into vitamin D. This disease is not often seen in this country but is common in India and the Orient where dairy products do not form one of the dietary staples. Osteomalacia is most common in women who have had rapid successive pregnancies with loss of calcium to the growing fetus, through lactation, and indoor life.

The offspring of osteomalacic mothers are predisposed to rickets and may even at birth show evidences of the disease. Breast feeding of such an infant by a mother already inadequately supplied with calcium aggravates the situation. Infantile rickets usually occurs before three years of age. Although fetal rickets and osteomalacia are fundamentally the

the same process, the picture differs because of the growth factor. The resorption of trabecular bone in children is followed by the formation of fetal fiber bone derived from fibrous tissue. The decalcification is often very slight. In the adult the formation of fiber bone hardly ever occurs and thus replacement of the decalcified bone is only limited, and the osteomalacic process is the outstanding picture. The administration of calcium without vitamin D seems to have little effect on the disease, whereas vitamin D alone appears to bring about better utilization of calcium; the administration of vitamin D and calcium give the best results.

These patients show a low serum calcium, a normal or slightly lowered serum phosphorus; phosphatase is low or absent in adults with osteomalacia, but is elevated in fetal rickets. Urine calcium and phosphorus are low or absent.

The chief complaint of patients with osteomalacia is pain in the bones and general malaise. In severe cases tetany may occur. Babies with rickets show swelling of the joints and delay in closure of the sutures.

The X-ray picture of osteomalacia shows a generalized decalcification of the entire skeleton which is most extensive in the pelvis, thorax, and extremities. Eventually the loss of calcium may be so extensive that satisfactory X-rays cannot be obtained. The characteristic deformity of the pelvis consists of an increased convexity of the sacrum, marked narrowing of the outlet and deformation of the pelvis producing a wedge-shaped pelvis. The pelvis may become markedly asymmetric.

It must be admitted that osteomalacia rarely produces cysts of the bone although occasionally it does. It should probably not be considered a cystic disease of the bone, but it is included here to complete the picture of parathyroid disease.

In rickets occurring at a later age the clinical signs include rapid fatigue and difficulty in mounting stairs; the gait becomes stiff and there are pains in the back and hips. The epiphyses become tender and swollen; this is most marked in the tibia, radius, and ulna. Swelling of the costochondral junctions produces the rachitic rosary. There may be genu valgum or kyphoscoliosis. Signs of infantilism and hypogenitalism are frequent. Adductor spasm is probably a reflex mechanism due to the pain caused by abduction. Tetany may occur.

The outstanding finding by X-ray is delay in calcification of the epiphyses. In extreme cases there is no ossification at the age of twenty years. The epiphyses are abnormally broad. The diaphysis is not sharply separated from the epiphysis but its edge is frayed and irregular. The proliferating cartilage penetrates deeply into the diaphysis causing cupping of its end. The cortex of the bone is poor in calcium and atrophic. The bone is less sharply demarcated than usual due to a broadening of the osteoid tissue around the trabeculation.

When healing in rickets occurs, calcification takes place where the original preparatory calcification zone was situated. The calcification zone often lies in the middle of the hypertrophied epiphysis. These calcification lines are permanent and are always indicative of healed rickets.

VII. Albright's Syndrome

In 1937 Albright et al[23] described a new syndrome consisting of a characteristic multifocal fibrous dysplasia of the bone associated with pigmented areas in the skin and endocrine disturbances causing sexual precocity in the female. In 1938 Albright, Scoville, and Sulkowitch[24] reported cases of sexual precocity in the male with this syndrome.

The etiology of this bizarre syndrome has not yet been determined. In their original paper Albright et al suggested that the distribution of the cutaneous and bone lesions might be due to an embryologic or neurologic disturbance. It has been noted that the cutaneous and bone lesions tend to occur in the same dermatome. Albright felt that an embryologic etiology would be more likely if the pigmentation were due solely to melanoblasts of mesodermal origin. Then an embryologic defect in a sclerotome could be associated with both the cutaneous and bone lesions. The distribution of the pigmented areas is such as to suggest a mesodermal origin, but the histologic evidence indicates that most of the melanoblasts are of ectodermal origin. This would require an embryologic disturbance affecting both ectoderm and mesoderm. The tendency for the diseased bones to be smaller than the rest of the bones suggests a connection with Ollier's disease as this is one of the characteristics of that condition.

As a possible explanation of the precocious puberty Albright suggested the following: The follicle-stimulating

hormone stimulates precocious puberty in the female but the luteinizing hormone causes it in males. It is possible that girls reach puberty before boys because follicle-stimulating production starts before that of luteinizing hormone.[25] Smith has shown that the gonad-stimulating hormones are present in the anterior pituitary before birth. Therefore, the onset of puberty is not due to the onset of the production of these hormones. Some other mechanism must come into play, possibly a releasing mechanism. There is some evidence that this mechanism may be connected with nerve impulses. The fact that the rabbit usually ovulates only after coitus suggests a nerve mechanism for the release of pituitary hormones. Furthermore, the fact that the only two patients in Albright's original series[23] who became pregnant both had twins, he believed to throw additional weight behind this theory since an excess of follicle-stimulating hormones causes multiple follicles to ripen in the ovary.

In a later paper Albright[24] considered that the precocity seen in this syndrome might be due to a central nervous system lesion rather than to a primary lesion of the endocrine system. Ford and Guild[26] had recently called attention to precocious puberty in girls following injuries involving the region of the hypothalamus. They reported two cases in which measles encephalitis was followed by precocious puberty in girls and one case in which epidemic encephalitis was followed by precocious puberty in a boy. They stated that not a "single case has yet been described in which precocious sexual development

has been definitely connected with hypophyseal tumors of any type." They also cited evidence that the precocious puberty seen in cases of pineal tumors is due to the involvement of the walls of the third ventricle and hypothalamus by tumor, not to a hormone produced by the tumor or to destruction of the pineal by tumor.

Clinically the disease occurs in complete and incomplete form. It is a disease of childhood and appears to be self-limiting in that the active phase probably terminates simultaneously with the premature fusion of the epiphyses. Nearly all victims of the complete type develop symptoms before the age of ten. In the incomplete form patients may be thirty, forty or older before clinical manifestations appear. There is no evidence that the disease is hereditary; in no case have other members of the family been affected.

Symptoms referable to the bony lesions, such as pathologic fractures or skeletal deformities, usually are first noted. These may be apparent as early as the first and second years and are almost always present by the tenth year. Occasionally in the female irregular menstrual bleeding is the presenting symptom. Although it has been noted as early as the first year of life, its onset is usually delayed until after the appearance of bony symptoms. The quiescent phase is slowly reached when the epiphyses unite with the shafts. Most cases come under observation when the symptoms are well advanced, but in four cases[27] followed from infancy because of icterus gravis neonatorum, the early stages of the bony

lesions and the appearance of cutaneous pigmentation were both observed. The active phase of the disease does not lead to a fatal termination and the only deaths recorded have been from intercurrent causes, but it tends to leave the patient with skeletal deformities which sometimes cripple her activities.

The skeletal abnormalities are spotty in distribution and consist of multiple localized lesions with normal bone elsewhere. The lesions in many cases show a tendency to be unilateral in that they group themselves in one digit or one extremity. There is no generalized decalcification as in hyperparathyroidism. The most frequently seen individual lesion is an area of rarefaction simulating a cyst. By X-ray it is impossible to differentiate a bone cyst filled with fluid and an area of bone destruction filled with fibrous tissue. These cysts vary markedly in size, shape, and density. Some may be sharply defined with definite margins, while the majority fade out gradually into normal bone. Both membranous bone and cartilaginous bones may be involved, but lesions in the long bones differ in form from those in the bones of the skull. There are multiple areas of fibrous dysplasia which start in the marrow spaces and gradually expand. They originate in the diaphysis but not in the epiphysis. The original bony architecture is absorbed and circumscribed areas of rarefaction become visible in the X-ray. Fresh bone may be irregularly deposited in these areas. The cortex is thinned by continuous growth from within and the bone weakened until finally the whole shaft may be expanded. In the absence of trauma the progressive lesion is

painless. Skeletal deformities are apt to follow union of pathologic fractures and tend to become more disabling as further fractures occur. Coxa vara is the commonest deformity, but genu valgum and kyphoscoliosis are also frequent. Deformities may be produced also by slow bending of softened bone without actual fracture. The femora are apparently invariably attacked, one or both being involved in all the published cases; they are affected more severely than other bones.

The changes in the skull differ in form from those in the long bones although the essential pathologic process is probably similar. The commonest change is an involvement of the face and base of the skull in a sclerotic overgrowth. This change, if present in the bones of the face, is usually unilateral and imparts a gross asymmetry. The eyeball on the affected side tends to proptosis. The sclerotic process in the base of the skull may press on the cranial nerves, especially the optic nerve, with resultant visual disturbance. The bones of the vault of the skull may also be involved in a patchy and irregular thickening resembling in X-ray pictures the appearance of Paget's disease.

Skeletal precocity occurs with greater frequency than sexual precocity and is common to both sexes. The skeletal precocity is generalized and is not confined to those bones which show radiologic evidence of fibrous dysplasia. The precocious development of the epiphyses may be associated in the early stages with rapid growth of the skeleton so that the child is often large for its age. As epiphyseal union also is accelerated,

growth ceases prematurely so that the adult patient does not become a giant. These bony changes point to an endocrine origin as they affect all bones uniformly.

The menses are irregular and scanty at first, but soon afterward the secondary sexual characteristics are normal in type, remaining essentially feminine and showing no tendency to virile features. Possibly an analagous development takes place in the internal generative organs as McCune and Bruch[28] observed an unusually enlarged uterus in their patient when four and a half years old. The urinary excretion of gonadotropic and estrogenic hormones has been studied in a fair number of cases by different investigators, but no significant elevation of these hormones has been reported. Exploration of the adrenals and ovaries was undertaken in one case[23] but no abnormality was found. Ovarian tumors have not been palpable.

It is of interest that, although intellectual precocity has been observed in cases of precocious puberty from other causes it has not been observed in this disease in either sex.

Nodular or diffuse enlargement of the thyroid gland has been noted in a number of cases. Its frequency would indicate that it is more than an accidental association. Some of these cases have been accompanied by elevated basal metabolic rates.

Aside from enlargement of the bones of the face, coarseness of facial expression, slight prognathism, other signs of acromegaly, such as enlargement of the pulp of the

fingers and grooving of the tongue have been absent. There has been no gigantism.

The cutaneous pigmentation generally has not been noted until after the appearance of other symptoms. It has varied from multiple large disfiguring areas to small inconspicuous foci. The affected regions are light brown, not elevated, and retain their normal texture. The most frequent sites of location are the lower lumbar region, the buttocks, and the thighs. There is no correlation between the amount of pigmentation and the extent of the bony dystrophy.

The neurological symptoms associated with leontiasis ossea have been explained on the basis of compression of the cranial nerves and other structures by bony overgrowth. The common symptoms noted have been visual deterioration, anosmia, and deafness. A similar mechanism involving the vertebral column may explain the alterations in the abdominal and cremasteric reflexes associated with impaired cutaneous sensibility reported by Albright.[24]

Microscopically the bone lesions show fibrous dysplasia with a few osteoclasts. Skin biopsy shows melanin in the melanoblasts of the epidermis and corium. The amount of pigmentation varies roughly with the degree of involvement of the skeleton. When the bone disease is unilateral or almost unilateral, the pigment tends to be unilateral or almost so and on the same side as the bone disease.

Calcium and phosphorus determinations in this disease are usually within normal limits. Occasionally confusion may

be caused by a blood calcium above 11.0 mgs. and a phosphorus below 3.0 mgs. The serum phosphatase is usually raised.

Albright's syndrome has often been confused with Recklinghausen's disease. The X-ray picture of the long bones may simulate the lesions of hyperparathyroidism, but the polycystic appearance of the femur in Albright's disease is distinctive. The involvement of the skull in Albright's syndrome is quite different from that due to hyperparathyroidism. Patients with Albright's disease give a history of skeletal abnormality in childhood; hyperparathyroidism is usually active in adult life. Furthermore, the normal blood and urine findings, the pigment spots, and sexual precocity should negate a diagnosis of hyperparathyroidism. Paget's disease simulates the same X-ray picture as Albright's; however, it occurs later in life and biopsies tend to disprove it by failure to find the characteristic mosaic pattern. Ollier's disease is never associated with precocious puberty or pigmented spots. Xanthomatosis is another differential diagnosis, but the finding of a normal blood lipoid pattern and the absence of foam cells on biopsy are against it.

VIII. Xanthomatosis

There are three diseases usually included under the xanthomatous diseases--Hand-Schuller-Christian's disease, Gaucher's

disease, and Niemann-Pick's disease. Hand-Schüller-Christian's disease is the most important of the three; the other two are very rarely seen.

The syndrome known as Hand-Schüller-Christian's disease is characterized by: 1. Multiple round defects in the skull; 2. Exophthalmos which is often bilateral; 3. Diabetes insipidus; 4. Other pituitary signs, especially infantilism.

The first case of this syndrome was published in 1893 by Hand[29] who gave a correct description of the clinical syndrome together with the gross pathology found at autopsy. Hand believed that the yellow spots in the vault of the skull were caused by tuberculosis. Schüller[30] again described the syndrome in 1915 and explained the symptoms on the basis of pituitary dysfunction. In 1919 Christian[31] published a monograph on the subject. Rowland[32] in 1928 demonstrated that the manifestations of Hand-Schüller-Christian's disease consists of a proliferation of fibrous tissue with nests of foam or xanthoma cells in it. These foam cells are filled with cholesterol esters. Chester[33] observed that the main lesion consists of proliferating reticulo-endothelial cells and histiocytes. In addition, there are also signs of inflammation. Many of the histiocytes take up cholesterol esters and are thereby transformed into xanthoma cells.

The lipoid granuloma proliferates in the skull and causes areas of bone resorption. Furthermore, it attacks the orbit and the retro-orbital localization causes exophthalmos. Finally, involvement of the hypophysis and the neighboring centers by the lipoid granuloma may be followed by diabetes

insipidus or by infantilism, sometimes also by dystrophia adipsogenitalis. Occasionally the granuloma grows in the mandible causing progressive loosening and falling out of the teeth. Localization of the granuloma in the middle ear may result in otitis media and even meningitis. The disease may also attack other bones and in some instances the skin and different parenchymatous organs are affected. The disease is often fatal. On the other hand, it is certain that the disease is not always incurable as several cases are known in which the bone lesions have disappeared spontaneously.

Involvement of the lungs may cause an obliteration of a large number of the pulmonary capillaries which later results in dyspnea and right heart failure. Localization in the aorta and walls of major blood vessels often accounts for the extensive arteriosclerosis which is reported in these patients. The lipoid granuloma is also found in the mucous membranes and especially where there is connective tissue, such as tendon sheaths, fascia, periosteum, peritoneum, pleura, and dura. When the lesions are found in the internal organs, they are less in the skin and vice versa, and when more in one organ, they are less in another.

In the typical fully developed cases the most striking findings are bone defects which may appear in any part of the skeleton but are located particularly in the skull. They vary in size and shape and are filled by yellow granulomatous tissue which originates in the dura or periosteum. The lipoid granuloma occurs particularly at the base of the brain surround-

ing and sometimes raising the hypophysis out of the sella turcica, invading the orbits, accessory sinuses, and mastoid cells. In the advanced stage of the disease the granulomatous tissue becomes firm and fibrous and may lose its bright color. Occasionally cysts develop, generally in relation to the bone defects and these contain yellowish or reddish semifluid material.

There is a high incidence of anomalies in patients with Hand-Schüller-Christian's disease. These include blue sclerae, embryonal lobing of the kidneys, defective vena cava, cryptorchidism, clubfeet, supernumerary teeth, etc.

The onset of this disease often occurs during the second, third or fourth years following one of the infectious diseases of childhood. Convalescence seems prolonged; there is increased irritability, excessive thirst, exophthalmos, sore mouth with loose teeth or vague pains. There may be a limp or postural defect or cyst-like swelling on the head or body. Examination reveals defects in the bone. The disease progresses slowly and irregularly. There may be periods of unexplained fever. The skin becomes pale, often with a yellow tint, dry and scaly, or there may be a fine papular eruption on various parts of the body. The spleen, liver, and lymph nodes may be enlarged. Growth is arrested and emaciation is present. The child becomes dyspneic and cyanotic or pale and anemic. The heart may dilate a little. Death often occurs in two to four years from respiratory or cardiac complications or severe anemia.

In other, more protracted cases there may be few symptoms at first. Growth is retarded, however. Bone defects may grow smaller and disappear during remissions. Exophthalmos, polyuria, and polydipsia also lessen during remissions. In the prepubital years the child may grow fat with the appearance of dystrophia adiposogenitalis or pituitary hypogenitalism with signs of mental retardation. These patients may live into the second or third decade.

Adult cases may take the form of Simmonds disease or acromegaly with lipemia and glycosuria. The bony changes in the adult are more often of the acromegalic type. The diabetes insipidus may persist and a mild atypical form of diabetes mellitus may develop.

In certain rare forms the skin lesions may dominate the picture. In childhood the lesions are scattered over the body; in the adult they are more typically seen on the eyelids, face, ears, and hands. Glycosuria and icterus are frequently seen in adults with this disease; rarely are children so affected. Pain in the head, hips, neck or back may be noted and palpation may reveal areas of tenderness and bony abnormalities. This pain is rarely severe. Occasionally fractures occur.

The most important diagnostic feature on microscopic examination is the typical foam cell. This cell varies in diameter from twenty to forty microns or more. It has a large amount of cytoplasm and one or two small nuclei. In the fresh state the cytoplasm is filled with small droplets of a fatty

substance. The nuclei are small with a finely granular chromatin structure. Sometimes the cells are fused into foam cells with twenty or more nuclei. Frequently typical foreign body giant cells are seen. At first the yellow tissue is composed almost entirely of foam cells, but later leukocytes, lymphocytes, and plasma cells appear. In the older lesions there is connective tissue proliferation. When the fibrosis is advanced, the foam cells degenerate and lipid is freed in the tissues, cholesterol crystal formation and cholesterol clefts are then seen. The fibroblastic cells are increased in number and lie in twisted bundles giving a scirrhous appearance to the tissue. In very old lesions there are few foam cells and many eosinophils. Many of the glandular organs show occasional clumps of foam cells in the connective tissue around the small blood vessels. In the bone marrow there are scattered islands and small clumps of foam cells and many foreign body giant cells. The bone trabeculae are eroded and in many places the rarefaction of bone extends through the spongiosa and cortex producing bone defects. The foam cells are thought to originate from reticulum, vessel endothelium, and from the histiocytes of the perivascular connective tissue.

Many people believe that this disease is primarily a disturbance of cholesterol metabolism. However, in recent years there has been some difference of opinion. The lesion consists essentially of granulation tissue, partly of inflammatory origin, in which large numbers of xanthoma cells are found. Ceelen,[34] Watgen[35], Gerstel[36], and others feel that

Hand-Schüller-Christian's disease starts with the development of a granuloma in which only afterwards cholesterol esters may or may not be deposited. The primary process, therefore, is believed to be the formation of xanthomatous tissue in which there is a secondary infiltration with cholesterol esters. There are certain points which seem to favor this opinion: Most patients with tuberous xanthomatosis of the skin show marked hypercholesterolemia, whereas in Hand-Schüller-Christian's disease, it is only occasionally high. Secondly, in genuine xanthomatosis of the skin with marked hypercholesterolemia the bone marrow is usually completely devoid of xanthoma cells. Thannhauser[37] feels that the cholesterol esters in the foam cells are the result of faulty metabolism of cholesterol within the cells. If it is assumed that Hand-Schüller-Christian's disease consists primarily in the formation of granulomatous tissue with secondary cholesterol deposition, then cases must occur with a pure granulomatous proliferation without secondary precipitation of cholesterol esters. These cases may be synonymous with Siewe-Letterer's syndrome.

Some people believe that the etiology of Hand-Schüller-Christian's disease is to be found in a disturbance of the total lipid metabolism. As evidence of this they cite the fact that in many cases the blood cholesterol is within normal limits, but if determinations of all the blood lipids are made, a disproportion will be uncovered.

Cases of this disease occur in which the cranio-

hypophyseal localizations of lipoid granuloma are not present but in which the lipoid granulomatosis is situated in the rest of the skeleton only. In these cases the diagnosis is often missed.

Hand-Schüller-Christian's disease is often confused with Recklinghausen's disease. The biochemical picture in Recklinghausen's disease is not seen in Hand-Schuller-Christian's disease, where the blood and urine phosphorus and calcium are normal and the phosphatase is not elevated. Slight hypercholesterolemia may be found in Hand-Schüller-Christian's disease and when present is helpful. The X-ray picture of Recklinghausen's disease shows a generalized fibrocystic degeneration of the skeleton in which the cortex of all the bones is affected. In lipoid granulomatosis multiple bone lesions resembling bone cysts or giant cell tumors are seen, but the unaffected portion of the skeleton is completely normal. Recklinghausen's disease occurs more frequently in adults, Hand-Schüller-Christian's disease in children. Pain may be an outstanding complaint in Recklinghausen's disease, whereas in lipoid granulomatosis it is less severe or absent. The biopsy specimen in old healed lesions of Hand-Schüller-Christian's disease may be very similar to that in hyperparathyroidism, but specimens from recent lesions will show the presence of xanthoma cells. On heating unstained microscopic sections in Hand-Schüller-Christian's disease doubly refractive drops will be formed which can be recognized under the polarization microscope.

The finding of bone defects, exophthalmos, diabetes insipidus, swollen tender gums and loose teeth or dwarfism should suggest the diagnosis of xanthomatosis. In less typical cases symptoms referable to the liver, spleen, lymph nodes, respiratory, cardiac, renal, nervous or endocrine systems may be the only manifestations. The X-ray is of great importance in diagnosing this condition. The bone defects are chiefly in the membranous bones. Irregular defects with sharply defined edges and a normal appearance in the surrounding bone are indicative of this affection. In the skull the inner table is especially involved. No other disease shows such extensive destruction of the cranial and facial bones. In the long bones the destruction is frequently at the distal end of the bone, the epiphysis not being involved.

IX. Eosinophilic Granuloma

Closely allied to Hand-Schüller-Christian's disease and perhaps an incipient form of it is the so-called eosinophilic granuloma. The first reference to this pathologic entity in the literature occurs in 1929. Since then there have been many references to it. Unnecessary and extensive surgery has been done in this condition because of a mistaken diagnosis. Most cases undergo spontaneous healing.

The majority of cases have occurred in patients under twenty-one. The skull was most frequently involved in these patients, next in turn were the frontal bone, the long bones,

the ribs, and scapula. In about half of the cases pain was a prominent symptom. The duration of the lesions varied from ten days to two months. The X-rays were commonly interpreted as suggestive of either osteomyelitis or tumor. In about half the cases the white count showed an eosinophilia between four and eleven per cent. There has been one report of eosinophilic infiltration of a lymph node near the lesion; in another case the sternal marrow showed increase in eosinophils.

Grossly the biopsy material was soft, cellular, yellow-brown, gray-white or gray-pink.

Farber[38] has reported four instances of solitary bone lesions of this type which have become multiple later on. Farber[38] and Gross and Jacox[39] believe that the solitary eosinophilic granuloma and Hand-Schüller-Christian's disease are different stages of the same disease. Both conditions show destruction and replacement of normal tissues by granulomatous tissue in which endothelial cells predominate. The latter may contain lipoid. Eosinophilic leukocytes are common to the lesions of both cases. In twenty-nine of eighty-four cases of Hand-Schüller-Christian's disease analyzed by Gross and Jacox[39] they noted eosinophils. Insufficient data is available for reporting the presence of hypercholesterolemia in cases of eosinophilic granuloma. Since no autopsies have been performed on cases of eosinophilic granuloma nothing can be said about visceral involvement in this condition. In both conditions there are various stages of healing with the

production of osteoid tissue, and bone may be encountered. The radiologic appearance of the osseous defects in Hand-Schüller-Christian's disease is very similar to that of eosinophilic granuloma. As in Hand-Schüller-Christian's disease the lesion of eosinophilic granuloma may progress spontaneously or with irradiation. All reported cases of eosinophilic granuloma have recovered in contrast to the thirty per cent mortality with Hand-Schüller-Christian's disease.

Letterer-Siewe's disease is another disease entity which seems related to Hand-Schüller-Christian's disease and eosinophilic granuloma. Letterer-Siewe's disease affects infants and children predominantly and is nearly always fatal. On X-ray examination the osseous lesions of this disease are identical with those of Hand-Schüller-Christian's disease. Histologically the lesions are usually devoid of lipoid, but cases have been reported where small amounts of lipoid were present in the reticulo-endothelial cells.

Wallgren and Glanzmann[40] look upon Hand-Schuller-Christian's disease as the chronic form and upon Letterer-Siewe's disease as the acute form of reticulo-endotheliosis. The paucity of lipoid in Letterer-Siewe's disease is explained on the basis of its rapid course, and, as already stated, some investigators regard eosinophilic granuloma as an incipient form of Hand-Schuller-Christian's disease.

X. Gaucher's Disease

Another rare form of xanthomatosis is Gaucher's disease which is characterized by an infiltration of reticulum cells and histiocytes in the spleen, liver, and bone marrow by kerasin, a nitrogen-containing lipoid. In spite of the enormous size of the liver and spleen, their function remains good for a surprisingly long time. In adults the disease follows a slowly progressive course; in infants and children, however, the course is rapid and malignant.

Pinguecula, a brownish thickening of the subconjunctival fibrous tissue, is sometimes seen in older individuals. A pigmentation of the skin, thought by some to be hemochromatosis, is sometimes observed. As in other disease with splenomegaly--anemia, leukopenia, and thrombocytopenia may occur. As a result of the thrombocytopenia, epistaxis and bleeding gums are seen. Melena is sometimes observed. The internal lymph nodes, in contrast to the peripheral nodes, are commonly enlarged and brown. Gaucher's disease is familial, often several individuals of one generation being so affected, but occasionally successive generations suffer from it.

The typical Gaucher's cell is large and wrinkled with a small, eccentric, pyknotic nucleus. Often multinucleated cells are found. These cells may also invade the lungs, kidneys, and bone.

The bone lesions when visualized by X-ray show swelling, decalcification, and change of structure. The femur

is most frequently involved and shows a swollen, bottle-shaped appearance. The cortex may be eroded by the proliferating Gaucher cells. Other bones may also be affected. Vertebral lesions may lead to gibbus formation. Swelling and tenderness of the bones may be a major complaint.

The diagnosis of Gaucher's disease should be entertained in a patient with the above clinical picture. The finding of splenomegaly in other members of the family is also a helpful point. Finally, punch biopsy of the liver or spleen will usually reveal the typical Gaucher cells. The presence of typical Gaucher's cells is the only positive proof of Gaucher's disease. If there is a hemorrhagic tendency, sternal puncture should be tried instead.

XI. Niemann-Pick's Disease

This disease was at first confused with Gaucher's disease. It is familial but not hereditary. Most cases have occurred in female Jewish children. The disease begins in infancy and is usually fatal within a few months. There is rapid enlargement of the spleen and liver with anemia and general wasting. Changes in the central nervous system indistinguishable from amaurotic family idiocy occur, and in a few cases the typical changes in the retina have been seen.

Differentiation from Gaucher's disease can be made with certainty only by splenectomy, splenic puncture or biopsy of one of the lymph nodes which shows the typical cells. The

typical Niemann-Pick cells are found in greatest numbers in the spleen, liver, lymph nodes, and bone marrow, but they are also present in nearly every organ of the body and in the blood. These cells contain large vacuoles in which lipid material can be easily stained. Similar vacuoles occur in the parenchymal cells of various organs. They have also been noted in the monocytes and lymphocytes of the blood. Special staining reveals that the stored substance in these cells is predominantly a phosphatide lipid, lecithin. In some cases an elevation of the blood lipids has been found.

XII. Multiple Myeloma

In 1873 Rustitzky[41] described multiple tumors of the bones consisting of proliferating bone marrow elements which may erode the cortex and ultimately perforate the bones and spread to the adjoining tissues. The latter happening, however, is rare. In 1899 Kahler[42] described a syndrome consisting of: 1. Deformation and abnormal fragility of the bones; 2. Bone pains; 3. Cachexia; 4. Presence of Bence-Jones protein in the urine. When this syndrome was present, multiple myelomas were found at autopsy. In the majority of cases multiple myelomas consist of proliferating plasma cells, but occasionally they are myelocytomas or erythroblastomas.

Multiple myelomas occur most commonly in the spine and ribs, secondly in the femora and skull, and thirdly in the clavicles and humerus. Due to thinning of the cortex, pathologic fracture is a common early symptom. Pain is also

a presenting symptom. There may or may not be swelling over the involved area. Swelling is often seen when the myeloma occurs in the ribs. Radiculitis is a very common symptom since the frequent involvement of the vertebrae results in vertebral collapse and compression of the spinal cord.

Sternal marrow puncture is one of the best diagnostic measures for multiple myeloma. The sternal marrow is almost always affected in these cases. Wintrobe[43] has pointed out that the plasma cells of myelomas differ from ordinary plasma cells in that the chromatin of the nuclei does not show the characteristic wheelspoke arrangement and the perinuclear clear areas are rarely seen.

Multiple myeloma may occur without X-ray evidence in the skull. On roentgenogram the lesions are comparable to those produced by metastases of malignant tumors, Hand-Schüller-Christian's disease, reticulo-endotheliosis, and osteomalacia. In some cases of multiple myeloma no typical lesions of decalcification are found in any of the bones. The only lesion may be a generalized decalcification.

Bence-Jones protein is an abnormal protein formed in the body in certain bone diseases. It is highly indicative of multiple meyloma. Magnus Levy[44] believes that part of the serum protein is formed in the bone marrow; as the result of proliferation of the tumor cells, an abnormal protein is produced which is secreted in the urine. Bence-Jones protein forms a precipitate when it is heated to 50-56° C., which disappears just before boiling occurs to reappear on cooling. It may be difficult

to demonstrate the presence of this protein when albumin and globulin also appear in the urine. Renal failure frequently occurs in the terminal picture of Kahler's disease. It is thought that the renal damage follows the precipitation of Bence-Jones protein in the tubules which ultimately leads to a hydronephrotic contracted kidney and to renal failure.

The blood total protein is increased in multiple myeloma. This is due to an increase in the globulin fraction. During the cachectic periods there is a diminution of the plasma protein, but even so it is still often increased. Marked increase in serum globulin is found only in liver cirrhosis, usually not marked lymphogranuloma inguinale, chronic uremia, subacute bacterial endocarditis, Schaumann-Besnier-Boeck's disease, kalar azar, and multiple meyloma. This elevation of the serum globulin gives positive Takata Ara and formol-gel reactions.

Amyloid is also frequently observed in multiple myeloma. Large deposits are often found in the joint capsules and the kidneys, sometimes in the intestines. The amyloid degeneration in the joint capsules may explain the frequent occurrence of joint pains and restriction of joint movements in patients with Kahler's disease.

Where there is rapid decalcification of the skeleton with this disease, hypercalcemia and hypercalcinuria have been noted. In contrast to hyperparathyroidism, however, the phosphorus is hardly ever decreased and may rise when renal failure supervenes. The phosphatase values are normal or slightly elevated.

Calcium metastases do occur in this disease, chiefly in the kidneys, lungs, and gastric mucosa. Occasionally hyperplasia of the parathyroids results from calcinosis of the kidneys.

In a small minority of cases there is a slight increase of the plasma cell content of the peripheral blood and sometimes there are a few myelocytes. A few cases of multiple myeloma have shown the picture of plasma cell leukemia.

In the diagnosis of this condition, the following points are helpful in differentiating it from other conditions: abnormal fragility of the bones and bone pain, cachexia, the X-ray picture, the finding of Bence-Jones protein, the blood chemistry, and occasionally the presence of plasma cells in the peripheral blood.

XIII. Paget's Disease

In 1876 Paget[45] described osteitis deformans. This disease rarely affects persons under forty years of age. In its later stages it produces such characteristic deformity that it can be diagnosed by clinical examination alone.

The head increases progressively in size becoming triangular in shape. The greatest increment in size seems to be in the superior part of the skull.

The tibiae and femora become swollen and curved outward, producing an increase in the anterior and lateral convexities and the patient appears bow-legged. The bones also fracture easily. The bending and fractures are due to a soften-

ing of the bone; although the bones are increased in diameter, their resistance is decreased. The body length diminishes since the spine is also involved in the disease. The softening causes kyphosis and in some cases the costal margins may rest on the iliac crests. The disease affects the base of the skull as a result of which the posterior part of the base becomes more elevated than the anterior fossa producing what is termed "convexobasia".

The fractures are generally located in the long bones or the spine. They are almost always transverse fractures. Although the break is caused by slight trauma, healing is not delayed and callus formation is satisfactory.

Severe rheumatoid pains are complained of by the victims of this disease. In most cases, however, they do not appear to be due to compression of the nerve roots. There is a narrowing of the foramen magnum by proliferation of the bone at the base of the skull so that it becomes pear-shaped or heart-shaped, but this does not seem to give rise to any symptoms. Deafness is frequently a symptom of this disease and here again it does not appear to be caused by compression of the eighth nerve by the proliferating bone. Marked arteriosclerosis is often observed even in young patients with Paget's disease.

X-ray examination of the bones in this disease shows a thickening of the cortex which results in narrowing of the marrow cavity. The new bone formation may also occur at the periphery producing an ossifying periostitis. The marrow cavity

is irregular and thick, gross bone trabeculae are found in the cortex. In fact, the entire architecture of a Paget bone is remodeled and completely different from a normal bone.

The skull has an appearance of cotton-wool which is hardly ever found except in Paget's disease. As soon as the skull is thus affected roentgenologic diagnosis of Paget's becomes relatively simple. When, however, the disease is localized in several vertebrae, the differential diagnosis between tumor metastasis and Paget's disease is often impossible. In the age group in which Paget's occurs arthritis is common and this too complicates the picture of Paget's disease. In fact, when arthritis is present, Paget's always begins in the vertebrae so affected. Fissure-like transverse lines in the long bones are believed to represent incomplete fractures. In Paget's disease the joints usually remain free although they may be involved by a co-existing arthritis.

Statistical studies by Schmorl[46] have revealed that Paget's affects the sacrum, pelvis, and spine most frequently. The disease is rarely seen under forty years although leontiasis ossea, which is a closely related disease, is seen much earlier, particularly in women.

Microscopic sections of Paget's disease show an irregular criss-cross pattern of thick and devious Haversian lines, the so-called mosaic pattern, instead of the regular curves of thin Haversian lines. The resorption of bone is greatly accelerated in this disease but at the same time rapid new formation of bone tissue takes place. This rapid recon-

struction of new bone causes the swelling of the bones. There is insufficient time for calcification of this new bone so that a large part of it remains as osteoid, which allows bending on weight bearing. There is a proliferation of blood vessels in this new bone which causes an increase in the temperature of the skin overlying the affected bone.

The serum calcium and phosphorus are not elevated in Paget's and there is no hypercalcinuria. The phosphatase is elevated and the increment depends upon the severity of the disease. In severe cases it may be twenty or thirty times the normal.

There may be a long history of aching of the bones or a spontaneous fracture may occur before the diagnosis is made. In other cases the diagnosis is made from an X-ray taken for some other reason.

In diagnosing this condition the history, biochemical picture, and X-ray should make the diagnosis comparatively easy. When confusion exists, a punch biopsy from the iliac crests will usually make the diagnosis. The skeletal metastases of prostatic carcinoma often give the same clinical and radiologic picture as Paget's. In this case the acid phosphatase determination will differentiate between the two.

There have been numerous reports in the literature of sarcomatous change in the bones in long-standing cases of Paget's. In a number of cases this change has occurred simultaneously in more than one of the bones so affected.

% women up to 1990 with now in Schmorl's Series

The etiology of Paget's disease is unknown. It has

been suggested that it may be due to syphilis, inflammation, arteriosclerosis, changes in the nervous system, pituitary malfunction, and avitaminosis A.

XIV. Summary

In this paper the differential diagnosis of some of the more important cystic diseases of the bones has been considered; namely,---solitary bone cyst, giant cell tumor, von Recklinghausen's disease, hyperplasia of the parathyroids, osteomalacia and fetal rickets, Albright's syndrome, the xanthomatous diseases, multiple myeloma, and Paget's disease. The diagnosis of any one of these diseases is based on the correlation of many factors, among which may be mentioned age, sex, location of the bone defect, deformity, clinical history, X-ray picture, blood chemistry, and biopsy.

Sometimes in handling the differential diagnosis of such a number of syndromes charts are helpful. Very Good.

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