BONE

HYPOPARATHYROIDISM

HYPERPARATHYROIDISM

PAGET'S DISEASE OF BONE

HAND-- SCHULLER-- CHRISTIAN AND

LETTERER-- SIWE DISEASES AND

EOSINOPHILIC GRANULOMA (HISTIOCYTOSIS X)
THIS CRITICAL REVIEW OF LITERATURE CONCERNING SOME ASPECTS OF BONE AND SOLE OF ITS DISEASES HAPILY
HYPO - AND HYPERPARATHYROIDISII, PAGET'S DISEASE,
HAUSD - SCHOLLER - CHRISTIAN AND LUTPER - SIUE
DISEASES AND EOSINOPHILIC GRANULOMA (HISTIOCYTOSIS X) IS SUBMITTED IN SUPPORT OF CANDIDATURE FOR THE DEGREE OF MASTER OF DENTAL SURGERY.

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As a highly specialised form of living connective tissue, bone consists of two permanent elements: specialised cells and their product, the intercellular substance. Osteocytes and a calcified cementing substance with Fibrils constitute these so-called permanent elements of bone.

During active stages of bone turnover the transient elements of bone tissue are evident, viz; osteoblasts and osteoclasts.

OSTEOCYTES - Osteocytes are frequently, perhaps usually, osteoblasts which have become embedded within the bone matrix (Maximow & Bloom - 1952). Osteoblasts, osteocytes and osteoclasts are closely interrelated, in that transformations from one to another of the three cells are frequently observed. (Maximow & Bloom - 1952) (McLean & Urist - 1955).

Osteocytes are the cells of the mature bone whose specific function it is to maintain bone as a living tissue.

The cell body of an osteocyte is fusiform in shape extending numerous, branching processes in all directions, thus forming a syncytium with its fellows over variably wide areas. They are housed in lacunae and the cytoplasmic processes extend through apertures of the lacunae into cannalicules in the bone. The osteocyte undergoes transformations; it may assume the form of an osteoclast or of a reticular cell. (Weinmann & Sicher - 1955. McLean & Urist - 1955). Osteocytes are rich in glycogen; the cytoplasm is granulated and slightly basophilic. It may contain fat droplets which indicate a metabolic activity of the Osteocytes (Weinmann & Sicher - 1955). Mitochondria and a Golgi net are present and Hotchkiss - stainable granules have also been demonstrated in the osteocyte; those in
newly formed bone matrix contain many granules, whereas in bone that is producing less matrix they have few, if any granules (McLean & Urist - 1955).

In haematoxylin - eosin preparations the nucleus is darkly stained because of the course structure of the chromatin substance. Cells with two nuclei occur. (Maximow & Bloom - 1952); mitoses have not been described in osteocytes.

In sections of bone, the osteocytes present varying shapes due to the varying planes at which they are orientated. In a longitudinal section, the body of an osteocyte appears as an elongated oval, whereas a cross section reveals a shorter oval shape. Recognition of the course of the sectioned lamellae is made by a comparison of the shape of osteocytes in any section through bone.

**INTERCELLULAR SUBSTANCE** - The intercellular substance appears almost homogeneous in ground sections as well as in the decalcified sections stained with haematoxylin and eosin. It consists of a calcified collagenous substance that makes up the great mass of bones. By silver impregnation and other special methods, this portion can be seen to consist of fine collagenous fibrils which are arranged in bundles varying in thickness from 3 - 5 microns (Maximow & Bloom - 1952); they are united by an amorphous binding substance. The fibrils and cementing substance have nearly the same refractive index. The fibrils are, therefore, referred to as "masked". It is in this organic cementing substance that the mineral constituents of bone are laid down.

Polymerised glycoproteins to which the mineral salts are bound (i.e. mucopolysaccharide) mainly constitute the cementing substance. A specialised, thin layer of the intercellular substance directly adjoins the lacunae and the canalicules and forms a
sort of capsule for them. It differs from the rest of the inter-
cellular mass in that it lacks fibrils, and by not dissolving when
heated in a solution of strong alkali. Also it has different stain-
ing reaction (basophilia combined with argyrophobia) and a higher
refractive index. In ground sections this capsule appears as a
bright line around the osteocytes and their processes.

OSTEOBLASTS - There is no doubt that the osteoblasts are res-
ponsible for the formation and calcification of the intercellular
substance of bone tissue (Weinmann & Sicher - 1955). During active
growth they appear to be in a continuous layer, frequently connected
with one another by their cytoplasmic processes, on the surface of
bone. Their shape varies considerably, and there is good evidence
for a correlation of the shape and size of the osteoblasts and the

Where bone formation proceeds at a higher rate the osteoblasts
are of an irregular cuboidal shape measuring 15 to 25 microns in
diameter. In the intensely basophilic cytoplasm a Golgi net and
mitochondria are found. The spherical nucleus is eccentrically
located, always near that surface of the cell that is not in contact
with the bone. A vacuole in the neighbourhood of the nucleus con-
tains the attraction sphere and the centrioles.

Cuboidal osteoblasts are but rarely found in the adult skeleton.
Here, where bone formation is a slow process, the osteoblasts are
low-cuboidal or squamous in shape. The shape of the nucleus is
altered correspondingly and it appears much denser than in the large
cells typical for the period of rapid growth of the skeleton.

With histochemical techniques, the presence of granules stain-
ing by the Hotchkiss procedure (periodic acid - Schiff reaction)
can be demonstrated in the osteoblast when new bone is forming
These granules are absent when the osteoblast assumes the resting form (McLean & Urist - 1955).

Osteoblasts are united by intercellular bridges and in the course of bone formation some of them are surrounded by the intercellular substance, and thus become osteocytes. These intercellular bridges lengthen considerably during this process, developing into branching and anastomosing processes of the osteocytes.

The cytoplasm of the osteoblast stains intensely with basic aniline dyes, suggesting the presence of ribose nucleic acid. This, together with the presence of phosphatase in these cells, suggests that the cells are concerned with the synthesis of the proteins of the bone matrix (Maximow & Bloom - 1952). The intensity of alkaline phosphatase in these cells depends largely on the state of development and the location of them. Under the influence of the parathyroid hormone, the osteoblast may engage in phagocytic activity; may assume the forms of osteoclasts and osteocytes and take an active role in the resorption of bone. (McLean & Urist - 1955).

OSTEOCLASTS - The osteoclast is a giant cell with a variable number of nuclei, often as many as 15 or 20 (McLean & Urist - 1955). Weinmann & Sicher (1955) state that the number of nuclei may rise to 100. The nuclei resemble those of osteoblasts and osteocytes; the cytoplasm is often foamy; the cell frequently has branching processes. These cells may arise from the stromal cells of the bone marrow, or they may represent fused osteocytes liberated from resorbing bone or fused osteoblasts. (McLean & Urist - 1955) and (Maximow & Bloom - 1952). Weinmann & Sicher (1955) state that one can observe that osteocytes are incorporated into osteoclasts. In all probability they are then digested by these cells. It has been claimed that osteocytes liberated by the resorption of the intercellular substance may revert to fibroblasts or may differ-
entiate into either osteoblasts or osteoclasts. They refute these claims as being unsubstantiated by good evidence and as being highly improbable.

Where the osteoclasts are in contact with the bone, the protoplasm has sometimes a striated appearance. The acidophilic reaction of the cytoplasm of the osteoclasts is an important diagnostic character. Uninuclear osteoclasts do occur. The nuclei are poor in chromatin substance and, as a rule, contain one or two distinct nucleoli. During periods of rapid bone destruction several osteoclasts may be found to be connected by cytoplasmic bridges, thus forming a syncytium along or around bone trabeculae. They are often seen in more or less shallow grooves on the surface of the bone (Howship's lacunae).

Small cells with one or two nuclei may be diagnosed as osteoclasts by their relation to bone tissue and by their acidophilic cytoplasm.

Hotchkiss - stainable granules have been demonstrated in osteoclasts and are indistinguishable from those observed in osteoblasts and osteocytes. As in the case of the osteoblast and osteocyte, the osteoclast also can transform into reticular cells (McLean & Urist - 1955).

ARCHITECTURE OF BONE - Mature bone is lamellated. Osteocytes are found in and between the lamellae, perforating them with some of their processes to communicate with their fellows. The fibrils in the matrix are arranged in different directions in adjacent lamellae, each lamella being 4 to 12 microns thick. Such an arrangement of fibrils increases the resistance of bone to mechanical forces, especially to shearing forces. There is only one localization where bone is almost exclusively under tensile forces, namely in the innermost layer of the dental alveoli to which the
suspensory fibres of the periodontal membrane are attached. Here the direction of the fibrils is not subject to a regular change from layer to layer and thus the lamellae of the bone are indistinguishable.

The shape and arrangement of lamellae are markedly different in the two types of bone, which can be distinguished macroscopically as spongy or cancellous bone and compact bone.

**SPONGY BONE** - Spongy bone is simple in structure, but varied in form. It consists of bars, plates or tubules of bone of varying thickness and length and joined to a three-dimensional network. The single trabecula consists of a few lamellae, generally arranged parallel to each other or in concentric layers. The network is so arranged as best to resist the lines of maximum pressure or tension.

**COMPACT BONE** - In the compact substance, the lamellae are regularly arranged, in a manner closely connected with the distribution of the blood vessels which nourish the bone. These are cylindrical systems, each of which consists of a varying number of concentric lamellae (5 to 20) grouped around a narrow axial canal, a marrow canal, which contains blood vessels and a small amount of loose connective tissue. (Haversian system). The osteocytes of the Haversian system are arranged with their long axis parallel to the long axis of the system and their broad surface parallel to the lamellae. Circulation of tissue fluid through the syncytium of the osteocytes and into the intercellular substance, presumably takes place (Maximow & Bloom - 1952). The canaliculi of the lacunae in the outermost lamellae communicate but rarely with those of an adjacent Haversian system. (Weinmann & Sicher - 1955). In most cases they form short loops reaching back into the lacuna from which they arise.

Volkmann's canals link the Haversian blood vessels by short cross connections which perforate the lamellae of two adjacent
systems. Such canals also perforate the outer or inner layers of the compact bone to allow communication of the Haversian vessels with the vessels of the periosteum or the bone marrow.

The irregular spaces between the densely packed Haversian systems are occupied by the interstitial lamellae. Their origin is from partly destroyed Haversian systems or remnants from circumferential lamellae.

Outer basic or circumferential lamellae circle the entire shaft of bone during growth of a long bone in thickness. After completion of growth, similar lamellae are laid down on the inner surface (the inner basic lamellae) of the compact bone lining the marrow cavity.
Under normal conditions bone is undergoing metaplasia. Deposition and resorptive processes are going on side by side simultaneously. At any one time one process may greatly exceed the other.

Bone consists of organic matrix and inorganic matter. Bone inorganic matter is in the form of crystals, which at once suggests formation by precipitation, and that the precipitation of the salt in question must be influenced by the appropriate ion concentrations of the fluid from which it is precipitated.

Bone tissue of the body presents a huge surface area, cancellous bone surface area per unit of bone being greater than that of compact bone. Bone surfaces can be divided into 3 types -

1) those where bone is being laid down
2) those where bone is being resorbed
3) those where the status quo is being maintained

Under normal conditions (3) predominates.

BONE FORMATION - On a surface where bone is being laid down one sees microscopically a thin layer or seam of "osteoid tissue" next to the completed bone. The osteoid tissue represents extracellular, not-yet-calcified organic substance which has been laid down by the osteoblasts. The calcium salt is deposited in the osteoid tissue and may be seen with the microscope in suitable preparations as fine specks on the inner edges of the osteoid seams.

Why can the bone salt be deposited on osteoblastic surfaces at the same time as it is being absorbed from the osteoclastic surfaces, especially since both phenomena are probably occurring in intimate relationship to the same body fluid? At osteoblastic surfaces, something must take place which favours deposition. A local increase in calcium or phosphate ions would favour such precipitation. Several theories which have been propounded to explain the deposition of the salt, fail to explain the existence of uncalcified cartilage or even blood vessels. The only theory specifically providing for local calcification
is Robison's (1923).

This hypothesis suggests that an enzyme made by the osteoblasts or odontoblasts or ameloblasts or cementoblasts) which by its action increases the inorganic phosphate locally in bone-forming (or tooth forming) surfaces, favours bone salt deposition on said surfaces.

There is considerable evidence that an enzyme, alkaline phosphatase, may be responsible for a local increase in phosphate ions. This enzyme has the property of splitting inorganic phosphate from organic phosphate compounds. It is found in sizeable amounts in the teeth, skeleton, intestinal tract and the kidneys.

There is normally a small amount in serum, and is probably a reflection of the phosphatase formation in bone (Albright & Reifenstein 1948). In the skeleton and teeth it is only found when and where calcium is being deposited, thus the serum phosphatase level is high and those conditions where matrix is being laid down in excess (e.g. during growth, rickets, osteomalacia, osteitis fibrosa generalisata, osteitis deformans, etc.) In the absence of any other cause for a higher phosphatase level such as liver disease or obstructive jaundice a high serum phosphatase level is probably indicative of increased osteoblastic activity. The normal serum phosphatase level in adults is 3 to 5 Bodansky units; higher values (up to 10 Bodansky units) are found in children. (these values are equivalent to 5 to 10 King-Armstrong units per 100ml for adults, 20 to 25 for children 10 to 15 years, and 15 to 30 for children 2 to 10 years old).

There is very little organic phosphorus in plasma (and hence presumably very little in interstitial fluid) for phosphatase to act upon. Now, cartilage preparatory to calcification accumulates stores of glycogen which disappear during the course of calcium deposition. This suggests that phosphoric esters formed during glycogen breakdown might serve as substrates for bone phosphatase (Albright & Reifenstein -1948). The glycogenolytic cycle is initiated by the reaction:
Gutman & Gutman (1941) were able to demonstrate the presence of phosphorylase in growing cartilage and also in bone tissue, but not in articular cartilage. Since enzymes catalyse a reaction in either direction, it is possible, and they point out evidence that supports the possibility, that phosphorylase and not phosphatase may be the important dephosphorlizing enzyme.

In support of Robison's theory, split bones in vitro calcify at the ossifying zone if immersed in solutions of calcium glycerol - or hexose monophosphate, but not in solutions of calcium chloride and sodium phosphate. It is also in accord with the theory that other metals giving insoluble phosphates, e.g., Pb, Sr, Li, Ag, Ra, are deposited in bone if administered, and are dissolved from the bone under the same conditions as calcium (Thorpe - 1952).

In summary, therefore, the immediate cause of calcification may be a localised increase of phosphate ions; this increase may result from the splitting off of inorganic phosphate from organic phosphoric compounds by alkaline phosphatase and/or phosphorylase; the substrates for these enzymes to act upon may be built up by the enzyme phosphorylase.

**BONE RESORPTION** - Resorption refers to the destruction or solution of the elements of bone. In 1873, Koelliker described resorption, with its role in the growth and reconstruction of bone. He described and named the osteoclast and found that bone mineral and bone matrix are absorbed simultaneously, a fact repeatedly discovered in modern times; and he offered speculations concerning the mechanism of resorption to which relatively little has been added to this day.

Resorption is, in essence, the putting into solution of a complicated structure, in such a fashion that it disappears, its end -
products entering the blood stream. It always progresses inward from the surfaces of bone; it never arises within the deeper layers of the structure.

Of the components of bone, a small fraction is already in fluid form and hence easily disposed of; the remainder is in solid form, for the most part insoluble or soluble with great difficulty in the aqueous fluids of the body. That is to say that, in order to resorb bone, it is necessary that it be reduced to substances soluble in water and that these be transferred to the fluids of the body.

The occurrence of decalcification (halisteresis) of the living bone has never been proved and it seems certain that it does not take place (Weinmann & Sicher, 1955). Decalcification would entail a considerable rise in local acidity and there is not the slightest evidence of such a change in the pH of the tissue fluid.

Of the solid components of bone three substances together make up the main bulk. These are:

a) the bone mineral;
b) a fibrillar protein, collagen;
and c) an amorphous ground substance, characterised by its content of one or more polysaccharides. This is closely related to the interstitial fluid and may be made soluble by a change in its state of polymerisation. Such changes are accompanied by an increase in the concentration of mucopolysaccharides in the blood, indicating that they are readily transferred to the fluid component (McLean & Urist 1955).

Since no enzyme specific for the depolymerisation of chondroitin sulphate has been isolated, hyaluronidase is described as mediating this process.

One can dissolve collagen rather readily, at the temperature and hydrogen ion concentration of the body fluids, by digesting or disintegrating its protein structure by various proteolytic enzymes, including pepsin. In the body a specific enzyme, collagenase, would
serve to digest collagen; but it has not been shown that this enzyme actually participates in bone resorption. (McLean & Urist - 1955).

Koelliker, in 1873, concluded that the osteoclast erodes bone by chemical means, without further specifying the nature of the chemical action required. A group of compounds known as chelating agents, of which the prototype is ethylenediamine tetra-acetic acid (versene) has been introduced to support a theory of resorption (Weinmann & Sicher - 1955) and (McLean & Urist - 1955).

Chelating agents are characterised by the formation of very poorly dissociated complexes with metallic ions. They also exhibit greatly increased stability, lowered solubility in water, and changes in the dielectric constant. These characteristics differentiate chelate structures from such simple complexions as are formed by calcium with citrate; from the physiologic point of view the important difference is that the ability of a chelated complex to ionize in solution is very much below that of calcium citrate.

One of the obstacles to forming a hypothesis for the resorption of bone is that the solution of bone salt, collagen and ground substance takes place at the hydrogen ion concentration of the body fluids. This obstacle is removed by the fact that it is possible even in neutral or strongly alkaline solutions to decalcify bones and teeth with chelating agents for histologic purposes. It may therefore be safely assumed that the bone salt may be dissolved whenever another substance with a stronger affinity for calcium ions is in a solution in contact with bone (McLean & Urist - 1955).

If it be assumed that there is continuously applied to the surface of bone a solution which will depolymerize mucopolysaccharides, digest collagen, and hold calcium in firm combination, then this constitutes a basis for a working hypothesis for the mechanism of the resorption of bone. Such a mechanism would only require certain enzyme systems and an organic substance to combine with calcium.
This does not conflict with any known facts, but there is no positive evidence that it adequately describes the process. Nor is it suggested that any known chelating agent is present in bone; the possibility is that substances having similar properties may be formed in the organism (McLean & Urist - 1955; Weinmann & Sicher - 1955).

The assumption of a humoral as against a cellular destruction of bone is disproved by the obvious fact of strictest localisation of bone resorption to the area covered by osteoclasts. Sometimes bone apposition occurs in close approximation to an area of bone resorption (Weinmann & Sicher - 1955).

It has not been possible to demonstrate that the osteoclast ever does ingest debris or mineral, even under conditions furnishing abundant evidence of phagocytosis of these substances by other cells in the bone marrow in the immediate vicinity of bone undergoing resorption. Therefore, the possibility that resorption of bone ever occurs by osteoclastic phagocytosis may be excluded. (McLean & Urist -1955)

Is there sufficient evidence to implicate the osteoclast in resorption at all? An exhaustive review by Hancox (1949) concludes that there is no direct evidence that osteoclasts erode bone but that their constant occurrence in zones where resorption is taking place is more than incidental. McLean & Urist (1955) concur in this statement and will continue to assume that osteoclasts do bring about resorption of bone, either by some such process as that suggested or by some other unknown chemical action at the surface of bone.

If we accept this view, how is the process controlled? It certainly does not occur spontaneously or at random, and there are marked differences in the location and rapidity of resorption, according to the physiologic and structural needs of the moment. The influences which evoke and control osteoclastic activity must be looked for and these may be found either generally, throughout the organism, or locally, in circumscribed areas.
Even under humoral control there are differences in the responsiveness of particular bones or particular locations in bones to the stimulus carried in the blood. In both clinical and experimental hyperparathyroidism the appearance of osteoclasts is a prominent feature of the histologic picture. Cell transformations have been frequently observed and have added strength to the belief that osteoclasts may arise from other cells characteristic of bone and may return to their former states or be transformed to reticular cells in the bone marrow (McLean & Urist - 1955).

The influences of local factors in the resorption of bone are most easily seen during its growth. Some of the factors, at least, are local especially those related to the strains and stresses to which a particular bone is exposed. Weinmann and Sicher (1955) cite two possibilities. The first possibility is that ageing or necrosis of bone, manifested by ageing or necrosis of osteocytes, leads to a chemical change of the intercellular substances. At the surface of the bone, cells of the adjacent connective tissue would be stimulated by these chemical changes to differentiate into osteoclasts. A second possibility is that the stimulus for the differentiation of osteoclasts is an increase of pressure in the tissue adjacent to the bone. These authors are more inclined to believe that pressure leads to osteoclastic resorption of bone primarily causing a circulatory disturbance in the nutritive tissue of bone.

McLean and Urist (1955) believe these theories to be oversimplifications, and state that a great deal more information is required before it will be possible to account for the stimulus to osteoclast formation by local influences.

Resorption of bone is always accompanied by proliferation of the adjacent connective tissue. This includes not only the mitotic division of cells and the elaboration of intercellular substance but also the formation of new capillaries.

In summary, resorption is mediated mainly, but perhaps not
exclusively, by osteoclasts. Large numbers of these cells accompany osteoclastic resorption in all animals following administration of the parathyroid hormone. Resorption occurs regularly, in both normal and pathologic conditions, under the influence of local mechanical stimuli. Osteoclasts dissolve organic and inorganic material of the interstitial substance of bone simultaneously. For the solution of organic materials, they provide the needed enzyme. It is not yet known how they dissolve inorganic salts, but it is a reasonable assumption that instead of acid, they make use of substances that form soluble complexes with calcium, perhaps to be identified as chelating agents.
BODY FLUIDS IN RELATION TO BONE

Normal serum calcium value is 10.0mg. per 100cc plus or minus one mg. (Keating - 1947; Albright & Reifenstein - 1948). At this level a considerable amount of calcium is excreted in the urine so that on a calcium intake of 0.05mg. there is a constant drain of calcium from the body. The threshold for calcium excretion in the urine is about 7.0mg. per 100cc. Calcium is also apparently excreted into the gastro-intestinal-tract since on a very low calcium intake the faecal excretion may be greater than the intake. Other sources of calcium loss are the lactating breast and the placenta (one quart human milk = 400mg. Ca.) The latter becomes a source of appreciable calcium loss only during the last two months of pregnancy.

Since over 99% of the body calcium is contained in the bones or teeth, it follows that if the calcium output is greater than the calcium intake, the deficit will have to come from the bones (or teeth).

When a tooth is being laid down there can be a-calcification if the calcium metabolism is faulty, once formed, however, there is no de-calcification.

Phosphorus, like calcium, is found in large amounts in bones and teeth Ca : P ratio approx. 2 to 1) and in small amounts in body serum. There, the "inorganic" or "phosphate" phosphorus or "serum phosphorus" has a normal level for adults of 3.2mg. plus or minus 0.5 mg. per 100cc (Albright & Reifenstein - 1948). The level is 1 to 2 mg. higher in growing children. There are, in addition, in the body many organic phosphate compounds such as nucleo-proteins, phospholipids, and various phosphate esters which liberate phosphate ions on hydrolysis (Keating - 1947a). Thus, a negative phosphorus balance does not necessarily mean that phosphates are leaving the bones. (Albright & Reifenstein - 1948; Keating - 1947).
Many inferences to be drawn depend on the assumption that any abnormality in the fluid in intimate contact with bone will be reflected in serum.

Calcium in serum is said to be composed of three fractions (Albright & Reifenstein - 1948).

a) Calcium ions, (45% Keating - 1947a)
b) Calcium bound to protein, (55% Keating - 1947a)
c) Almost negligible, diffusible but unionized fraction.

To the clinician it is important to realize that the body fluids are either saturated or at a constant degree of supersaturation or undersaturation in respect to some salt of calcium and phosphate so that, in the absence of any fluctuation in the pH, a rise in calcium ions will lead to a fall in the phosphate ions and vice versa (Keating - 1947a).

For all practical purposes the product of the total serum calcium (mg per 100cc) and the serum phosphorus (mg per 100cc) remains approximately constant. (circa 30 - 40 for adults; 40 - 55 for growing children).

Albright & Reifenstein - (1948) state that the kidneys under normal conditions keep the blood electrolytes at such levels that the interstitial fluid is constantly under-saturated with respect to the bone salt so that normally there is a constant dissolution of calcium and phosphorus from bone-resorbing surfaces. It is clear that the rate of bone resorption will be increased by any influence which decreases in the body fluids the calcium ions, the phosphate ions, or the carbonate ions and vice versa. Thus an acidosis will hasten bone resorption (c.f. decalcification with ammonium chloride therapy). An influence which lowers the calcium ions but at the same time raises correspondingly the phosphate ions will not necessarily hasten bone resorption. It will depend on which factor is relatively the more changed (c.f. lack of decalcification with hypoparathyroidism).

Now in bone formation the rate of mineral deposition is going
to depend on the activity of the osteoblasts in laying down the organic matrix (osteoid). Provided the composition of the body fluids is not too abnormal, bone salt will be deposited in maximal amounts once the matrix is laid down.

Any slight change in the ion product probably influences bone resorption.

What influences osteoblastic activity? Most authors agree that there is considerable evidence that mechanical stresses play a large part. (Keating - 1947a) Albright & Reifenstein - 1948).
"The oral specialist must orient his thoughts along lines of general skeletal abnormalities if he is to recognise the true nature of many of these lesions. While the mandible has a number of disorders peculiar to it, it is also vulnerable to the general bone diseases".

(Knabe - 1957)
CARDINAL METABOLIC CHANGES INDUCED BY, AND MODE OF
ACTION OF, PARATHYROID HORMONE

If one removes the parathyroid glands from a normal human, four cardinal metabolic changes occur:

1) Immediate decrease in phosphorus excretion in the urine.
2) Serum phosphorus level rises.
3) Serum calcium level falls (almost simultaneously).
4) Diminished calcium excretion in urine.

If one administers parathyroid extract, the functions are altered in the opposite direction producing,

1) hyperphosphaturia,
2) hypophosphataemia,
3) hypercalcaemia,
4) hypercalcuria.

Knowledge of the action of the parathyroids is based on three sorts of observations:

1) the study of the effects of experimental parathyroidectomy
2) the study of the effects of administering parathyroid hormone experimentally to normal or parathyroidectomized animals, and
3) clinical observations of parathyroid insufficiency and hyperfunction occurring in man as the result of disease.

It is generally agreed that the chief if not the sole role of parathyroid hormone is the preservation of the normal concentration of the calcium ions on the body fluids. (Keating - 1947a). Much difference of opinion exists as to the mechanism involved.

One school believes that the hormone acts directly on bone tissue to cause its dissolution (Thompson & Collip - 1932), and that the electrolyte changes are secondary to the bone changes. The members of this school believe that this resorption is mediated, either by action of the hormone on the osteoclasts, (Weinmann - 1945), or
by stimulating some other mechanism to this end. According to these workers the hypothetical sequence of events would be as follows:

1) Parathyroid hormone expedites resorption of bone.
2) Increased calcium from bone elevates serum calcium.
3) Elevated serum calcium leads to increased urinary excretion of calcium.

The other school (Albright & Reifenstein - 1948 are strong adherents) believes that the hormone acts on the electrolyte equilibria of the body fluids, and that the bone changes, when they occur, are secondary to the chemical changes.

Albright & Reifenstein believe the sequence of events is something as follows:

1) Parathyroid hormone in some way affects the phosphate in the body fluids such as to render it more readily excretable by the kidneys, producing a decrease in the serum phosphorus level.
2) This tends to render the body fluids less saturated in regard to whatever equilibrium constant governs the serum calcium and phosphorus values.
3) Resorption of the calcium-phosphate salt from the bone resorbing surfaces is thereby increased.
4) An elevated serum calcium level results with a depressed serum phosphorus level.
5) The higher serum calcium level leads to an increased calcium excretion in the urine.
6) This loss of calcium in the urine is a factor tending to cause undersaturation of the body fluids again so that unless there is a supply of calcium from the gastro-intestinal-tract, the bones will have to supply the deficit.
7) There will result, therefore, a decrease in the total amount of bone tissue and the bones will become weak.
8) As the bones become weak they will be more subject to stresses and strains; this will stimulate the osteoblasts to lay down more osteoid tissue, which will be calcified (vide infra) since the local calcifying factor (phosphatase - phosphorylase mechanism) will more than offset the decreased saturation.
9) The drain of calcium and phosphorus into osteoid tissue will further tend to undersaturate the blood and hence further increase the bone resorption. The result is a vicious cycle.
Marking back to step 8, it is a fact that the boost from the local calcifying factor of inorganic phosphorus is much more effective with hyperparathyroid serum than with normal or hypoparathyroid serum. (Albright & Reifenstein - 1948). In an attempt to explain this let us assume that the serum calcium in mgs. \( \text{OC} \left( \text{Ca}^{++} \right) \) and that inorganic phosphorus in mgs. \( \text{OC} \left( \text{PO}_4^{3-} \right) \).

Also assume the calcium times phosphorus product of 60 is necessary for precipitation of the calcium - phosphate salt and that the local calcifying factor boosts the level of inorganic phosphorus locally by 3 mgs.

<table>
<thead>
<tr>
<th>Then</th>
<th>Ca</th>
<th>P</th>
<th>Product</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>10 x</td>
<td>4</td>
<td></td>
<td>40</td>
<td>(normal serum)</td>
</tr>
<tr>
<td>10 x</td>
<td>(4+3)</td>
<td>= 70</td>
<td></td>
<td>(normal serum + boost from local calcifying factor)</td>
</tr>
<tr>
<td>20 x</td>
<td>2</td>
<td>= 40</td>
<td></td>
<td>(hyperparathyroid serum)</td>
</tr>
<tr>
<td>20 x</td>
<td>(2+3)</td>
<td>= 100</td>
<td></td>
<td>(hyperparathyroid serum + boost etc.)</td>
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<tr>
<td>2 x</td>
<td>20</td>
<td>= 40</td>
<td></td>
<td>(hypoparathyroid serum)</td>
</tr>
<tr>
<td>2 x</td>
<td>(20+3)</td>
<td>= 46</td>
<td></td>
<td>(hypoparathyroid serum + boost etc.)</td>
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</tbody>
</table>

This agrees with the clinical fact that one can have in growing children generalized decalcification with hyperparathyroidism but normal deposition of calcium in the growing epiphyseal cartilage.

An observation which is more easily explained on the assumption that the hormone does act directly on bones is as follows: - patients with hyperparathyroidism and bone disease, shortly following the removal of the parathyroid tumour, regularly show a fall in both the serum calcium and phosphorus levels while the bone tissue by biopsy shows a complete disappearance of all osteoclasts. This failure of the serum phosphorus to rise is hard to understand if we believe Albright and Reifenstein's theory.

However, these authors believe that for some reason or other the serum phosphorus level under these circumstances is not a true
reflection of the interstitial fluid phosphorus level. The phosphorus must be retained somewhere. In patients with hyperparathyroidism but no bone disease, the serum phosphorus level does rise promptly on removal of the parathyroid tumour (Albright & Reifenstein - 1948).

Also, those who believe parathyroid extract acts directly on bone tissue might argue that the bone salt is dissolved from bone by the hormone but that the phosphate is excreted more readily than the calcium. Against this argument is the fact that when bone salt is dissolved as a result of acidosis, as with ammonium chloride administration, the calcium and phosphorus excretions are simultaneous.

Whereas the theory which holds that the parathyroid hormone acts directly on bone tissue might possibly explain the high serum calcium with hyperparathyroidism and the low serum calcium with hypoparathyroidism, how is it to explain the low serum phosphorus with hyperparathyroidism and the high serum phosphorus with hypoparathyroidism? (Keating - 1947a), (Albright & Reifenstein - 1948).

Many patients with severe and long-standing hyperparathyroidism never do develop any bone disease. This suggests that the bone disease, when present, is a secondary complication, not the primary disorder.

Albright & Reifenstein - (1948) state that the number of osteoclasts seen in experimental hyperparathyroidism depends on the duration of the condition. They quote this as evidence against the conjecture, that the osteoclasts by their own vital activity are the cause of bone destruction in this condition (see p. 13). They state that if such were the case, one would find just as many osteoclasts early in the condition when the serum calcium and the urinary calcium excretion are maximal, as late in the disease.

Finally, in patients with renal insufficiency and resulting phosphate retention, it is impossible to raise the serum calcium with parathyroid extract. This is consistent with the hypothesis
that the initial action of the hormone is to increase the excretion of phosphates and once this has been interfered with no other sequelae can occur.
PARATHYROID HORMONE

The active principle of parathyroid hormone was first extracted by Hanson (1923) and later by Collip (1925). The latter used acid extraction and isoelectric precipitation. The hormone is a protein with a small molecule (M.W. about 20,000). Studies have shown that the presence of free amino groups is necessary to its activity. It is destroyed by protein digestion and is therefore ineffective if given by mouth (Keating - 1947a).

Collip's dried product contains 15.5% nitrogen and traces of iron and sulphur. It is an amorphous powder, soluble in water and in 80% alcohol but insoluble in either, acetone and pyridine. Its potency is destroyed by heating for an hour with 10% hydrochloric acid or 5% sodium hydroxide, and by incubation with pepsin or trypsin (Albright & Reifenstein - 1948).
HYPOPARATHYROIDISM

The relatively minute quantity of calcium not stored in the bones or teeth is in solution in the fluids of the body, where it induces a number of vital functions. These include the permeability of membranes, the excitability of nerve and muscle, the action of the heart, and the coagulability of the blood. There is considerable evidence that the stimulus causing the parathyroid glands to produce more hormone is a concentration of ion calcium in serum below normal. (Keating - 1947a).

AETIOLOGY - Hypoparathyroidism may result from accidental removal of, or damage to, the parathyroid glands in the course of a thyroid operation, or in rare instances from congenital absence of these glands. (Thoma - 1954). Since there generally are accessory glands, complete ablation is rare.

PATHOLOGIC PHYSIOLOGY - In hypoparathyroidism there is a tendency to supersaturation of the blood (i.e. serum phosphorus level rises first and serum calcium level falls secondarily). One would expect, therefore, a decreased bone resorption; this in turn would make the bones less subject to stresses and strains so that bone deposition would also be decreased. In hypoparathyroidism there is a slight increase in the density of the bone. (Keating - 1947a; Albright & Reifenstein - 1948).

SYMPTOMATOLOGY - The most striking clinical feature is increase in neuromuscular excitability dependent on the hypocalcaemia and producing the symptom complex known as tetany.

ACUTE or MANIFEST tetany may appear soon after parathyroid ablation and reappear in acute episodes from time to time. (Keating - 1947a). Acute tetany may be described by the following train of symptoms. The patient first complains of numbness and tingling of the fingers and toes, later of the mouth, and eventually of much of the body, but es-
especially the extremities. This is followed by contractions or spasms of muscles, particularly in the hands and feet, where the contractures have a form characteristic of tetany, called carpopedal spasm.

Laryngospasm is particularly likely to occur in children (Keating - 1947a). Spasms have also been observed to occur in the muscles of the eyes, the oesophagus, the stomach, bronchi, intestine, and heart. Severe tetany may terminate in generalized epileptiform convulsions.

Albright & Reifenstein (1948) state that symmetrical, bilateral, punctate calcifications of the basal ganglia of the brain tissue, giving a characteristic picture by x-ray of the skull, are not uncommon. They consider this one more piece of evidence that the changes in hypoparathyroidism are in the direction of supersaturation of the body fluids with calcium phosphate.

Latent tetany is that condition existing in the absence of acute tetany, or in the intervals between attacks. It is accompanied by vague symptoms which of themselves do not provide any clue to the diagnosis. Fatigue and muscular weakness are the most constant of these symptoms. In the presence of latent tetany, however, the characteristic hyperexcitability of nerve and muscle may be demonstrated by three clinical procedures:

1) Chvostek's sign, which is a twitch of the facial muscles elicited by tapping the facial nerve; (Albright & Reifenstein - 1948) describe three degrees of Chvostek's sign)

2) Trousseau's sign, which is a characteristic carpal spasm brought on by mechanical occlusion of the circulation of the arm; and

3) Erb's sign, which is an alteration in the response to stimulation of muscle by galvanic current.

Epileptic seizures most often accompany chronic tetany of long standing (Keating - 1947a).
CHRONIC tetany is accompanied by degenerative or trophic disturbances, which include:

1) bilateral, symmetrical, cerebral calcification
2) cataracts, (apparently due to hypocalcaemia)
3) defects of hair; skin and nails, (i.e. coarse, dry and scaly skin; hair thin and patchy on head and absent in axilla and pubic regions; eyelashes and eyebrows scanty; finger and toe nails atrophied and presenting appearance of moniliasis of the nails), and
4) defects in the teeth.

BLOOD CHEMISTRY - Parathyroid insufficiency is characterised by a low level of calcium and an increase of inorganic phosphorus in serum. There is little or no calcium in the urine, but excretion of phosphorus may be normal.

DENTAL CHANGES - It is noted that the local calcifying factor is relatively ineffective for the high serum phosphorus and low serum calcium levels in hypoparathyroidism.

From an historical point of view these dental changes are most interesting, since Erdheim (1917) in Vienna first demonstrated a-calcification of the dentine of rats teeth following parathyroidectomy whilst investigating the relation of calcium metabolism to the parathyroid glands.

Albright and Strock (1933) found that, when hypoparathyroidism develops before the teeth have formed entirely, aplasia or hypoplasia of the teeth occurs.

Keating (1947a) et al studied spontaneous parathyroid insufficiency occurring in two sisters and recorded classical symptoms of hypoplasia and aplasia of the teeth.

Resch (1947) found that hypoparathyroidism of long standing had no effect on the developed tooth. The dental caries index was not increased. Children born during the period of tetany readily developed caries of the deciduous teeth, which resulted in malocclusion and altered jaw development.
DIAGNOSIS - Once the condition is suspected clinically, the diagnosis is confirmed by the characteristic chemical findings, viz. a low serum calcium, a high serum phosphorus, a normal or even low serum phosphatase level, and usually an absence of calcium in the urine.

In a totally a-parathyroid patient the serum calcium will fall as low as 4.5 mg./100 cc and the serum phosphorus level may reach 12 mg./100 cc. Because of the decrease in osteoblasts, one would expect the serum phosphatase level to be low and, as a matter of fact, it does seem to be slightly low in many patients (Albright and Reifenstein - 1948).

If the serum calcium is below 7 - 8 mg./100 cc., the threshold for calcium excretion, there will usually be an absence of calcium in the urine.

DIFFERENTIAL DIAGNOSIS - The syndrome of tetany is not peculiar to parathyroid insufficiency. For all practical purposes, one can consider that there are two causes of tetany: hypocalcaemia and alkalosis (tetany due to alkalosis may be entirely due to some secondary change in the availability of calcium ions).

The causes of hypocalcaemia other than hypoparathyroidism are rickets or osteomalacia and renal insufficiency with urea and phosphate retention.

In rickets or osteomalacia, the low serum calcium value is characteristically coupled with a low or a normal serum phosphorus value. High serum phosphorus values are most unusual. The serum phosphatase level, which is normal or even low in hypoparathyroidism, is high in both rickets and osteomalacia.

Steatorrhoea, of which sprue is an example, probably leads to hypocalcaemia because vitamin D, being fat soluble, is dissolved in the unabsorbed fat. The condition hence results in hypovitaminosis D; the blood chemical findings, therefore, are those of osteomalacia.
In renal insufficiency with azotaemia one finds phosphorus retention with a compensatory lowering of the serum calcium level. There is, however, in renal insufficiency as compared with hypoparathyroidism a lesser degree of hypocalcaemia, for the same degree of hyperphosphataemia. One seldom meets tetany in renal insufficiency with hypocalcaemia because of the associated acidosis which inhibits tetany (Albright & Reifenstein - 1948).

TREATMENT - Parathyroid tetany is solely a consequence of the hypocalcaemia. Tetany may be treated by the administration of calcium, or by employing agents which elevate the serum calcium. Vitamin D and dihydrotachysterol, or A.T. 10, are usually employed for this purpose (Keating - 1947). A.T. 10 like Vitamin D is a photochemical derivative of ergosterol and Albright and Reifenstein prefer its use as its action more closely resembles that of the hormone than does the action of Vitamin D.

A simple method like the Sulkowitch test (vide infra) for calcium in the urine is used to prevent the development of a hypercalcaemia by an overdose of Vitamin D or A.T. 10.

All forms of treatment are based on the rationale that there should be a high intake of calcium and a low intake of phosphorus. Milk is contra-indicated. Calcium-gluconate or lactate can be substituted with aluminium hydroxide to decrease phosphate absorption. The patient may also be kept slightly acidic with calcium chloride to alleviate tetany. (Albright & Reifenstein - 1948).

Parathyroid extract is not used in the therapy of hypoparathyroidism. Its drawbacks are:

a) expensive
b) often causes a local reaction
c) its effectiveness wears out apparently because of anti-body formation.

In acute emergency 10cc of calcium gluconate may be administered intravenously.
PSEUDO - HYPOPARATHYROIDISM - The cause of this disturbance is not a lack of parathyroid hormone but an inability to respond to it. These cases may respond to dihydrotachysterol. (Albright, Burnett, Smith & Parson (1942).
PRIMARY  HYPERPARATHYROIDISM

DEFINITION - By "primary hyperparathyroidism" is meant a condition where more parathyroid hormone is manufactured than is needed. By "secondary hyperparathyroidism" is meant a condition where more parathyroid hormone is manufactured than is normal but where this hormone is needed for some compensatory purposes.

HISTORY - In 1891 von Recklinghausen described the appalling malady now known as osteitis fibrosa cystica generalisata. His report was based on autopsy findings in a series of sixteen patients suffering from a variety of bone diseases. Three cases exhibited the bone changes of widespread fibrosis, cysts and giant cells. (Schneider - 1953). Albright & Reifenstein (1948) dispute some of these cases as being confused with polyostotic fibrous dysplasia, a then unknown condition.

Askanzy (1904) was the first to describe a case of osteitis fibrosa which was associated with a parathyroid tumour. (Thoma - 1954). Parathyroid enlargement was also noticed in other decalcifying diseases, such as rickets and osteomalacia. Since the parathyroid enlargement in the latter conditions appeared to be secondary, the idea became prevalent that the changes of the parathyroids in von Recklinghausen's disease were secondary also. (Keating - 1947).

Mandl - (1926) reversed this idea by effecting a remarkable cure of von Recklinghausen's disease through the removal of a parathyroid adenoma (Thoma - 1954)

The term "hyperparathyroidism" was introduced by Barr, Bulger and Dixon in 1929. Albright, Aub and Bauer (1934) called attention to the frequency with which renal stones occurred in hyper-
parathyroidism with skeletal changes, and demonstrated that hyper-
parathyroidism can exist without the extreme changes seen in von
Recklinghausen's disease, and that in some patients skeletal in-
volvement is entirely lacking.

In ten years, Albright and his colleagues amassed data on
a remarkable series of 68 cases of this disease. Analysis of their
experience indicated hyperparathyroidism to be considerably more
common than had been supposed. They found that hyperparathyroidism
occurred more often without skeletal changes than with them and they
showed that, both from a standpoint of incidence and from that of
hazard to life, renal involvement was a more serious and important
consequence of hyperparathyroidism than skeletal involvement.

AETIOLOGY - Primary hyperparathyroidism may be due to a
single adenoma or a carcinoma of one of the four glands, to multiple
adenomata, or to hypertrophy of all parathyroid tissue. (Albright
& Reifenstein - 1948)

The parathyroid glands combined usually four in number, weigh
from 120 - 150 mg. Each gland measures approximately 6 by 4 by 3 mm.
The parathyroids originate from the branchial clefts in close associ-
ation with the anlagen of the thyroid gland and the thymus. Ordin-
arily they occupy positions on the dorsal surface of the lateral
lobes of the thyroid. Sometimes more or less than four glands
exist and, occasionally, one or more of them may occupy anomalous
positions either within the thyroid or distant from it. (e.g. within
the upper mediastinum)

Under low magnification parathyroid tissue from an adult, with
its islands of epithelial cells dispersed with fat cells, looks not
unlike bone marrow. The fat cells, appearing at puberty, increase
in number with age until about 40 years.

The parathyroid cells are of three principal types: (Keating -
1947a).
1) Chief cells, which are small, dark-staining cells with relatively scant protoplasm;

2) oxyphil cells, which are much larger than the chief cells, have smaller nuclei, and stain intensely with acid dyes, and

3) "wasserhelle" cells, or water-clear cells, which are still larger and characterized by a large amount of water-clear protoplasm containing many vacuoles. The chief cells are ordinarily the most abundant. The oxyphil cells do not appear until puberty, after which they increase in number with age. The "wasserhelle" cells usually remain relatively few. Albright & Reifenstein (1948) describe the "wasserhelle" cell as a chief cell with a vacuolated appearance.

The epithelial cells form cords and occasionally follicles. After puberty the latter may contain colloid giving an appearance not too unlike thyroid tissue. The functional significance of these cell types is not well understood.

The parathyroid glands usually weigh more in women than in men (Schneider - 1953)

In an attempt to explain the cause of parathyroid overactivity or enlargement, Albright and Reifenstein -(1948) quote four well-recognised conditions in which one encounters hyperplasia of the parathyroid glands, namely,

a) rickets or osteomalacia,

b) pregnancy,

c) renal insufficiency of the type associated with phosphate retention. (Pappenheimer & Wilens (1935) state that the increase in size is proportional to the severity of the renal lesion)

d) calcium deprivation

All of these four conditions have a tendency to a low serum
calcium value and it seems not improbable that the normal stimulus to parathyroid hormone production is a serum-calcium-value-below-normal. These authors conclude by stating that it seems possible that parathyroid adenomata formation may be connected with the following sequence of events:

A. Some situation tending to lower the serum calcium level,
B. Stimulation of all parathyroid tissue,
C. Formation of many circumscribed "germinative centres" (Erdeheim - 1907).
D. Loss of the part of one or more of these centres of their property of being controlled by normal stimuli.

There seems to be an interrelationship between pituitary, parathyroid and islet tissues (Cushing & Davidoff -(1927), Kepler, Rynearson, Sprague, and Keating (1947); Shellburne and McLaughlin (1945), ) but this as yet is inexplicable.

Considerable circumstantial evidence was presented for hypertrophy of the parathyroids which suggested that the condition might be secondary to an excess of some pituitary parathyrotrophic substance. There is no evidence to confirm this hypothesis. It seemed possible that the extraordinary enlargement of the parathyroid cells might be due to the storing of parathyroid hormone, but no appreciable deviation in the hormone content was found from that of normal tissue. (Albright & Reifenstein -1948).

Rogers and Keating (1947) conclude that the parathyroid pathology cannot be explained by hypertrophy alone. Thus the nature of the condition remains entirely obscure.

CLINICAL FINDINGS - This disease generally affects the middle-aged and is seen more commonly in women than in men, the incidence being about three to one (Chaudhry, Hayes and Gorlin - 1958); Thoma - 1954). The clinical findings in hyperparathyroidism can be divided into three headings,
1) those due to bone disease,
2) those due to disease of the urinary tract,
3) those due to hypercalcaemia per se.

1) Bone disease played an important part in the early history of hyperparathyroidism, but it is a mistake to think of bone disease as an essential part of the disease. In many cases of severe hyperparathyroidism there is no bone disease at all. (Coleman - 1954). Albright, Aub and Bauer - (1934), and Keating and Cook (1945) have presented evidence that the disease predisposes to bony lesions but that it does not necessitate their development.

When bone disease does occur it consists of a generalized decalcification with or without superimposed cysts and tumours and is called osteitis fibrosa cystica or osteitis fibrosa generalisata. The condition is not an inflammation (Albright & Reifenstein - 1948).

Keating (1947 and Schneider (1953) have called attention to the fact that the most marked susceptibility of bones to resorption and tumour predilection in hyperparathyroidism dysfunction occurred at the sites of most active bone formation, namely, the metaphysis in the tubular bones, the costochondral junctions, and the bones of the skull and jaws. Moreover, Albright and Reifenstein (1948) have attested that the lamina dura about the teeth is another common site of early bone resorption, although by no means pathognomonic (Cahn - 1948). Although a generalized condition, (Albright and Reifenstein -1948), hyperparathyroidism does not attack all bones or all areas of one bone to the same degree (Weinmann - 1945). It has been suggested by many authors (Thoma - 1954; Weinmann - 1945; and Jaffe - 1948) that a case of local injury provides a locus minoris resistentiae for a pathologic exaggeration of the skeletal reaction.

The bone changes consist mainly of a more or less extensive resorption of mature lamellated bone and its replacement by spongy bone of the immature, coarse, fibrillar type and fibrosis of the bone marrow
in these foci (Weinmann - 1945). Some cases have superimposed cysts filled with fluid and lined with fibrous tissue; these cysts are almost certainly degenerative phenomena. A good many cases, however, do not have cysts (Albright and Reifenstein - 1948).

Bone tumours, which are commonly present in the bone disease associated with hyperparathyroidism, are not as a rule referred to in the descriptive name of the disease. They consist of solid masses of soft tissue without bone, composed of the supporting cells of the bone marrow, osteoblasts and osteoclasts. Thoma - (1954) thinks these lesions may be due to trauma during the course of the disease. Intermedullary haemorrhage can cause resorption of bone and cyst formation. These bone tumours have been called "osteoclastomata" (Hunter and Turnbull - 1931), but "osteoblastomata" would be equally suitable except that an osteoclast is a more imposing looking cell than an osteoblast.

The formation of new bone about a bone tumour is ascribed by some investigators as acting as a barrier against its further progress. It seems more in agreement with the fundamentals of bone biology to view this compensatory osteoblastic activity as a response to mechanical stimuli. In the case of a mandible affected, the reactive apposition of new bone on the cortical surfaces of the mandible may be interpreted as an attempt by the organism to reinforce the mandible weakened by the resorptive process of the expanding tumour.

All degrees of skeletal resorption are met with clinically, from the patient with no bony changes to the patient with practically complete loss of skeleton.

Symptoms resulting from involvement of the skeleton may be summarized as follows:

a) With minimal bone disease: vague aches and pains, backache.

b) With osteitis fibrosa cystica: bone tenderness pathologic fractures, decreased stature, pigeon breast and other deformities, cysts and tumours, particularly in the jaw, metacarpals,
and ends of long bones.

Bone tenderness is a very constant feature. Surprising is the rapidity with which it disappears after the removal of the tumour of parathyroids. (Albright and Reifenstein - 1948). Mandl's historic case (1926) illustrates this feature well.

Bone in hyperparathyroidism is brittle, so that fractures, rather than bending, occur. When the vertebrae are affected, crushing of the vertebrae and herniation of the nuclei pulposi occur, producing decrease of stature, a "pigeon-breast" deformity of the chest, and a disappearance of the neck into the thorax.

It is a fact that one may have severe hyperparathyroidism and show no clinical, roentgenological, or histological evidence of bone disease (Keating - 1947). Albright & Reifenstein (1948) state that hyperparathyroidism brings about a change in the blood chemistry of the body which results in there being an increased excretion of calcium in the urine. Other things being equal, this increases the chances of the patient being in negative calcium balance, bone disease develops; if the patient happens to ingest sufficient calcium to compensate for the loss in urine and faeces, the calcium balance is not negative and bone disease does not develop. For all practical purposes, it usually comes down to whether or not the patient drinks milk.

Keating (1947) does not believe this condition is as simple as this, as he states that there are cases of relatively severe hyperparathyroidism without involvement of bone and with rather low calcium intakes. He thinks that there is reason to believe that other unknown factors may be involved. Such factors might conceivably include individual variations in the capacity of the kidney to excrete calcium, of the skeleton to mobilize it, or of the alimentary tract to absorb it.
Clinical findings associated with the urinary tract can be by far the most serious and important consequence of hyperparathyroidism. (Keating - 1947). The symptomatology associated with the urinary tract may be divided into three parts:

a) that due to hypercalcuria and hyperphosphaturia,
b) that due to the formation of kidney stones, and
c) that due to the calcium deposits in the kidney parenchyma.

Marked polyuria and polydipsia are usually associated with the hypercalcuria and hyperphosphaturia of hyperparathyroidism. Polyuria is attributed to the primary diuretic action of the hormone as well as to the increased excretion of calcium and phosphorus through the kidneys. Polydipsia results from excessive loss of body fluids. (Chaudhry, Hayes & Gorlin - 1958). Almost all patients with hyperparathyroidism have a marked oliguria following the successful removal of the parathyroid adenoma. (Albright & Reifenstein - 1948).

Because of the polyuria and polydipsia, severe cases of hyperparathyroidism have been faultily diagnosed as diabetes insipidus. There is, however, another cause for the polyuria in patients with hyperparathyroidism, namely, tubular damage. This may occur in association with nephrocalcinosis, but also without demonstrable nephrocalcinosis by x-ray. Although a certain degree of renal damage is reversible (Albright & Reifenstein - 1948), for the most part it is irreversible and it is for this reason that hyperparathyroidism must be detected early. A dentist is frequently in the position to do this. (Cahn - 1952).

As a result of secondary involvement of the urinary tract these symptoms occur: (Thoma - 1954) -

In nephrocalcinosis, renal insufficiency and uraemia.

In cases of renal calculi, renal pain, renal colic, urinary obstruction and infective pyelonephritis and uraemia.
3. Clinical findings due to hypercalcaemia per se exhibit diminished neuro-muscular activity of both skeletal and smooth muscles, causing; (Chaudhry, Hayes and Gorlin - 1958) -

Gastrointestinal symptoms: anorexia, nausea, vomiting, abdominal pain, constipation.

Neuromuscular symptoms: fatigue, lassitude or stupour, weakness, loss of muscle tone, hypermobility of joints, muscular atony.

An increased serum calcium leads to its deposition in soft tissue organs, especially in blood vessels and urinary tracts. A sense of dryness in the nose and throat with dysphagia has also been observed with hypercalcaemia (Albright & Reifenstein - 1948).

All these clinical findings are rarely found in one patient. (Schneider - 1953). Burket (1957) states that frequently hyperparathyroid patients appear older than their chronologic age. He goes on by stating that painful symptoms in this disease are often mistaken for arthritis or neuralgia and purpuric manifestations are common.

BLOOD CHEMISTRY - Keating (1947) states that regardless of its manifestations, primary hyperparathyroidism is always characterized by an increase of calcium and reduction of phosphorus in serum. If the patient has a marked degree of the disease, these values will be sufficiently abnormal so that other diagnostic procedures are superfluous. (Albright & Reifenstein (1948). However, Levy (1952) presented a case of hyperparathyroidism with normal blood chemistry. A negative calcium balance was the only clue. Snapper (1949) has pointed out that the blood chemistry may well be within normal limits in patients with hyperparathyroidism. The kidney tubules normally reabsorb calcium to maintain a blood level of from 9.5 - 10.5 mg%. Under the influence of excessive parathyroid hormone the tubules no longer efficiently reabsorb calcium so that increased amounts of this mineral are lost in the urine.
Logan - (1939) demonstrated experimentally that the phosphate excretion increased and the plasma inorganic phosphate usually decreased during the first hour after the injection of excessive parathyroid hormone. The serum calcium also increased within this short period. It would be reasonable to suppose from these experiments that the resorption of bone was almost immediate. Schneider (1953) states that the serum calcium may go as high as 24 mg./%, while phosphorus is decreased as low as 1 mg. per 100cc. There are cases ranging from a marked degree of the disease all the way down to the normal state.

The serum phosphatase level is perfectly normal if the hyperparathyroidism is not associated with bone disease and hence should not be used as a test for hyperparathyroidism. The test should only be used in determining the degree of bone disease once the diagnosis has been established (Coleman - 1954).

**URINARY ANALYSIS** - There is an increased urinary secretion of both phosphorus and calcium. The calcium precipitates out as a phosphate salt especially if the urine is alkaline, since the phosphate ion is always in excess. If the urine is acid and oxylate is present, calcium oxylate will form, and precipitation may occur in the kidneys or other parts of the urinary tract (Thoma - 1954). In health about 75% of the ingested calcium is excreted in the faeces and about 25% by way of the urine. In hyperparathyroidism the reverse is true (Cahn - 1952). When there are signs and symptoms of hyperparathyroidism and the blood chemistry is apparently normal carefully controlled studies of calcium excretion in the urine must be done, and these are best done with the patient in hospital. The Bauer-Aub diet is the one generally used (100 to 125 mg. calcium per day) and the patient is kept on this for three days and then a twenty-four hour specimen of urine is examined for calcium. Normally
a patient on this diet would not excrete more than from 100 to 150 mg of calcium per diem. Any amount above this would be significant of a negative calcium balance. In primary hyperparathyroidism 3 times the normal is usually excreted (Thoma - 1954).

There is a rough test that gives fairly accurate results and can be done in the office. This is the Sulkowitch test, (Cahn - 1952). A solution known as the Sulkowitch solution is used. This consists of:

- Oxalic acid 2.5 gm
- Ammonium oxylate 2.5 gm
- Glacial acetic acid 5.0 cc
- Distilled water q.s. add 150 Occ.

The patient is asked not to drink any milk or eat any cheese for three days. The morning specimen of the fourth day is examined. The urine should be neutral or slightly acid. This can be determined with litmus. If the urine is alkaline, a drop or two of glacial acetic acid is added until slightly acid.

Five c.c's of urine are placed in a test tube and about 2 cc of the Sulkowitch solution are added. The speed with which the precipitate forms and its degree of intensity are noted. The results are registered as from zero to 4 plus. A zero test would signify a hypocalcaemia, while a 3 to 4 plus would indicate a hypercalcuria and strongly suggest a hypercalcaemia. This is a rough test. If there is a consistently high positive Sulkowitch over a period of time, more detailed studies of the urinary calcium excretion must be done.

**JAWS AND TEETH** - It is interesting to note that quite a few cases of hyperparathyroidism have now been reported where only the jaws have been noticeably affected, the rest of the skeleton being free from changes at least radiographically. Cahn (1952) makes the observation that the jaws are continually subjected to trauma especially when teeth are present and this makes the jaws vulnerable and renders them a fertile diagnostic field. The bone resorption in the jaws results in an osteoporosis, and sometimes large osteoclastomas form which may be the first symptoms recognised. The tumours may be peripheral or
central. The central tumours appear more frequently. (Thoma - 1954; Coleman - 1954; Levy - 1952; Kock - 1950; Cahn - 1948; Keating - 1947). Tumourous formations are more common in the mandible than in the maxilla. (Koch - 1950). Whereas every case of epulis is certainly not hyperparathyroidism, this diagnosis must be carefully considered in such a case (Albright and Riefenstein - 1948).

Although not pathognomonic (vide supra) the disappearance of the lamina dura occurs frequently in hyperparathyroidism. (Keating - 1947). Some attempt to explain this was made by Coleman in 1954 by stating that continued eruption, mesial physiologic migration, and active function of the teeth, when present, stimulate new bone formation and old bone removal at various areas of the alveolar surfaces. These sites of active bone growth and alteration suggest rapid apposition, increased rate of reconstruction, and concomitantly more rapid resorption of bone. This explanation may shed some light as to why certain areas of the lamina dura may be resorbed early in this disease.

Weinmann and Schour - (1945) and others have stated that the teeth, unlike bone, do not participate in the resorptive process. Thoma (1936) and Keating and Cook (1945) have reported evidence of root resorption, but expressed the opinion that it was attributed to pressure atrophy of the expanding tumour and not to the disease itself. The teeth are generally highly calcified, especially if the disease started at an early age, and therefore resist decay (Thoma - 1954).

In cases of severe hyperparathyroidism with bone disease of the jaws marked malocclusion and prognathism have occasionally resulted. The teeth frequently loosen and fall out, so that many patients who have hyperparathyroidism are edentulous. Surprisingly, however, in some instances the teeth remain firmly in place. (Keating - 1947). Schour and Massler - (1943) regard malocclusion as one of the first signs of the disease. The teeth tighten if the disease has been cured. Extensive diffuse and nodular calcification is reported by
Burket (1957) to occur within the dental pulp.

Following the loss of all the teeth, the maxillary and mandibular bones furnish an unsatisfactory base for artificial dentures because of their poor quality. In hyperparathyroidism, sections of the jaw bones can be removed with ease with an ordinary scalpel.

S Bingarn and Gerot (1939) reported a case of hyperparathyroidism which demonstrated the oral aspects of the disease and emphasized the importance of the dentist's ruling out a systemic background of any oral lesion of an unusual nature.

Keating (1947) quotes a case of Hannon and his associates (1930) as illustrating almost all the dental changes described in hyperparathyroidism. Cahn (1951) presented a case with recurrent masses on the mandibular gingiva and cyst-like lesions very like periapical granulomata or radicular cysts occurring in the mandible. This patient had suffered from renal calculi. Snapper (1949) has reported the case of multiple, recurrent tumours of the jaws that were variously described as giant-cell tumours and osteofibromas with no other radiographic changes in the skeleton. Incidentally, this was a case with normal blood chemistry as was Levy's in 1952.

Inasmuch as parathyroid insufficiency can induce-intrinsic defects in teeth during their period of development, it is reasonable to expect that hyperparathyroidism occurring in childhood might do likewise. Hyperparathyroidism has rarely been observed in children, and unfortunately few data have appeared concerning dental findings in such cases. Thoma (1954) reported the case of a 15-year-old boy with an epulis which proved to be due to hyperparathyroidism. The duration of the hyperparathyroidism was about 7 years. Pathologic examination of two premolars and a first molar removed from this boy is of special interest. Resorption was apparent only at the root surfaces in contact with the giant-cell tumour. The premolars showed marked contour lines made up of strips of densely staining dentine adjoining a strip of poorly calcified structure. In the pulp there were small cysts
with vacuolisation of the odontoblastic layer. In some places there was complete atrophy of odontoblasts, and tubular dentine had been deposited. Pulp nodules and interstitial deposits of calcium were found. There was no evidence that resorption had taken place inside the teeth at any time. The disturbance in dentine formation apparently took place during active phases of hyperparathyroidism. There was no evidence of caries in the patient's mouth.

**X-RAY FINDINGS** — Roentgenographic diagnosis of osteitis fibrosa generalisata offers little difficulty. One looks for generalised decalcification. As evidence of this it is often helpful to know whether or not the lamina dura is still intact. If it is not, the inference is that general decalcification is present. At first evidence of osteoporosis, there is a general, fine, miliary or granular mottling. (Thoma — 1954). Especially characteristic is the even ground-glass appearance of the skull, which in Albright & Reifenstein's (1948) experience, is not met with in any other condition except renal osteitis fibrosa generalisata or renal rickets. The thickness of the skull is not affected.

Cahn (1948) states that the widening of the intertrabecular spaces imparts a bubblelike appearance to x-ray pictures, and it seems to him to be more characteristic, more so than the loss of the lamina dura.

One looks for "cysts" and "tumours". Both of these appear on the X-ray as cysts. Furthermore, an area of fibrosis where the bone trabeculae are mostly destroyed will also appear cystic. Albright & Reifenstein (1948) refer to these as "pseudocysts". The correct interpretation of the underlying lesion in some cases must be deferred until the hyperparathyroidism has been cured, when the true cysts will remain as cysts, and the "pseudocysts" and tumours will turn into bone. A subcortical "cyst" is most suggestive of hyperparathyroidism. (Keating 1947).

Sometimes the "cystic" lesion
will appear septate or multilocular due to irregular erosion of the cortex, (Cahn – 1948), and in rare instances they will expand the surface (Coleman & Thoma – 1954). The bones most frequently involved in generalised osteitis fibrosa, in order of their incidence, are: the long bones, calvarium, mandible, maxilla, pelvis and phalanges. The maxillary sinus may become invaded by giant cell tumours of the maxilla.

The rarefaction of the entire skeleton is not always equally distributed, but in most cases is more pronounced in the extremities, skull, and jaw than in the vertebral column. In addition there is apparently a tremendous acceleration of bone metaplasia resulting in complete disorganization of the normal architecture of bone. In the skull this produces a characteristic ground-glass of miliary type of osteoporosis which is also seen to advantage in the jaw. The entire skeleton, but particularly the long bones, is the site of widespread fibrotic changes, with irregular coarse trabeculae and thin, fibrous cortical bone (Keating – 1947).

In cases of mild hyperparathyroidism, dental x-rays have a special value. The technical superiority of x-rays of the bone surrounding the teeth plus the special advantage provided by the uninvolved teeth as a gauge of density make dental x-rays particularly useful in the recognition of mild degrees of skeletal involvement. Mild demineralization, early distortion of the trabecular pattern, and disappearance of the lamina dura sometimes provide more specific clues to the diagnosis than do changes elsewhere in the skeleton.

HISTOPATHOLOGY. – Osteitis fibrosa, which is a histologic sign for a number of diseases, of which hyperparathyroidism is one, is due to replacement of the normal marrow by fibrous tissue. (Schneider – 1953). There is an increase in the supporting cells of the bone marrow. These cells, it has been suggested, give rise to osteoblasts and osteoclasts, and
since both of these latter two cell types are increased, it is perhaps not surprising to find an increase in the parent cell type. (Albright & Reifenstein - 1948).

Osteoclastic resorption, which appears very active along the enlarged blood vessels in the Haversian system of the cortex and principally in the spongiosa, is the dominant change in the bone. Osteoclasts are seen in large numbers in lacunae alongside bone trabeculae, in vascular canals, and under the periosteum (Thoma - 1954).

Apposition is not necessarily part of the disease, but must be looked at as a process of repair. (Schneider - 1953). The osteoblasts are plumper than resting osteoblasts and have an abundant granular oxyphilic cytoplasm. Often two or more rows of cells closely packed can be seen around the bone trabeculae, indicating great cell activity. (Thoma - 1954). The resorptive process exceeds the deposition so that cement lines of bone apposition are missing and there is little or no mosaic pattern present. (Schneider - 1953). Thoma (1954) states that in generalised osteitis fibrosa the normal bone trabeculae are replaced by woven bone. Generally there is only slight evidence of new bone formation (Burket - 1957).

One especially typical condition of generalised osteitis fibrosa is the dissecting of trabeculae by osteoclasts.

Fibrosis of the bone marrow is a conspicuous feature. A coarse network forms in the marrow spaces replacing resorbed trabeculae. Hyperaemia and oedema occurs in the bone marrow and in the pulps of the teeth. (Thoma - 1954). Some vessels contain thrombi both new (contain red pigment), and old (contain brown pigment or haemosiderin).

Cysts are frequently seen but are not an essential part of the disease; they may be small and only visible with the microscope; or they may be large enough to be demonstrable in x-rays. They are caused by degenerative changes. (Schneider - 1953), are characterised by their lack of specific lining (Weinmann - 1945), and contain an albuminous fluid, with or without red corpuscles (Hunter & Turnbull - 1931). These cysts may be a transitional stage of osteoclastomas.

Osteoclastomas are focal accumulations of foreign body giant cells, and are frequently encountered in the jaws, a fact which may be due to the abundant blood supply, as extravasation of erythrocytes, haemorrhages, and the accumulation of iron pigment favour their formation. (Thoma - 1954).
Jaffe (1953) describes the pathogenesis of "brown tumours" as follows:

In a bone area which has undergone considerable resorption and extensive replacement by fibrous tissue, haemorrhage into the replacement tissue may occur. It is the discolouration by blood and haemosiderin that gives the lesional area its brownish colour.

Small, multinuclear giant cells, which are often clumped or bunched, appear in the wake of the haemorrhage. They, along with the connective tissue stroma and the delicate trabeculae of osteoid and osseous tissue to be found in the lesional area, complete the resemblance of the individual "brown tumour" to the solitary giant-cell reparative granuloma of the jaw. As the osteoclastoma increases in size the cortex becomes involved; the bone expands by periosteal apposition, but it may be completely destroyed. However, the periosteum is never broken through (Thoma - 1954).

Osteoclastomas may be of very small dimension or may be so large that they can be detected radiographically.

The peripheral giant cell tumours which occur in the mouth resemble the ordinary giant cell epulis.

It might be argued that hyperparathyroidism causes bone destruction and that those patients on a high calcium intake are able to balance this destruction with new-bone formation. This is not the case because, if it were, one would see evidence of bone destruction and bone formation in bone biopsies.

COMPLICATIONS - Secondary infections of the urinary tract, purpuric manifestations (Burket - 1957) and anaemia (Custer - 1949) occur in hyperparathyroidism. Custer (1949) states that the fibrous reaction may be so widespread in advanced cases that myelophthisic anaemia develops. Anaemia in hyperparathyroidism may also result from chronic renal failure.

DIAGNOSIS - Early recognition of the condition is imperative if serious skeletal and renal complications are to be avoided, and imputuous and unnecessary removal of sound functional teeth averted. Once hyperparathyroidism has been suspected, its confirmation, in most instances, depends on the finding of a high serum calcium level coupled with a low serum phosphorus level. If one has a patient with marked bone disease and the serum phosphatase level is not elevated, one is pretty safe in ruling out hyperparathyroidism as a cause of the bone disease. When there is no bone disease the serum phosphatase is normal.
The less the degree of hyperparathyroidism, the less the chemical findings will deviate from the normal. One is often asked how high the serum calcium level must be before one considers hyperparathyroidism. This is impossible to state.

Albright and Reifenstein (1948) state that one considers the diagnosis even with a normal serum calcium value. In these cases urinary calcium determination is important (Cahn - 1952).

In patients where small elevations in the serum calcium level are significant, the serum protein determination becomes of the utmost importance. The amount of ionised calcium depends on the degree of hyperparathyroidism (and perhaps other factors), (Keating - 1947.), while the amount of calcium bound to protein is a function of the amount of protein as well as of the amount of ionised calcium. Therefore, the ionised calcium may be slightly high due to a mild degree of hyperparathyroidism and yet, if at the same time the patient has a low serum protein level, the calcium bound to protein will be low so that the net result may be that the total calcium is normal. In instances where the serum protein is low it is necessary to make an allowance in the total serum calcium value for what the value would have been had the serum protein been normal. (Albright & Reifenstein - 1948).

From a dental aspect, no case of giant cell tumour, loss of lamina dura, widening of the periodontal shadow, and increase of the intertrabecular spaces should be allowed to go unchallenged, until every means has been exhausted to rule out hyperparathyroidism. (Cahn - 1952, Lvestedt - 1951).

In summary, the following may assist in diagnosis:

a) A persistently low serum phosphorus level.
b) High blood calcium level even when corrected for combined protein calcium.
c) Increased calcium excretion in the urine.
d) Kidney stones.
e) Persistence of the above findings.
DIFFERENTIAL DIAGNOSIS - Primary hyperparathyroidism in any stage must be differentiated from other conditions producing hypercalcaemia and in its skeletal form from other diseases accompanied by determinisation of the skeleton.

*Hypervitaminosis D* is the most important other condition producing hypercalcaemia. In a diagnostic sense, at least, it may almost exactly simulate hyperparathyroidism and can frequently be distinguished from it only by obtaining the history of ingestion of Vitamin D.

*Boeck's sarcoid* may produce bone changes, high serum phosphatase levels, hypercalcaemia and kidney stones. The absence of hypophosphataemia, of generalised decalcification, and the hyperproteinæmia in sarcoid are differential points (Albright & Reinfeldstein - 1948).

A bone disease to be the result of hyperparathyroidism must be generalised. However, whereas the resorption in the case of hyperparathyroidism may be generalised, it is possible for secondary lesions - "cysts" and tumours - to be localised. Under such circumstances, the superficial observer may have his attention called to the secondary lesions and miss the less conspicuous but more fundamental underlying generalised lesions.

*In osteoporosis* due to metabolic bone disease, the serum calcium and phosphorus values are normal. There is a normal or lower phosphatase level due to hypofunction of the osteoblasts (in the absence of liver disease). Calcium excretion in the urine may be increased markedly in the early stages, when it may give rise to kidney complications:
later stages of the disease it is normal or decreased. Hence, the hypercalcuria and the hyperphosphaturia disappear after the skeleton becomes demineralised in osteoporosis in contrast to hyperparathyroidism where they persist regardless of decalcification. The lamina dura is seldom absent in osteoporosis and the skull is almost never involved, whereas it is one of the first parts to become affected in hyperparathyroidism. Osteoporosis is the only metabolic bone disease which has a normal serum phosphatase level in the presence of markedly diminished bone density. (Albright & Reifenstein - 1948). There may be a hypercalcaemia in osteoporosis in the case where a large portion of an actively changing child's skeleton is suddenly put into forced disuse and the kidneys are unable to clear the serum of the excess calcium.

**Osteomalacia and Rickets** both present generalised decalcification and absent lamina dura, but deformities occur as a result of bending rather than fractures. Rickets has the additional differential point in that hyperparathyroidism does not cause wide and irregular epiphyseal lines. Whereas both osteomalacia and hyperparathyroidism with osteitis fibrosa generalisata have low serum phosphorus and high serum alkaline phosphatase levels, the serum calcium level is characteristically normal or low in osteomalacia and high in hyperparathyroidism.

**In osteogenesis imperfecta** the osteoblasts fail to form the normal amount of extracellular tissue - (i.e., too little bone matrix). The osteoblasts are increased in numbers, however, producing a moderate increase in the serum phosphatase level. Other tissues of mesen-
chymal origin are affected. The sclerae appear blue. The skull x-rays reveal a very thin skull, but not decaiofied, and these are enough to rule out hyperparathyroidism. The serum calcium and phosphorus will be normal and there will be no hypercalcuria or hyperphosphaturia. There probably will be a familial history of fractures.

Localised bone diseases can be differentiated from osteitis fibrosa generalisata by the demonstration of absence of decaification somewhere in the skeleton.

*Paget's disease* presents a "localised" skeletal involvement and there is a tendency to overgrowth of involved bones (vide infra). The serum calcium and phosphorus levels are normal, while the serum alkaline phosphatase is elevated more per unit of bone than it is in osteitis fibrosa generalisata. When the disease is advancing there may be hypercalcuria and even nephrolithiasis, but renal complications are less common than in hyperparathyroidism.

*Polyostotic fibrous dysplasia* has often been confused with hyperparathyroidism.

The characteristics of the syndrome are:

a) a disseminated osteitis fibrosa (both hyper and hypostotic) with a segmental distribution suggesting a neurologic or embryologic relationship.

b) areas of cutaneous and, rare, buccal pigmentation which have a distribution suggesting some connection between them and the bone lesions, and

c) sexual and somatic precocity in females but not in males. (Albright & Reifenstein - 1948).

Three points to differentiate this condition from hyperparathyroidism can be presented:

1) the bone lesions in polyostotic fibrous dysplasia are not generalised.

2) the bone lesions are hyperostotic as well as hypostotic, in hyperparathyroidism hyperostosis is most unusual, and
3) the serum calcium and phosphorus levels are normal in polyostotic fibrous dysplasia.

Both conditions can have a high serum phosphatase level.

Metastatic malignancy offers little difficulty in differential diagnosis. Areas of normal bone can almost invariably be found. The serum calcium may be high and there may be hypercalcuria and kidney stone formation. The serum phosphorus is usually normal, while the phosphatase level may be elevated. A primary site is to be looked for (e.g. breasts, prostate, kidneys, bronchus or thyroid).

Multiple myeloma may be most difficult to distinguish from hyperparathyroidism. The x-ray picture, although in most cases the lesions are more sharply demarcated, can be quite similar. One expects punched out areas in the skull rather than a diffuse "moth-eaten skull". When the serum calcium is high in multiple myeloma, so too is the calcium excretion in the urine and nephrolithiasis may be present. The high serum calcium level is usually coupled with a normal or high serum phosphorus level. In some cases, however, the serum phosphorus level is low, just as it is in hyperparathyroidism. (Albright and Reifenstein - 1948). The presence of plasma cells in the peripheral blood and hyperglobulinaemia or large amounts of Bence-Jones protein in the urine are strongly suggestive of multiple myeloma, while a positive finding in a sternal biopsy or puncture is pathognomonic. The serum phosphatase is rarely, if ever, elevated in myeloma, an important differential point.

Albright & Reifenstein (1948) state that lymphoma, benign metastasizing haemangeoma, Gaucher's disease, histiocytosis, chronic radium poisoning and renal osteitis fibrosa generabisata all might occasionally be mistaken for osteitis fibrosa generalisata.

According to Burket (1957) the oral findings, particularly those of the jaw bones, might be differentiated from Paget's disease, multiple myeloma, ameloblastoma and osteomalica.
Ameloblastoma is rarely bilateral, and it usually involves the mandible. The x-ray findings will permit a differential diagnosis. Biopsy studies may be required to differentiate it from fibrous dysplasia.

Keating (1947) states that hyperparathyroidism should be considered -

1) in all cases of cystic demineralising diseases of bone,
2) in all cases of renal calculi or of renal insufficiency of indeterminate origin,
3) in cases of unexplained polyuria and polydipsia, and
4) in cases of severe and unexplained gastro-intestinal symptoms.

TREATMENT - Primary hyperparathyroidism, it is agreed by most authors, is and will probably continue to be a surgical disease. A high calcium intake can prevent a negative calcium balance in hyperparathyroidism and even produce a strongly positive one, but it is the kidney complications which are the serious and irreversible ones. Furthermore, the hypercalcaemia persists in patients on a high calcium intake and with it the symptoms dependent on the hypercalcaemia per se. A high phosphate diet is not recommended because, although it may elevate the depressed serum phosphorus level, lower the elevated serum calcium level, and decrease the increased urinary calcium excretion, such therapy increases tremendously the already high phosphate excretion in the urine and must materially increase the danger of nephrolithiasis and nephrocalcinosis. X-ray therapy is ineffective (Keating - 1947).

Surgical removal of a parathyroid tumour or subtotal removal of primary hypertrophy is the only effective means of correcting the condition. If a patient has marked bone disease and a high serum phosphatase level, the complete elimination of the state of hyperparathyroidism at one sitting will lead to severe post-operative
tetany (Blum and Cahn - 1951). In the case of kidney damage with a
tendency to phosphate retention, one removes less parathyroid tissue
than one otherwise would. (Albright & Reifenstein - 1948).

"Parathyroid poisoning" (vide infra) should be averted and
further kidney damage prevented before operation. Unnecessary in-
gestion of calcium and phosphorus (i.e., milk and cheese) should be
avoided. Fluid should be forced. If there is any suggestion of para-
thyroid poisoning or renal insufficiency intravenous saline should be
administered.

Prognosis - the ultimate outcome of the treatment depends on
the extent of damage to the renal parenchyma. Renal insufficiency
may be progressive in spite of the cure of hyperparathyroidism (Chaudhry,
Hayes and Gorlin - 1958)

The prognosis of hyperparathyroidism which is uncomplicated by
bone disease is excellent. Prompt adjustment of serum calcium and
phosphorus values is the rule after successful surgical treatment. In
the case where osteitis fibrosa generalisata complicates the disease,
tetany is the danger. Both serum phosphorus and calcium levels fall,
and the elevated serum phosphatase will actually rise further. (Al-
bright and Reifenstein - 1948). These findings are explained by the
energetic osteoblastic activity that occurs. The hungry bones use
up the calcium and phosphorus more quickly than it can be supplied
and the tetany is due to the insulation of the bone with osteoblasts
from the body fluids, and it cannot give up its calcium and phosphorus
to these body fluids. Albright and Reifenstein (1948) state that it
is impossible to elevate the serum calcium with parathyroid hormone.

The problem is to keep the calcium in the blood from going into
the bones. A low phosphate intake is indicated. The less the phos-
phate the less the precipitation of calcium into the bones. Hence,
the patient should be on a high calcium, low phosphorus regimen.
In patients with very high serum phosphatase levels, the tetany encountered after the removal of a parathyroid tumor may be much more severe.

In time the bones become "filled in", the serum phosphatase falls; and the hypocalcemia and tetany disappear. The end state of the skeletal lesions is not normal bone, at least not within the first five years (Schneider - 1953). It must be remembered that, although the bone is resorbed in osteitis fibrosa generalisata, the framework on which to build bone is actually increased. Thus the marrow spaces are crowded out by tissue which is forming bone matrix. Now, when the parathyroid tumor is removed and all bone destruction is stopped, the repair process proceeds a great deal further than to the restitution of the normal amount of bone tissue. One encounters a very dense skeleton; the skull for instance, instead of consisting of two plates with diploe between is composed of a solid mass of bone (Albright and Reifenstein - 1948).

The bone lesions containing fluid always remain, while the "pseudo - bone cysts" become reorganized and eventually filled in with bone.

PARATHYROID POISONING - The danger signals which suggest the onset of parathyroid poisoning are rising serum phosphorus and non-protein nitrogen levels and a sharp fall in the urinary volume. About 17 mg/100 cc is the critical level of serum calcium above which poisoning is to be feared (Albright & Reifenstein - 1948).

The sequence of events leading to death may be as follows: an increasingly high serum calcium value, inspissation of blood dependent on the hypercalcemia, a resulting acute failure of kidney filtration, rapidly rising serum phosphorus and non-protein nitrogen levels, precipitation of calcium phosphate salts into the tissues and chemical death (Keating - 1947; Albright & Reifenstein - 1948).

SECONDARY HYPERPARATHYROIDISM - Secondary hyperparathyroidism
is a compensatory and probably essential adjustment by the body to the effects of some other primary condition, and probably occurs under the following circumstances:

(i) calcium deprivation due to diet,
(ii) pregnancy,
(iii) lactation,
(iv) rickets and osteomalacia, and
(v) chronic nephritis.

It should not be treated surgically. A remarkably effective regimen has been devised for improving the chemical and skeletal status of patients who have renal osteitis and renal rickets. This does not, unfortunately, modify the course or improve the outlook of the underlying renal disease. (Keating - 1947).
HISTORY - in 1876, at a time when bone diseases were not well understood, Sir James Paget read a paper entitled "ON A FORM OF CHRONIC INFLAMMATION OF BONES", before the Royal Medical Chirurgical Society of London. (Thoma - 1958). He described in detail the physical, gross anatomic, and microscopic examination of the bone disease. Cooke (1957) states that it was Professor Czerny of Freiburg in 1873 who suggested the term "ostitis deformans", meaning an enlargement and disfigurement of bones resulting from some inflammatory process. Yamane & Fleuchaus - (1954) report that the existence of the disease had been recorded prior to Paget's publication by Wrany & Otto.

AETIOTOGY - Nothing is known of the etiology of Paget's disease, but much speculation has appeared in the literature. The early changes in the bone marrow are, by certain authors, interpreted as an indication of an infection or at least an irritation. Weimann & Sicher (1955) suggest that the development of osteogenic sarcoma in Paget's disease indicates an increased proliferative activity of the medullary connective tissue of the bones which, in its ultimate exaggeration, leads to malignant growth. These authors regard classification of Paget's disease as an hyperplastic osteitis as not entirely unjustified.

Snapper (1943) considers Paget's original idea, of a chronic inflammation of the bone as the causative agent, as outdated and abandoned by practically everybody. Relation of syphilis to Paget's disease has been suggested without proof, and Snapper (1943) found Paget's disease rare in China where syphilis is very common.
If one defines a localised bone disease as one that is not generalised, Paget's disease is localised (Albright & Reifenstein - 1948). This is strong evidence against its being a metabolic or endocrinologic disorder. Paget's disease has a spotty distribution and this fact is at least consistent with an infection, a tumour, a trophic nerve disturbance, or a vascular lesion. All these have been mentioned in the literature (Snapper - 1943; Spilka & Callahan - 1958).

Edholm, Howarth & McMichael (1945) found that the blood flow through bones involved with Paget's disease is increased up to twenty times the normal, and Albright & Reifenstein (1948) declare that there is a lot to suggest that the fundamental disorder is vascular. The condition increases with age; there is a tendency to arteriosclerosis in general and to arteriosclerosis of these arteries supplying the involved bone in particular; there is a tendency for the condition to run in families (Ruston -1956), although Yamane & Fleuchaus (1954) discredit this familial tendency. However, if the disease is on a vascular basis, it must be due to an abnormality that leads to too much circulation rather than too little. Thus, the skin overlying an involved bone shows an increase in temperature (Snapper - 1943); when Paget's disease involves the skull there is a marked increase in size and tortuosity of the superficial arteries of the temporal region. As a cause for too much blood flow, one considers a shunt between the arterial and venous systems (Albright & Reifenstein - 1948). Moreover, when the condition is sufficiently widespread there is a decrease in arterio-venous oxygen difference, an increased total blood flow, and heart failure. Snapper (1949) regards the apparent relation between arteriosclerosis and Paget's disease as a possible coincidence; or there may be a common factor which influences the development of arteriosclerosis and of osteitis deformans in the same way.
Neurotrophic changes, as a cause, are impossibly according to Snapper (1943).

Whereas it has been established beyond all doubt that Paget's disease is not a manifestation of hyperparathyroidism, there have been several cases where hyperparathyroidism was complicated by Paget's disease (Albright & Reifenstein - 1948). Since Paget's disease is a very common condition, (3% of everybody over 40 has Paget's disease according to Schmorl -(1932) it is not unlikely that the occurrence of the two conditions in any one individual is pure coincidence. On the other hand, it is just possible that the presence of hyperparathyroidism predisposes patients to develop Paget's disease.

There is no dramatic improvement in a Paget's case by removal of parathyroid tissue (Snapper - 1943) and Albright & Reifenstein (1948). It has been claimed that in many cases the pains of a Paget patient can be alleviated by parathyroid hormone injections (Snapper 1943). Different diseases, however, can be favourably influenced by parathyroid hormone and the improvement obtained by this preparation should not be used as a point in favour of the endocrine aetiology of Paget's disease.

Snapper (1943) states that in North China avitaminosis is frequently encountered in severe forms and yet Paget's disease is rare. This author also reports a case of monostotic Paget's disease apparently as a result of trauma.

Finally, from a genetic viewpoint, Griffin (1949) groups Paget's disease as one among "four distinct conditions exhibiting pathological characteristics of genetic origin".

CLINICAL FINDINGS - The characteristic features of osteitis deformans are objective in nature and insidious in onset. There are some conflicting reports in the literature as to which sex is more often affected. Thoma (1954) and Koch - (1950) regard the disease more common in women than in men. Jaffe (1933)
and Newman, (1946), found no appreciable difference due to sex, while Brunner, (1939) found the ratio of males to females to be 19 to 7 and Byatt and Ash (1952) quote the ratio as 41 males to 24 females. It is commonly accepted by most authors that the disease occurs in middle life or later. However, Rushton (1956) presents a case of what he calls familial Paget's disease in the maxilla of a young woman. Cahn (1953) felt that, in this case, there was more resemblance to fibrous dysplasia than to Paget's disease. Newman (1946) has reported 3 cases below the age of 40 years, the youngest being 21 years old, and Jaffe (1933) saw a man of 48 years of age suffering from Paget's disease in whom the first symptoms had appeared 20 years previously. It certainly appears that about 55 years may not be a not uncommon age for Paget's disease to start in the maxilla in cases which are not familial (Rushton, 1956). Osteitis deformans reaches its greatest height of destructive activity in later life (Karpwich, 1958).

Burket (1957) states that incidence varies in different studies from 1:10,000 to 1:150,000 hospital admissions, and he estimates that if X-ray examination is made on all hospital patients evidence of mild Paget's disease would be found in 1:3,000 patients examined. Originally classified as a rare affliction, Paget's disease has a recent increased incidence paralleling the current trend towards frequent dental and medical X-ray studies. Schmorl (1932) states that about 3% of all patients over 40 may be found to show some changes suggestive of this condition. Stafne and Austin (1938) report that 23 of 138 cases of Paget's disease (one out of six) had evidence of the disease in the maxilla or the mandible.

Paget's original description of the disease is quoted by Thoma (1958) and has not been improved upon by anyone. He stated:
"The disease begins in the middle age or later, is very slow in progress, may continue for many years without influence on general health, and may give no other trouble than those which are due to changes in shape, size, and direction of the diseased bones. Even when the skull is hugely thickened, and all its bones exceedingly altered in structure, the mind remains unaffected. The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen. The spine, whether by yielding to the weight of the overgrown skull or by change in its own structure, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide, the necks of the femora may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk."

The patient presents an "anthropoid ape" appearance.

Paget's disease is a chronic, progressive disturbance in bone metabolism characterized by an initial phase of deossification and softening followed by a bizarre, dysplastic type of recossification and not related to functional requirements. The two processes may take place simultaneously, or they may alternate. In the early phases of the disease resorption is usually more prominent, but in the advanced stages atypical osteogenesis becomes increasingly pronounced, resulting in the progressive enlargement and deformity of affected bones (Albright & Reifenstein - 1945, Spilka & Callahan - 1958, Cook - 1957). The disease seems to go into spontaneous remission sometimes, or has periods of apparently long quiescence (Seigol - 1954).

Several authors have described a monostotic, or localized, form and a polyostotic or disseminated, form of Paget's disease (Schmorl
1932, Glickman & Glidden - 1942, Olech - 1952). The polyostotic form may involve many bones, either simultaneously or progressively. Albright and Reifenstein (1948) have a case in which every bone is involved. Whether the monostotic form represents an early or underdeveloped stage of the disseminated condition, or whether it may be associated with microscopic changes in other bones that escape clinical detection is open to question. Olech (1952) reports a case of monostotic Paget's disease of the mandible and holds that this condition is a distinct entity. It is interesting that in Paget's disease the joints usually remain free. However, even if the osteitis fibrosa itself does not attack the joints, in some cases the picture is complicated by a coexisting osteo-arthritis (Snapper - 1943).

Paget's disease has a spotty distribution. The number of bones involved varies in different cases, but it has a predisposition for that part of the skeleton which is most subject to stresses and strains. (Weinmann & Sicher - 1955), (Albright & Reifenstein - 1948). Thus, the sacrum is the bone most often involved; the lumbar vertebrae are more often involved than the thoracic, and the thoracic more often than the cervical; the lower extremities more often than the upper. (Snapper - 1943). Why is the skull so often involved? The answer is not apparent, but even here stresses and strains play a part where the distribution of the involved area of the skull is apparently determined by the pull of the temporal muscles. (Albright & Reifenstein, - 1948) and (Siegel - 1954). There is apparently simultaneous involvement of many bones. Whether the disease first remains localized in one bone and rapidly progresses to other bones cannot be determined (Yamane & Fleuchaus - 1954).

In Paget's disease there is an increased turnover of bone and the life cycle of the newly formed bone is short. This must be the reason why the calcium content of the bone is low. (Snapper - 1943).
It follows that the calcium content of the Paget bone is low only during the active stage of the disease. During a remission calcification of the newly formed bone can go on, and in some cases even hypercalcification or sclerosis of the bone may result. Thus we see variations in bone density from osteoporosis to osteosclerosis in Paget’s disease. It is clear that the initial lesion is a localized factor causing bone destruction, which has no respect for structural requirements. (Albright & Reifenstein - 1944). Jacobs (1945) states that it is clear that, occasionally, a patient presents himself with circumscribed radiolucencies in the calvarium of the skull and a marked osteoporosis of the jaws. These cases when followed for years eventually develop typical Paget’s disease. Rushton (1948) presented a case with these characteristics, and it is Paget’s disease of the type, called osteoporosis circumscripta. In this condition there is a marked decrease in the density of the bone of part of the calvarium, the borders of the affected area being irregular and sharply demarcated from the normal bone, but there is rarely any thickening of the bone.

Osteoporosis circumscripta was first described by Schuller in 1926, and its association with Paget’s disease was suggested by Sosman (1927) and supported by later observations. In his view osteoporosis circumscripta represents the absorptive-destructive phase of Paget’s disease with the productive phase held in abeyance. The association of osteoporosis circumscripta of the cranial bones is of particular interest as it has been reported several times. Kasabach and Gutman collected five cases from the literature and added two of their own (1937) and Elkeles (1947) published another as did Rushton in 1956.

In long bones, the bone repair usually occurs almost simultaneously with the bone destruction, and one seldom has the opportunity to see one process divorced from the other. (Albright & Reifenstein -
Knaggs (1925) described three typical stages in the skull:

1) **Vascular Stage.** The bone is red with very vascular connective tissue marrow.

2) **Stage of Advancing Sclerosis.** Sutures of the vertex are obliterated. Outer surface is smooth, but perforated by multitudinous minute apertures. The inner surface is similarly but less obviously porous. Bone contiguous to the inner surface of the vault is very condensed for a thickness of \( \frac{1}{4} \) to \( \frac{1}{2} \) inch, but is still finely porous. Outer surface is a thin line of condensed porous bone.

3) **Stage of Complete Diffuse Sclerosis.** The sclerosis has advanced across the diploic zone.

Increase in thickness of the bone is almost entirely outward. The earlier sclerosis of the inner portion of the vault may be explained by the compression of its interstitial substance owing to the resistance of the cranial contents to the inward expansion of the enlarging bone (Knaggs - 1925).

Albright & Reifenstein (1944) explain that in the skull, the reason why more osteoporosis circumscripta is encountered, than in other bones, is because there are fewer stresses and strains and hence less osteoblastic stimulation to over-production of bone. These authors state, that if a bone containing Paget's disease is immobilised as after a fracture, the following events occur:

1) Lack of stress and strain, in all probability abated by the alarm reaction of Selye (Ordinarily such a curtailment of tissue formation due to injury may be overlooked, but in Paget's disease, where bone formation is rapid and extensive, any influence that suppresses it is
magnified), curbs the overactivity of the osteoblasts.

2). The initial disturbance causing bone destruction persists and there results a marked imbalance between bone destruction and formation.

3). The increased calcium and phosphorus coming from the bone leads to hypercalcuria and hyperphosphaturia, the capacity of the kidney to excrete calcium may be overtaxed with a resulting hypercalcaemia.

The above chain of events took place on two patients, reported by these authors, who sustained fractures in bones containing Paget's disease.

Although, in these cases, the broken bone becomes resorbed as a whole (Seigel - 1954), the fracture site shows a rapidly forming and calcifying callus (Snapper - 1943). Albright & Reifenstein (1944) attempt to explain this by the hypothesis that some local influence stimulating osteoblasts is set loose at the site of fracture.

Macroscopically, the involved bone is thickened and presents a rough, uneven surface. Long bones show considerable bending. The compact bone is replaced by spongy bone of varying density, and the marrow cavity may be narrowed. (Muir - 1951) and (Weinmann & Sicher 1955). If the cranium is involved it shows a progressive enlargement and the thickness of the calvarium may be 3 or 4 times the normal. The whole bone comes to have a fairly uniform porous appearance, while it shows a degree of softening which may be so marked that the bone may be cut. The density and arrangement of the diploe vary greatly. Areas of sclerosis and porosis may be numerous.

Weinmann and Sicher (1955), raise an interesting point with regard to the bending of long bones and the deformity of the cranial base. They state that these changes are described by certain authors
as if there were an actual bending or moulding of the softened bones. Now, Albright & Reifenstein (1944), state that due to the rapidity of bone formation, complete calcification of the new bone cannot take place. Therefore, a greater part of the newly formed bone tissue remains in the osteoid, non-calcified stage, and gradually the whole original structure of the bone is replaced by the abnormally proliferating, calcium poor Paget bone. However, Weinmann & Sicher (1955) hold that there is no reason to assume that bones in any stage of Paget's disease would consist entirely or mainly of osteoid tissue, which alone would make a mechanical deformation possible. They state that only a combination of Paget's disease with osteomalacia could account for an actual plasticity of bones, and that it seems that, at least in some cases, the bending of long bones is due to a combination of apposition and resorption. This interpretation is supported by observation of a curved and elongated tibia in cases in which the fibula is not involved by Paget's disease and has remained straight. An actual bending can never lead to lengthening of a bone, while curving resulting from growth changes necessarily entails elongation.

To the author, it seems that both these theories could account for the deformity of Paget bone. It may be that the bones are more susceptible to plastic deformation despite Weinmann & Sicher's (1955) dogmatic statement. Snapper (1943) states that Paget bone weighs less than a normal bone, although the latter may be smaller in volume.

When the whole picture of deformities develops the body height diminishes (Knaggs -1925; Snapper - 1943).

If the base of the skull is involved, it sometimes shows a characteristic deformity, bulging far into the cranial cavity (convexobasia), with severe damage to the brain as a consequence. (Weinmann & Sicher - 1955).

Occasionally a spontaneous fracture is the first sign of the disease. These fractures are nearly always transverse, and the
sites of predilection are the long bones, but compression fractures of the spine are also observed. (Snapper - 1943)

Bone in osteitis deformans is hyperaemic and by means of an electric skin thermometer, Snapper (1943) found the temperature of the skin above the diseased bone to be always 1.5 to 3.8°C higher than the skin of the normal side.

Symptomatically, Paget's disease is characterised by pain in the affected bones that may be described as rheumatic, gouty, or neuralgic; it is not accompanied by fever. No characteristic conditions of urine or faeces have been found. (Knaggs - 1925). The initial presenting symptoms may be obscure. "Dizzy spells" (Winslow - 1955) and tinnitus and moderate to total deafness (Curr - 1949; Spilka & Callahan -1958), have been reported. These are apparently due to involvement of the petrous temporal bone (Snapper -1943). Pressure on the involved bones at times causes exquisite pain and is usually most severe after the patient has stood for some time. (Burket -1957). Snapper - (1943) concludes that these pains are very seldom due to compression of nerves or nerve roots, even though narrowing of the foramina at the base of the skull occurs. He states that only rarely has atrophy of the optic nerve, presumably due to destruction of the optic foramen by proliferating osteitis deformans, been described. Occasionally the contours of the foramen magnum are changed and become pear-shaped or even heart-shaped.

Extensive arteriosclerosis is remarkably often seen in patients with Paget's disease, even when they are relatively young (Knaggs -1925). In contrast to Paget's (1976) statement mental abnormalities do occur. (Thoma - 1954).

BLOOD CHEMISTRY - The serum calcium and phosphorus are usually normal in Paget's disease, although there is a slight tendency for
the serum phosphorus to be slightly elevated (Albright & Reifenstein - 1948). The serum phosphatase level is higher per unit of bone disease in Paget's disease than in any other condition. This agrees with the marked overgrowth of bone which one finds in the disease. In the normal individual, values range from 1 to 4 Bodansky units, while in this disease we find values from 50 to 135. (Weinberger - 1954). In initial cases of monostotic Paget's disease, the phosphatase content of the serum may remain within normal limits - (Snapper - 1943).

URINARY ANALYSIS - Albright & Reifenstein (1948) report that when the disease is progressing, calcium and phosphorus excretions in the urine may be increased and they state that urinary calculi are not infrequent findings.

JAWS AND TEETH - Cahn (1951) states that many Paget patients complain of atypical facial neuralgia. Koch - (1950), Cooke - (1957), Hamilton - (1948), and Winslow - (1955) all support Cahn in their case reports.

Stafne (1938) found definite evidence of the disease in dental x-rays of 17% of the patients presenting lesions in other parts of the body. Novak and Burket (1944) reported several cases in which symptoms connected with the jaws led to the detection of osteitis deformans in the calvarium also. Usually the maxilla is involved and rarely the mandible. Both jaws can be involved together, (Cooke- 1957; Stafne - 1946). Thoma, Howe and Wenig (1945) and Olech (1952) report Paget's disease of the mandible as diagnosed by biopsy.

It may be possible that there is a tendency for the jaws to be affected particularly early. Paget's disease may occur in the maxilla and mandible without pronounced clinical enlargement. It is possible for microscopic bone changes to escape detection by the x-rays, (Glickman & Glidden - 1942). In the early stages, the normal trabecular pattern is converted to a fine lace-like pattern, the lamina dura around the teeth in the involved regions may disappear, and, in
many cases marked areas of resorption may be noted around the apical ends of the roots (Karpawich - 1958; Morgan et al - 1956).

In the jaws, the bone becomes enlarged and produces facial deformity with prosthetic difficulties. Progressive enlargement of the maxillary tuberosities occurs, so much so, that in some cases the patient is unable to close his mouth properly. Repeated fracture of a maxillary denture may occur because of these changes in the bone. In a middle-aged patient, these occurrences should suggest osteitis deformans. The chief complaint of a patient may be inability to wear dentures because the jaws "keep growing". (Stillman - 1951). Rushton (1956), thinks that an expansion of the maxilla may occur relatively early without evidence of sclerosis. In the late stages deformity progresses and dense, sclerotic bone, frequently surrounded by areas of osteoporosis, appears.

Cook (1957) presented 15 interesting case histories of Paget's disease; ten men and five women. Half the patients were below the age of fifty, including four in the fourth decade and one in the second. The maxilla was involved in all patients and the mandible in three patients. The symptoms most frequently present were facial deformity and thickened alveolar ridges. Dentures had to be eased or remade at frequent intervals, and where they caused pressure on the gingivae, necrosis of the underlying bone sometimes followed. Seven patients complained of an atypical facial neuralgia; it was intractable. Three were deaf. One patient experienced persistent bleeding after an extraction, and another had difficulty in having an ankylosed tooth extracted, and the extraction was followed by a severe, dry socket. Only two patients had their disease diagnosed by symptoms referable to other parts of the body before their jaws were involved. Burket (1957) states that the oral lesions are at times
exquisitely painful and may require alcohol injections of one or more divisions of the fifth nerve. Trismus was described by Spilka & Callahan (1958) in one of their patients who is suffering from Paget's disease, one of the sites of which is in the mandible. When the maxilla is involved and not the mandible the patient may present a tapering or inverted triangle face. There may be a marked protrusion of the upper lip, and the palate may be broad. The mucosa of the maxilla becomes stretched, and numerous fine capillaries become visible.

Rastall (1950) reported a case where the antrum was obiterated by Paget's disease and Spilka & Callahan (1958) recorded acute osteomyelitis superimposed on osteitis deformans of the mandible. Shklar & Meyer (1958) presented an extremely rare finding in a case of giant cell tumour of the maxilla in an area of osteitis deformans. Jaffe (1953) has reported a case of giant cell tumour arising in a skull involved by osteitis deformans.

The author has had the opportunity of seeing the mandible involved before, or if not then, much more rapidly than the maxilla, in four female patients. Two of these cases presented some slight radiographic changes in the maxilla. One case had the mandible affected and no evidence of the disease in other bones.

The teeth are frequently affected by the involved surrounding bone. Koch (1950; Burkett 1957; Rushton 1948; Hamilton 1948; Byatt & Ash 1952; Morgan et al 1956; and Weinberger 1954;) report hypercementosis in Paget's disease. Cahn (1948) believes that hypercementosis in Paget's disease is not coincidental. Weinberger (1954) states that the cementum in Paget's disease cannot be differentiated from the original cementum, although Morgan et al (1956) have observed that the cementum is inclined to be laid down in a series of irregular deposits, not as a smooth layer as is ordinarily seen in the deposition of cementum in hypercementosis. The author has noted hypercementosis in the hypotrophic type of Paget's disease in the maxilla. This
type of Paget's disease displays a reticulated or orange skin-like appearance of the trabeculations.

Some authors report resorption of the roots of teeth in this disease. (McCall & Wald - 1947; Morgan et al - 1956; and Karpawich - 1958). Burket (1957) describes a more than normal pulpal calcification and loose teeth due to bone destruction.

Thoma, Johnson and Cascario (1944) state categorically that if the teeth are present in osteitis deformans, they do not migrate as in acromegaly; the expansion of the maxilla occurs on the outside and inside of the dental arch. Glickman & Glidden (1942), Rushton (1948), and Yamane & Fleuchaus (1954) report diastema and migration of teeth. The author has seen some cases presenting teeth with violent lingual inclination, rotation and spaces. Although some of this malposition may be due to loss of interproximal contacts due to loss of teeth, it seems reasonable to include the bony enlargement as a contributing factor.

X-RAY FINDINGS – The X-ray picture of the bones shows characteristic changes long before deformities appear. Paget bone usually shows:

a) thickening and broadening of the cortex
   (hyperostosis)

b) modification of the structure of the cortex
   (remodelling)

c) increased transparency of the bone
   (porosis)

The thickening of the cortex may lead to narrowing of the marrow cavity. Frequently new formation of bone takes place at the periphery also, by way of an ossifying periostitis. The marrow cavity
becomes irregular and in the cortex a new and atypical framework of thick and gross bone trabeculae is formed. The architecture of the bone is remodelled, (Snapper - 1943), and loss of the normal architecture is perhaps the cardinal radiographic symptom. Irregular trabeculation with many elongated, rhomboid spaces of small or large dimensions appear. As a rule, only part of the bone is affected, the remaining parts being normal. The early latent osteitis deformans presents itself radiographically as a radiolucent, ill-defined, demineralized area or areas, with or without regions of increased density, sclerotic bone, and cortical thickening. Hyperostosis is produced by large deposits of porous bone evidenced by a widening and an increase in size of the trabeculae, with areas of increased density. These areas produce the characteristic "cotton-wool" appearance of the bone. Exceptionally, the x-ray picture of a sclerotic Paget bone may resemble a late stage of chronic osteomyelitis. (Snapper - 1943).

Often the x-rays of the curved long bones show one or more short fissure-like, transverse lines of rarefaction in the cortex, always situated on the convex side of the bone. These clear lines may represent incomplete fractures and may occur following slight trauma. After an additional slight insult, such an incomplete fracture may go to a complete transverse fracture (Snapper - 1943).

Characteristic are the changes in the skull. In the very early cases a large rarefied area may be the only change, generally spoken of as osteoporosis circumscripta. In other cases there is marked thickening of the calvaria, with the "cotton wool" appearance. This is hardly ever found other than in Paget's disease.

In the dental X-ray, Weinberger (1954) has observed two distinct patterns:

**Type one** - The bone pattern has a reticulated or orange-skin appearance. The trabeculations are finely meshed and run in one direction, from the distal superior aspect to the mesial inferior.
Type two - Areas of rarefaction and condensation are present as well as hypercementosed roots.

Type one is called the osteolytic or rarefying phase or hypotrophic period. One patient observed by this author has kept this pattern for five years.

Type two is the hypertrophic stage. Glickman & Glidden (1942) present x-ray criteria in the recognition of Paget's disease in the mandible and maxilla:

a) Alteration in size and shape of the marrow spaces and trabecular patterns.

b) Replacement of the clear-cut heterogeneous trabecular pattern of the maxillae and the comparatively regular arrangement of the trabeculae of the mandible by a hazy diffuse meshwork of closely knit, fine, linear, trabecular markings; absence of demarcation between the cortical and cancellous regions, and the presence of scattered circumscribed, sharply demarcated areas of bone rarefaction and condensation.

c) Alteration in peripheral contour.

d) Absence of clearcut lamina dura in relation to root surfaces.

The appearance of osteosclerosis may be a relative matter, inasmuch as bone may sometimes be sclerotic only in regard to the surrounding osteoporosis. Often large areas of periapical rarefaction occur and must not be confused with infective periapical rarefaction. It has been noted that the jaw picture may antedate by several years the radiographic appearance of the disease in the rest of the skeleton.

The earliest change observed by Cooke (1957) in dental x-rays was an osteoporosis that was most severe around the teeth. The trabeculae became less well-defined until a definite radiolucent area
formed in most instances. The lamina dura was lost and the teeth appeared to be floating on the bone rather than being supported by it. In this osteolytic stage, resorption of the apices of the teeth was observed in two patients.

HISTOPATHOLOGY - The histologic changes in Paget's disease are changes of the bone tissue itself and of the bone marrow. Since the local destructive factor has no respect for the mechanical requirements of the skeleton, the changes in the bone can be characterized as a combination of destruction and repair both of which occur without relation to the statics or the dynamics of the involved bone. The result of this oscillating transformation of the bone is always an enlargement, but not always an increase in the volume of bone tissue. The change in the marrow progresses through the stage of serous inflammation to fibrosis. The change however, is reversible (Weinmann & Schier - 1955).

The confusing variability of a Paget bone is mainly due to the combination of three variable factors:

a) variable ratio of osteoclastic and osteoblastic activity in a certain area,

b) variable speed of the destructive and reconstructive processes,

c) frequency of local remission of the pathologic process, followed sooner or later by resumption of the active changes.

Local differences in the ratio of osteoblastic activity are responsible for the development of sclerotic or porotic areas, often in closely adjacent areas of the same bone. Resorption proceeds in attacks which, after a variable time, are reversed into periods of apposition. These sequences of destruction and repair being repeated in the same area leads finally to the development of mosaic
bone, one of the characteristic features of Paget's disease as described by Schmorl (1930) and Knaggs (1925). The lines separating one bony area from the other are mostly reversal lines, rarely resting lines. They are wide and stain dark blue in haematoxylin-eosin stained specimens. (Weinmann & Sicher - 1955). The mosaic bone pattern may be interpreted as a graphic record of repeatedly interrupted alternating periods of bone resorption and formation. This process prohibits the formation of trabeculae composed entirely of regularly lamellated bone.

The disease shows evidence of excessive lacunar resorption and apposition of an inferior type of bone. An active area is characterized by the presence of numerous osteoclasts and osteoblasts. Sometimes, osteoclasts and rows of osteoblasts alternate on the surface of one trabeculum. The marrow in such areas is always of the fibrous variety (Gluckman - 1943). The presence of cavelike indentations along the periphery of bone trabeculae is only morphologic evidence of bone resorption. Osteoclasts are found in greatest numbers in the zones of active bone formation and are infrequent where there is no osteogenic activity. Where osteoblasts are active, the bone trabeculae are often covered by a layer of osteoid tissue of variable thickness (Weinmann & Sicher - 1955).

During the time of remission, the bone in a wide area may be aplastic and in such areas the bone marrow may revert to the fatty type. Sooner or later the period of inactivity comes to an end and destruction of the resting bone starts again. Weinmann & Sicher (1955) describe the early stage of recurrence by tunnelling resorption of the bone trabeculae, removing first their central part. Such newly formed marrow spaces are filled with fibrous marrow which replaces the fatty marrow in the zone of renewed activity.
The type of bone formed varies considerably and is probably dependent on the speed of its formation. Thus, we see that, in zones of high activity, characterized by a great number of osteoblasts, bone of the immature, coarse fibrillar type is laid down. The degree of immaturity, which varies, can be determined from the degree of irregularity in arrangement of the osteocytes. The more rapid formation of bone tissue is also responsible for a lag in calcification, resulting in formation of a rather wide layer of osteoid tissue. The failure of calcification may also be correlated with the total amount of bone formed in the entire skeleton. (Weinmann & Sicher 1955).

In periods preceding remission or during remission, when bone formation is slow, mature lamellated bone is laid down. The irregular appearance of the mosaic bone is due not only to its composition of fragments formed at different times, but also to the differences in the level of differentiation of the fragments. The contrast between pieces of immature bone and of lamellated bone is striking.

In the maxilla and mandible, Glickman (1943) remarked that the periosteum cannot be sharply demarcated from the underlying newly formed bone. The periosteum undergoes gradual changes so that the connective tissue and bone are fused by a series of gradual alterations in cell and intercellular substance. The elliptical cells of the periosteal connective tissue are altered in such a way that the connective tissue cells ultimately become osteocytes. Although from a morphological standpoint, there is a stage in this transition which conforms with the polyhedral contours characteristic of osteoblasts, this stage merely represents a transitional phase and is in no way separated from the numerous other stages. The intercellular fibres which surround the elliptical connective tissue cells undergo an associated metamorphosis concomitant with the cellular changes and become a moderately coarsely granular bone matrix in which osteocytes are contained. Thoma (1954) also believes that periosteal new
bone formation occurs, though it is disputed by some writers. Schmorl (1930) believes it to be very active in the acute part of the cycle. According to Pick (1933) it is formed as lamellae parallel to the periosteum.

The clear-cut demarcation between the subepithelial connective tissue lining the maxillary sinus and underlying bone is in sharp contrast with the findings described above in relation to the periosteum, surrounding the periphery. The connective tissue cells and fibres of the sinus floor are horizontally disposed and lie in close apposition with a smoothly linear, sharply outlined bone margin (Glickman - 1943). The histologic picture of the marrow is not changed at first, save by exudate. Only in places where there has been much resorption and in parts where there is great mechanical stress is there a fibrous proliferation from the endosteum (Thoma-1954). Throughout the marrow, regardless of its nature, the blood vessels are markedly dilated, which would indicate that an active exudation is taking place. Diapedesis of red cells into marrow is not uncommon. Small haemorrhagic areas with scattered areas of blood pigment were noted by Glickman -(1943) Small zones of myeloid haematopoiesis are occasional findings. The marrow also contains many osteoclasts, scattered calcific nodules, and fragments of necrotic bone. Calcification of the media in the arteries and arteriolar sclerosis was also noted by Glickman - (1943). Knaggs (1925) believes that lymphocytic infiltration of the marrow is a rather constant finding, and fibrosis of the marrow seems to be preceded by a peculiar oedema. It is controversial whether the medullary changes are primary or secondary changes in the bone tissue. Bones of the skull which contain cellular marrow show primary changes in arrangement and size of the blood-forming cells. The fibrosis of marrow seems to follow the first destructive bone changes. In long bones
the youngest resorptive spaces are already filled with fibrous marrow. (Weinmann & Sicher - 1955)

Thoma (1954) quotes a case studied by Rushton (1938). Two teeth were examined histologically. They were from a patient with Paget's disease and displayed enormous over-growth of cementum, but considerable resorption had taken place previously and at repeated intervals. This cementum was poorly differentiated. The pulps were replaced by secondary dentine containing a few tubules, mostly derived from the odontoblastic layer, and some acellular calcified material. Thoma (1954) also presented some teeth he examined, with similar findings.

COMPLICATIONS - Paget's disease in itself does not endanger life and most of the patients with osteitis deformans reach old age. The disease has been known to last as long as 20 to 30 years. (Burket - 1957). Paget patients often show premature and advanced arteriosclerosis; small wonder that many of them seek medical advice for heart failure, renal insufficiency, hypertension, etc. These conditions, however, have no aetiological connection with Paget's disease (Snapper - 1943). Muir (1951) states that an effect like arterio-venous communication is brought about by the abnormal vascularity of the bones; cardiac output is much increased and there is marked tendency to cardiac failure. The occurrence of forms of dementia and cases of compression of the spinal cord due to collapse of one or more vertebrae affected by osteitis deformans have been mentioned in the literature.

Snapper (1943) quotes 10% of his patients as suffering from renal stones. The possibility that the decalcification of the skeleton which must always accompany Paget's disease may be a reason for the frequency of renal stones cannot be denied. On the other hand, it should not be forgotten that nephrolithiasis usually brings the patient to the radiologist.
As the site of predilection for Paget's disease is found in the sacrum, pelvis and lumbar spine, an x-ray examination for renal stones gives the best opportunity for the discovery of Paget's disease. Thus, the simultaneous occurrence of renal stones and osteitis deformans may be coincidental.

Fractures occur in the disease. Albright & Reifenstein (1944) warn that when a patient with Paget's disease is immobilised, the danger of a so-called "chemical death" exists. To control this, all that is needed is a low calcium diet and sufficient fluid by vein, if necessary to control the serum and urinary calcium concentrations. Immobilisation should be kept to the absolute minimum, and mobilisation should be begun as early as possible, not only to avoid a chemical death, but to avoid extreme atrophy of the bones.

Deafness appears to be due more to the involvement of the bony labyrinth than to infringement of the nerve (Snapper - 1943). Loss of sight has been reported by Thoma (1958) as a complication. He quotes Cahn's (1941) case of tic douloureux associated with Paget's disease.

Anaemia may occur in the later stages of Paget's disease when a number of the bones are involved, especially the vertebrae, and the marrow spaces extensively fibrosed (Custer - 1949).

Karpawich (1958), reported a case of Paget's disease with osteogenic sarcoma of the maxilla. Spilka and Callahan (1958) and Clompus (1943) and Kienboch and Selka (1935) all reported cases of sarcoma developing in Paget bones. Muir (1951) regards osteogenic sarcoma as rare after the age of 30, except in association with Paget's disease of bone. Seigel (1954) quotes that in 6 to 10% of cases death has resulted from osteogenic sarcoma. Snapper (1943) regarded 10% as an overestimation, especially in these times where x-rays have enabled us to diagnose many more cases of slightly to moderately advanced Paget's disease. However, there is a definite relationship between Paget's disease and osteogenic sarcoma. Karpawich (1958) states that the chief
characteristic is a malignant change of the bone-producing cells, although bone formation and destruction may go on in the same tumour. Changes which may be found are bone destruction, periosteal reactions, and soft tissue changes. These may be manifested by the moth-eaten appearance of the surrounding bone, the radial spicules of bone giving it a "sun-ray" effect, or a periosteal reaction which may be noted in adjacent areas.

Osteogenic sarcoma arising in Paget's disease gives evidence of the malignant change by the rapid appearance of a new mass. The lesions may show both bone destruction and new bone formation. Its treatment is very unsatisfactory. The prognosis is poor, particularly in patients beyond the age of 50 years. The case with a long history and a well differentiated and localised tumour made up of adult tissue has a greater degree of hope than the one whose history shows it to be rapidly growing and whose histology denotes a very undifferentiated osteolytic tumour.

The electric tests of teeth involved may be found to be negative. (Thoma - 1958)

In the operative treatment of Paget's disease in the jaws there is a very real danger that operation will be followed by necrosis, the reason being that if some of the avascular, sclerosed bone masses are left exposed to infection their death and extrusion are inevitable. Even the ordinary extraction of teeth from such patients may be followed, as Burkett (1957) points out, by the establishment of sinuses which will not heal. Osteomyelitis is a very real danger.

Rushton (1948) advocates, in such cases, not to leave any sclerosed bone near the surface and to suture with extreme precision.

DIAGNOSIS - After an oral and regional physical examination, apical and occlusal X-rays are taken. These, plus paranasal sinus and lateral and postero-anterior jaw films, must surely be termed prerequisites to the diagnosis of any osteitic lesion whose identification is not immediately apparent. These should be followed by an adequate clinical
history, complete physical examination, skull and total bone survey, repeat jaw films, blood chemistry findings and biopsy.

DIFFERENTIAL DIAGNOSIS -

ORAL AND REGIONAL PHYSICAL EXAMINATION - This usually reveals nothing positive in early osteitic deformans. There is no tumescence, parasthesia, loosening of teeth, or lymphadenopathy. This procedure should however, eliminate such local factors as tooth abscesses, periodontal abscesses, granulomas, and pericoronary infections. One may have to exclude infective hyperplasia of the bone (condensing osteitis), thermal hyperplasia of the bone, or cementoma (Weinberger - 1954), which may be displayed in the initial x-rays.

With these factors that are of distinctly local nature having been eliminated, the other causalgias that might produce such an x-ray picture must be considered.

AN ADEQUATE CLINICAL HISTORY - would suggest the routine elimination of such bone conditions as rickets, osteomalacia, disuse osteoporosis, senile osteoporosis, postmenopausal, osteoporosis, parathyroid administration, and overdosage of vitamin D.

GENERAL PHYSICAL EXAMINATION - would readily distinguish those osteolytic disease which evidence gross systemic pathologic findings. This would include sprue, Enoch's sarcoid, pancreatic steatorrhea, Cushing's syndrome, acute osteomyelitis, carcinomatosis, sarcomatosis, lipid storage diseases (Gaucher's & Heimmann - Pick), and Hand-Schuller-Christian disease.

SKULL AND TOTAL BONE SURVEY - is a primary rule and is carried out whenever a bone disease of undetermined etiology is identified. Certain neoplastic lesions can be discounted immediately on the grounds that, whereas they may be osteolytic in character, their x-ray presentation simply does not resemble the picture of Paget's disease. This group would include odontogenic cysts (including follicular and dentigerous),
myxomatous cysts, cavernous angiomas, ameloblastomas, and central mixed tumours, all of which produce defects that are cystic or polycystic in appearance and are often multiloculated, as well as chondromas, giant-cell tumours, and myxomas, which are, generally speaking, circumscribed, solid and well defined.

This is not to negate the importance of biopsy and blood chemistry findings in such cases, for all lesions which fail to heal should be biopsied, and no diagnosis of bone defects should be made on the basis of x-ray findings alone. They are not, however, readily confused with Paget's disease.

Also readily eliminated are osteopoikilosis, which is characterised by a speckled appearance of bone, widely disseminated, round or oval, and distinctly circumscribed spotty shadows of calcium density, and leontiasis ossea, which involves the base of the skull and the facial bones, primarily, and has a homogeneous sclerosis, no rarefaction, and no cotton wool appearance.

Of those remaining diseases whose x-rays commonly tend to simulate osteitis deformans the following radiologic and physical factors should be considered:

1) Primary hyperparathyroidism produces a generalised type of osteoporosis or foci of osteitis fibrosa with or without cysts. In addition to a host of physical findings absent in Paget's disease, including muscular hypotonia, polydipsia, and polyuria, this disease gives an x-ray picture of diffuse osteoporosis and, if cysts are present, they are multiple, trabeculated structures with a spongy appearance. Giant-cell bone tumours may present themselves and the disease, unlike Paget's involves the entire skeleton. The periosteal new formation of bone, frequent in Paget's disease is absent in hyperparathyroidism. In Paget's disease the trabeculae start nowhere and end nowhere;
in osteitic fibrosa generalisata there may be extreme resorption, but those trabeculae that are left are in good mechanical arrangement.

2) Chronic or "dry" osteomyelitis, which causes expansion of bone and is not accompanied by suppuration, must be differentiated. It shows mottled osteoporosis with maximal cortical involvement. The infectious process seems to extend in all directions from the periosteum and cortex. Sequestration is seldom seen. Clinically the cardinal signs of soft tissue inflammation often precede radiographic evidence.

3) Polyostotic fibrous dysplasia usually involves many bones but it may be monostotic. Unlike Paget's disease it is a disease of childhood, although the disease areas never reossify and it may not be discovered until adult life. There is a substitution of the bone substance by dense fibrous connective tissue. Radiographically, there is an irregular fibrocystic appearance with coarse loculations and honeycombing, and it commonly shows more perimeter than Paget's disease. It is sometimes distinguished by its association with endocrine disturbances and skin pigmentation in the pattern of Albright's syndrome.

4) Fibro-osteomas vary greatly. They may show either radiopacity or a circumscribed radiolucency with an osteitic margin; on the other hand, they may be cystic. There are usually islands of greater density due to partly calcified ostecoid tissue, and the ossifying fibrous tissue may give an irregular, granular appearance. They are almost always well defined in contradistinction
to osteitis deformans.

5) Osteogenic sarcoma (including osteosarcoma, reticulum-cell sarcoma, Ewing's sarcoma, chondrosarcoma, etc.) generally presents periosteal formations which appear as rods or lamellae extending vertically from the bone into the edges of the tumour, giving the characteristic "sun-ray" effect. There is always lack of a definite outline of demarcation of the tumour because of its invasiveness, but the deossification of bone is compensated for by the formation of new bone at the periosteal surface, away from the tumour. (It should be noted that all tumours eventually present masses and often produce asymmetry, loosening of teeth, and paraesthesia while osteitis deformans evidences only soft tissue swelling).

6) Metastatic carcinomas occur late and are usually secondary to primary tumours of the prostate, breast, lung, thyroid, parotid gland, and lip. The appearance is usually that of spongiosclerotic localized new bone formation, and the skull may show multiple demarcated areas of sclerosis. The increase in bone density is compact and fairly regular in shape, as contrasted to the bizarre disorganized trabeculation of Paget's disease, and multiple punched-out osteolytic areas may be seen throughout the skeleton.

7) Multiple myeloma (plasmacytoma) has characteristics similar to Paget's disease, and, again requires biopsy for definite diagnosis. Radiographically, the individual lesions appear more cystic, nodular, and well circumscribed. There is bone destruction but no bone formation. Most significant however, is the fact that the lesions are multiple and are found over the entire skeleton. Affected areas, particularly the mandible, are characteristically rounded,
multiple, and grape sized. They may enlarge and merge, forming oval, punched-out or elongated rarefied distribution.

Once the differentiation has proceeded to this state, wherein a presumptive diagnosis may be approached, the next logical step should be a body fluid analysis.

A complete blood and urine work-up with emphasis upon the results of the blood chemistry findings, provides a most efficient screening technique in the further differentiation of Paget's disease. An elevation of the serum alkaline phosphatase level, with all other levels remaining normal, is the most important finding. This, while not pathognomonic for the disease, is extremely significant. Primary hyperparathyroidism with osteitis fibrosa will also show an increased serum alkaline phosphatase level, but of necessity it must concomitantly show elevated calcium and decreased inorganic phosphorus levels, whereas these fractions do not vary in osteitis deformans.

This feature distinguishes it from all other nondietary osteolytic diseases, with the exceptions of osteogenic sarcoma, osteoplastic bone metastases, and multiple myeloma. Of these, blood chemistry and urine assays may suggest the elimination of the last two, inasmuch as:

1) An elevated serum acid phosphatase in addition to an elevated serum alkaline phosphatase is strongly indicative of a metastasizing carcinoma. (Yamane & Fleuchans - 1954; and Spilka & Callahan - 1958), and,

2) Multiple myeloma shows a great increase in the blood globulin fraction and thus the albumin globulin ratio (normally 1.3 to 3.1) is grossly distorted. In addition to hyperglobulinaemia, a hypercalcaemia and the presence of Bence-Jones proteinuria are fundamental
diagnostic findings in these diseases.

BIOPSY - or TISSUE SECTION, is the most definitive diagnostic procedure, and any bone lesion whose aetiology is not immediately apparent, regardless of appearance, demands histopathologic study.

TREATMENT - At present no efficient way of treating Paget's disease is known. In certain cases administration of calcium and phosphorus and ultraviolet rays has resulted in some improvement, (Snapper - 1943). Since the initial lesion is increased bone resorption, Albright and Reifenstein (1948) deem it logical to administer those agents which decrease bone resorption. Specifically, most of these authors' patients receive at least two glasses of milk or buttermilk daily, and 50,000 units of Vitamin D concentrate three times weekly. Alkalinizing salts are seldom used because of the danger of causing kidney stones while on a high calcium and phosphorus regimen. In female patients, after the menopause, oestrogen therapy is probably indicated to enhance compensatory bone repair. Vitamin C in large doses, for reasons which are not apparent, seems to benefit some cases. The results of therapy, unfortunately, are impossible to evaluate. (Albright & Reifenstein - 1948). The rationale of this treatment seems to be to help prevent bone fractures (Stillman - 1951).

Low calcium, phosphorus, and vitamin D intakes and a high water intake are prescribed for patients with Paget's disease who are immobilized (vide supra). Since oestrogen therapy decreases the calcium excretion following orthopaedic operations, it might also be tried under these circumstances.

In male patients where the production of sterility would be a factor of importance, oestrin therapy is probably contraindicated. (Albright & Reifenstein - 1948).

Snapper (1943) states that many authors have reported
transient improvement of the bone pains after x-ray irradiation of
the diseased parts of the skeleton. The use of parathyroid hormone
and A T 10 has been said to relieve pain in Paget patients (Snapper
1943). Laminectomy must certainly be considered when the Paget degener-
ation of the spine leads to compression of the spinal cord.

Although there is no specific treatment of Paget's disease, care-
ful management is needed to avoid complications when the jaws are
involved. The teeth and gingivae must be carefully attended to in
order to avoid inflammatory episodes that may lead to osteomyelitis.
If a tooth is to be extracted, it must be done surgically and the
socket sutured afterwards to control haemorrhage and infection, and
to avoid the development of oro-antral fistula in the upper jaw.
(Cooke - 1957)

Dentures must be well designed and if necessary frequently
remade to avoid any pressure necrosis of the bone.

In the late stages of the disease, analgesics will be needed
to relieve the continuous dull ache, and in severe instances an alco-
hol injection into the trigeminal ganglion may be necessary. A
patient with Paget's disease of the jaws should be examined every
year to avoid complications associated with the natural and artifi-
cial teeth.

PROGNOSIS - The prognosis of Paget's disease is poor, insofar
as a cure for the complaint is concerned.

LEONTIASIS OSSEA - There have been references in the litera-
ture about the relation of Paget's disease of the maxilla to leonti-
asos ossea. (Robinson & Fogel - 1956; Snapper - 1943); (Cook
1957; Cahn - 1953). It is the author's feeling that perhaps the
term "leontiasis ossea" is used too loosely. One tends to get
reports, similar to Lyon Harris' in 1948, of leontiasis ossea, which
may have been an atypical form of osteitis deformans. If a condi-
tion is Paget's disease of the maxilla and/or mandible, let us call it
Paget's disease.
History and Classification - Reticuloendothelial cells, which although situated in many different parts of the body, have certain similarities in morphology and function. Their best known function is phagocytosis, but they are able also, after a process of differentiation, to become cells of the circulating blood. The formation of antibodies is a further function of those cells which are widely distributed throughout the body in lymph nodes, spleen, liver, bone marrow and connective tissue (Shira - 1953).

A disturbance of the reticuloendothelial system may affect any of the tissues or organs in which the cells are located.

About 1893, Hand first presented a report of a 3 year old patient who had membranous bone defects, diabetes insipidus, exophthalmos, liver and spleen enlargement, and abdominal petechiae. Bronchopneumonia caused death after 2 months, from the first examination of the child. Tubercular lesions were diagnosed, but Hand questioned their relationship to the triad of symptoms. In 1920, Christian presented his report stating that there were, to that time only two additional cases recorded in the literature.

All these three cases showed similar skull defects and evidence of disturbed pituitary function, and he thought that the bone changes might owe their origin to dyspituitarism. Schuller (1915) stated that he believed these lesions in bone presumably could have been due to dysfunction of the pituitary, since experimental evidence at that time showed that an extirpation of the hypophysis in young animals, certain disturbances such as decreased calcium in bone with "holes" and disturbances in the formation of teeth would result.
Christian's case (1920), in a five year-old girl, presented the symptom complex of very extensive skull defects, diabetes insipidus, and exophthalmos. Schuller (1915 – 1930, quoted by Sleeper – 1951), presented three cases of children with multiple skull defects irregular with sharp outlines, presenting varied symptoms and signs of adipsogenesisitalia, dystrophia, dwarfism, exophthalmos, and diabetes insipidus. The disease was first called Schuller-Christian disease, and later, since this symptom complex had previously been described by Hand (1893) and because of the similarity of his case to these others, it was termed Hand-Schuller-Christian disease.

As reports of cases increased, it was found that other bones of the skeleton were affected, as well as lymph nodes, skin, mucous membranes and visceral organs. A rapidly fatal condition affecting infants and very young children was reported by Letterer in 1934, and in 1933 all previously reported cases were grouped into one category by Siwe. Abt and Denenholtz (1936), suggested the name Letterer-Siwe's disease which has since been used. In this condition the viscera were attacked and infiltrated by masses of histiocytes.

In 1940, Lichtenstein and Jaffe (1940) and Otani and Ehrlich (1940) reported a tumour of bone they called "eosinophilic granuloma of bone" and "solitary granuloma of bone" respectively. Lichtenstein and Jaffe (1940) described several cases of solitary bone lesions which were apparently inflammatory in nature and whose cytologic picture was characterised by the presence of large numbers of histiocytes. They reviewed the previous literature and found that the presence of eosinophila in such lesions was reported earlier but was misrepresented as known disease processes with special characteristics (i.e., eosinophilic reaction, etc.).

Green and Farber (1942) state that before the granulomatous character of this lesion was recognised, the first few cases were diagnosed as a peculiar form of osteomyelitis, or neoplasm, probably an
atypical myelocytic myeloma.

Jaffe and Lichtenstein (1944) discovered that these lesions were not necessarily solitary but that multiple bone lesions of this nature may affect the skeleton. In 1942, because of the peculiar granulomatous character of the lesion, Green & Farber proposed the name "destructive granuloma of bone". Jaffe & Lichtenstein objected to "destructive granuloma of bone" as nondescript, because gummatous syphilitic lesions involving one or more bones are destructive granulomas.

The term "solitary granuloma of bone" (Otani & Ehrlich - 1940) was also called nondescript since it leaves out the idea of eosinophils, which characterise the lesion histologically, and also because the process may be present in several bones.

Green & Farber (1942) stated that "in a somewhat older stage of the disease process, eosinophils are no longer present". However, Jaffe & Lichtenstein (1944) have never seen a disappearance of eosinophils before complete healing has occurred.

In general, the term (eosinophilic granuloma of bone) has become accepted in the literature published subsequent to these early reports. It is pathologically descriptive and does not limit the disease as a solitary lesion of bone.

The problems of terminology and pathogenesis have been chronic ones with these syndromes, and Niemann - Pick, and Gaucher's diseases. At the time of the original observations and descriptions of these diseases, they were all considered separate entities. They later became fused into one grouping which was called either xanthomatosis or lipodystrophy, because it was felt that they share the common root of faulty lipid metabolism. At present, Niemann - Pick's disease and Gaucher's disease are linked and are considered separately from the first three diseases. (Ross et al - 1956).
Such authors as Rouland (1928), Pick (1933), Grady & Stewart (1954), and others regarded Hand-Schuller-Christian disease as a storage disease. It was Hallory, in 1942, who was one of the first to no longer consider it a storage disease of lipid metabolism, since it invariably shows "histologic characteristics of a granulomatous process accompanied by significant grades of inflammatory reaction, both leukocytic and fibrotic." The lipidisation and cholesterinisation of the cells in Hand-Schuller-Christian disease occurs only as the disease progresses and is secondary to the disturbance of cellular metabolism. Hallory based his conclusions on factors which show that:

1) Cholesterol feeding in rabbits will produce a storage of this substance in tissues, but there is no granulomatous reaction as seen in lesions of Hand-Schuller-Christian disease;

2) Hypercholesterolaemia is not a constant finding which one might expect;

3) The early lesions of Hand-Schuller-Christian disease show a granulomatous reaction without lipidisation, and only with progression of the disease does this cholesterinisation occur;

4) There is no familial or racial predisposition as seen in storage diseases;

5) Familial xanthomatosis which is characterised by cutaneous xanthelasma, hypercholesterolaemia, and extensive deposits of cholesterol and its esters in tendon sheaths, and other tissues is not associated with granulomatous reactions and never shows the destructive lesions of bone which characterise Hand-Schuller-Christian disease.

Otani & Ehrlich (1940) in their original publication regarded eosinophilic granuloma as a separate clinicopathologic entity, not to be confused with xanthomatosis or systemic reticuloendothelial
granuloma which is the generic term used by Wallgren (1940) to include Letterer-Siwe disease and Hand-Schüller-Christian disease. However, Farber (1941) is given full credit for the idea of interrelating the lesion of eosinophilic granuloma to that of Letterer-Siwe disease and Hand-Schüller-Christian disease on the basis of the pathologic studies and clinical and x-ray characteristics of the three diseases. He states that they differ from one another only in the degree and site of involvement and the duration of the process. In 1944, Lichtenstein agreed that all three conditions represent variations of the same basic disease process.

Classically, Hand-Schüller-Christian disease has been considered a specific entity; however, current thinking places it as one expression of a larger basic classification. Mallory (1942) has segregated the patients with this disease, into three groups:

1) The disorder may manifest itself in infancy or very early childhood in an often rapidly, fatal form in which the histiocytic lesions are widely distributed through the soft tissues (especially the lymphoid tissues) and the skeleton. The clinical picture was described as Letterer-Siwe disease, reticulothesis, or non-lipoid histiocytosis.

2) The disorder may appear in children or adults in a chronic form in which the histiocytic lesions are similarly not limited to the skeleton and tend to undergo collagenisation and lipidisation and in which the prognosis is often still grave because of the possibility of damage to the lungs, heart, brain and pituitary gland. This is described as Hand-Schuller-Christian disease, or lipogramulomatosis.
The disorder may be seen in children or young adults in a relatively benign and more localised form in which the lesions occur only in the skeleton (single or multiple) and whose prognosis is less severe since they apparently heal after simple curettage and often resolve without any specific treatment. This is called eosinophilic granuloma of bone.

Egelbræth - Holm, Teilum, and Christensen (1944) showed that the question is one basic disease. On a basis of five cases showing a gradual transition from solitary eosinophilic bone granuloma to fully developed Hand-Schüller-Christian syndrome, they declare that the concept of eosinophilic granuloma has to be taken as a not altogether infrequent clinically monosymptomatic form of Hand-Schüller-Christian disease, which most often heals without becoming generalised, while in rare cases it is generalised and then often accompanied by other classical symptoms from the triad characteristic of Hand-Schüller-Christian disease.

With the histopathologic changes as a basis, four histogenic phases are stated:

1) A hyperplastic proliferative phase with more or less diffuse reticulo-histiocytic proliferation (corresponds to Letterer-Siwe's disease);

2) a granulomatous phase where, besides newly formed capillaries and collagen fibrils as basic elements, also histiocytes can be observed among which numerous eosinophilic leucocytes with polymorph nuclei; also giant cells can be seen, together with a commencing phagocytosis of lipoid and haemosiderin (this phase corresponding to the eosinophilic bone granuloma and certain cases of Hand-Schüller-Christian disease);

3) a xanthomatous phase (corresponding to most instances of Hand-Schüller-Christian disease), and
4) a fibrous, reparative phase. Of course the transitions between the different phases are vague.

Love and Fashena (1948) have had a chance to inspect a patient for more than four years, and they have seen how during this time a deposit of lipoid took place in the tissue that was previously characterised as eosinophilic bone granuloma.

Gross and Jacox (1942) presented a case of Letterer-Siwe's disease along with one of eosinophilic granuloma and one of Hand-Schuller-Christian disease. The striking microscopic similarities were well brought out, and the fact that there are no constant findings in any of these conditions and that there seems to be such an overlapping in various phases of each of them emphasises the point that they may be different aspects of the same disease. Mallory (1942) supported this from his studies. Green and Farber (1942) described a sequence of transition from eosinophilic granuloma with strands of histiocytes and eosinophils to "foam cells" to reorganisation and bone.

Lichtenstein and Jaffe (1944) disputed that this transition is true in all cases, and they cited a case in which evidence leaned toward multiple bony lesions of eosinophilic granuloma which healed by resolution, rather than through the stages of lipidisation and connective tissue scarring. They felt that no disease should be classified as Hand-Schuller-Christian disease, unless at least some of the lesions have the character of a lipogranuloma.

In 1947, Lichtenstein and Jaffe agreed that there probably was a relationship between eosinophilic granuloma, Hand-Schuller-Christian and Letterer-Siwe's disease. However, they felt that there should be at least a clinical distinction between them.

Thannhauser (1947), stated that any attempt to classify eosinophilic granuloma and Hand-Schuller-Christian disease as separate
disorders is not warranted.

Many other authors concur in the opinions of Green & Farber (1942), and Mallory (1942), and Thannhauser (1947) that these diseases represent variation in degree and phase of the same basic disorder which is a disturbance of cellular metabolism of the reticuloendothelial system (Gross & Jacox, 1942; Versiani, Figueiro, and Junqueira, 1944; Schuknech & Perlman, 1948; Layman & Sevenants, 1948). Love & Fashena (1948) and Thoma (1954) presented cases of patients who had mandibular lesions from which biopsies were taken and a diagnosis of eosinophilic granuloma made. Both these patients later developed diabetes insipidus.

There emerged by 1944, a provisional new concept of the conditions previously designated eosinophilic granuloma of bone, Letterer-Siwe disease and Hand-Schuller-Christian disease as interrelated syndromes of the same malady. The pathologic common denominator may be a distinctive and apparently specific inflammatory histiocytosis (Holst, Husted & Pindborg - 1952; Lichtenstein - (1953).

We must obviate further confusion by an attempt to coin some appropriate broad, general designation for the malady as a whole, which is applicable to any or all of its manifestations and still is relatively brief and simple. In the absence of any positive knowledge in regard to specific etiology beyond a suspicion of some as yet unrecognised infection, any such provisional designation must of necessity be a descriptive one expressed in terms of the essential pathologic changes characterising the condition.

The author favours the "histiocytosis X" used by Lichtenstein in 1953. It appears that some designation built around histiocytosis is appropriate, since this term has the connotation usually of an inflammatory proliferative reaction, and it is the one feature common to all the various pathologic expressions of the disease. It has the advantage of brevity, and as Lichtenstein (1953) puts it, the name " by impli-
cation, emphasises the necessity for an intensive search for the aetio-
logic agent".

The term "histiocytosis X" may be appropriately qualified to emphasise the significant peculiarities of any individual case. Viewed in this light, pertinent cases are atypical only if our con-
cept of what is typical remains stereotyped, and similarly, the need to trace "transitions" from one disease to another exists only if we persist in thinking in terms of rigid compartments.
CLASSIFICATION OF HISTIOCYTOSIS X

HISTIOCYTOSIS X
localised to bone (eosinophilic granuloma, solitary or multiple).

HISTIOCYTOSIS X
disseminated, acute or subacute (Letterer-Siwe or L - S Syndrome).
With destructive skeletal lesions (E - G).
With transition to chronic phase (S - C).

HISTIOCYTOSIS X
disseminated, chronic (S - C syndrome).
With destructive skeletal lesions (E - G).
With early extraskeletal lesions (indicate sites), resembling (E - G).
With acute or subacute exacerbation (L - S).
With involvement predominantly in bones, lungs, pituitary, and/or brain, skin mucous membranes (oral, anal, genital), liver or lymph nodes, etc., (in varying combinations as the case may be).

According to Lichtenstein (1953), there need not be the triad described by Hand (1893) for the condition to be labelled histiocytosis X, S - C. Cahn (1955) states that this may be a little confusing, for the descriptions of both Schuller and Christian emphasise characteristic signs and symptoms that are pathognomonic for a phase of a generalised disease.

Lichtenstein (1953) stated frankly that this term "histiocytosis X", is still inadequate, but that it is more definitive than "reticuloendotheliosis" by which name the syndrome is also known, for
two reasons; firstly that histiocytes present in the tissue sections are already well differentiated and exhibit phagocytic activity, and secondly that "reticuloendotheliosis" is a general term indicating only proliferation of the reticular endothelial cells. Since this may occur in neoplasia and as a response to abnormal lipid storage, as well as in inflammatory hyperplasias, it is too inclusive for use with the syndrome under discussion. In defence of this title he went on to say, "histiocytosis" has the connotation of an inflammatory proliferative reaction and it is the one factor common to the variants of the disease syndrome, whether or not the lesions also show an eosinophilia or whether or not fat-laden histiocytes are present."

Ross et al (1956) used Lichtenstein's "chronic disseminated histiocytosis X" to describe Hand-Schuller-Christian disease.

AETIOLOGY - The aetiology of histiocytosis X is unknown. Originally questioned as a result of dyspituitarism (Hand - 1921; Christian - 1920), it was later believed to be a manifestation of infiltration of reticuloendothelial cells with lipoid, with a hypercholesterolaemia being primary and absorption by the reticulum cells a secondary feature. It is now believed that the disease is primarily a granulomatous process (Mallory - 1942; Farber - 1941; Green & Farber - 1942), and others; with lipidisation of cells occurring secondarily. Hypercholesterolaemia is not a constant finding in the disease (Mallory - 1942), and therefore it cannot be put on this basis.

Infection, trauma, neoplasia, and a metabolic disturbance have been presented as theories regarding its aetiology. It is now thought that the granulomatous lesion, now observed, in this disease is specifically an inflammatory process, and that the cholesterol found in the cells is not the cause of the disease but rather an
associated feature. The proliferation of reticulocytes and histiocytes initiates the granulomatous process and only much later is lipoid deposited. (Mallory - 1942). A virus could be a possible cause. (Holst, Husted & Pindborg - 1952).

CLINICAL FINDINGS - The mildest and most favourable expression of the disease histiocytosis X is represented by cases presenting one, several or occasionally many destructive foci within the skeleton and otherwise showing neither apparent constitutional indications of illness nor any discernible evidence of cutaneous, pulmonary, hypothryseal, or other extraskeletal involvement. The pathologically descriptive name of eosinophilic granuloma of bone still seems an appropriate designation for such instances, which merit special consideration by virtue of their auspicious prognosis. Lichtenstein (1953) regards this skeletal localisation as an indication of successful confinement of the aetiologic agent, which may well account for the favourable outcome.

The lesion is usually seen in children and adolescents and occasionally young adults. Most of the cases reported in the literature were in children (Kaufman - 1951). It is extremely rare in persons over 25 years. However, Ōtani and Ehrlich (1940) reported a case in a 35 year-old man, and Versiani et al (1944) in a 50 year-old woman. Dundon, Williams and Laipply's review (1946) contained a case at 58 years. There seems to be no doubt that males are attacked more frequently than females, although some authors have collected their material among soldiers and in this way made an evaluation of the proportion according to sex difficult.

Any bones of the skeleton with the exception of the hands and feet may be involved. It has a predilection for the skull, ribs, femur, tibia, pelvis, humerus, clavicle and jaws. (Sleeper - 1951; and Peracchio - 1958.)
From an x-ray or even from a biopsy of eosinophilic granuloma alone one cannot make any reliable forecast as to prognosis, since this depends largely upon whether there is associated visceral involvement. In certain cases, it may be necessary to reserve judgment. Lichtenstein (1953) quoted a case of a three year old girl exemplifying all the various clinical expressions of histiocytosis X. While the lesion is frequently observed as an apparently isolated skeletal manifestation, it may also develop in the course of disseminated histiocytosis X. That it may do so occasionally in acute or subacute disseminated histiocytosis X (L-S) has been known for some time. That it often does do in cases of chronic disseminated histiocytosis X (S-C) as either an early or late manifestation, has likewise been established, and is no longer a matter of conjecture (Lichtenstein - 1953).

Lichtenstein (1953) thinks that the lesion of eosinophilic granuloma seems to represent the pathologic expression of early, rather rapidly developing reaction to the etiologic agent, and as such it may appear not only within bone, where its presence was first recognised, but also in other sites, notably in lymph nodes, the skin, the oral cavity, and the anogenital region, as well as in lungs and possibly other viscera (if the whole picture were to be revealed). Holst, Husted and Pindborg (1952) and Osborne, Freis, and Levin (1944) support Lichtenstein (1955) with their case reports.

It is evident that the initial pathologic picture is essentially that of an inflammatory histiocytosis, which may or may not be accompanied by intense eosinophilic reaction, but which, in any event, exhibits no significant tendency at the outset toward lipidisation. The picture of lipogranuloma so-called, viewed in proper perspective, apparently represents the late, or end phase
of the evolution of this histiocytic lesion, and it has been given
undue prominence and importance in the past through the observation
largely of post-mortem material. (Lichtenstein - 1953).

The clinical characteristics of eosinophilic granuloma vary
with the localisation of the lesion. If it occurs in bone without
expansion, invasion, or interference with adjacent structures, there
may be no symptoms at all. More frequently, there is localised
tenderness, pain and swelling. Constitutional symptoms such as
malaise, headache, fever and anorexia may be present. In most
cases which involve the ribs, scapula, long bones, and clavicle,
there is usually a history of pain, sometimes brought about by a
strain or blow to the area. In the lesions of the skull, a swelling
over the affected area is often present which is of moderate con-
sistency and sometimes not painful at all; however, pronounced
neurologic symptoms do occur. Macroscopically, the contents
from the bone defects are like granulation tissue, and according to
the amount of blood present may have a reddish, yellowish, reddish-
brown or greyish colour. The eosinophilic bone granuloma may
progress very rapidly. (Sleeper - 1951; Holst, Husted & Pind-
borg - 1952).

Nerves, such as the facial and auditory may be involved,
producing paralysis, deafness, vertigo, tinnitus and nausea. (Os-
borne, Freis & Levin - 1944).

From reports of Lever (1947), Lewis & Cornia (1947) and
Weidman (1947) it is shown that the relationship between eosinophilic
granuloma of skin and eosinophilic granuloma of bone has not yet been
established, and perhaps is more apparent than real (Sleeper - 1951).
However, if we use Lichtenstein's (1953) classification we may recog-
nise transitional forms to the acute or subacute disseminated histio-
cytosis X (L - S).

Brayshaw and Orban (1953) reported a case of eosinophilic
granuloma where x-ray therapy led to complete recovery. There have been reported cases of eosinophilic granuloma which healed spontaneously (Dedolph, 1957).

Letterer—Siwe disease (acute or subacute disseminated histiocytosis X (L-s)), occurs in young children, usually at the age of 2 or 3, and commonly runs a fatal course lasting only a few months. Many parts of the body may be involved; namely the bone-marrow, spleen liver, lymph nodes and visceral organs. It is manifested clinically, in varying degrees, by splenomegaly and hepatomegaly and enlargement of the lymph nodes; by characteristic purpuric or ecchymotic cutaneous eruptions; by persistent, intermittent, low-grade fever; by a tendency to haemorrhage without a reduction in the blood platelets; and by destructive lesions in the bones (Shira, 1953). The bone lesions, caused by an accumulation of the rapidly proliferating histiocytes in the marrow, usually occur in the calvarium, but other bones may be involved. Sleeper (1951) states that there are neither hereditary nor familial characteristics in this syndrome.

Rowland (1928) represented the general clinical findings in 14 cases of Hand-Schuller-Christian disease and they are as follows:

1). Occurred in early childhood, from 2 to 7 years
2). Sex about equal
3). Past history and familial history negative, although one of the common infectious diseases usually antedated onset.
4). Trauma was sometimes associated with bone defects.
5). Notable lack of subjective symptoms
6). Diabetes insipidus most notable clinical finding, but not present in all cases.
7). Retardation in growth apparent in most instances. Dystrophia adiposogenitalis may develop.
8). May show retardation in mental development
9). Few cases show chronic otorrhoea
10). Exophthalmos in almost every instance.
11) Manifest lipoaemia not observed in any case.
12) Prognosis is better than clinical symptoms suggest
13) Yellow colouration of skin frequently present

He stated that in any case of bone defect, especially of the cranium, of polyuria, polydipsia, exophthalmos, loose teeth, and spongy gums, dwarfism or adiposogenital dystrophy, Hand-Schüller-Christian disease must be considered.

The condition has a special predilection for childhood, although it has been seen in adults and even elderly people. (Schüller-1939; Thoma-1954; Ross et al-1956; Versiani-1944). Thoma (1954) states that males are more commonly affected, and he regards the syndrome as congenital and familial, occurring predominantly in Jews. It often takes a fatal course, about a third of the cases terminating fatally. (Snapper-1949). Death is usually due to the damage to the hypothalamus, pituitary gland, lungs or heart, but the disease is not always incurable. Some bone lesions have disappeared spontaneously and others responded to radiotherapy (Snapper-1949). The illness may start insidiously and progress slowly for months and years.

Intermissions and new attacks may follow. (Schüller-1939).

The classical triad, namely bony defect in membranous bones, diabetes insipidus, and exophthalmos is not always seen in the disease clinically, depending upon the target localization of the granulomatous tissue. Sleeper (1951) stated that the absence of exophthalmos and diabetes insipidus does not preclude a diagnosis of Hand-Schüller-Christian disease since these symptoms depend upon involvement of the orbit and/or the pituitary gland, which sites are not always target areas.

Lichtenstein (1953 stated that skeletal defects need not be situated in the calvarium and that many patients likewise fail to
exhibit either exophthalmos or diabetes insipidus. For that matter, even when the full Christian triad is present, it does not necessarily establish a diagnosis of chronic disseminated histiocytosis X (S - C), inasmuch as it has also been observed in the acute form of the disease (L - S). He goes on to say that as for diabetes insipidus in particular, we now recognise that its manifestations may result directly from involvement of the pituitary, its infundibulum or the tuber cinereum, in the absence of skull defects. In fact, skeletal defects in general should no longer be considered a sine qua non for diagnosis of the disease, since they may be absent, or if they do appear, they may not become manifest until lesions in extraskeletal sites are well established.

Many authors have reported cases of Hand-Schuller-Christian disease with manifestations of various types. Grady & Stewart (1934) had a three year old girl with pain, tenderness and discharge from both ears, and a partial facial paralysis. Rosenwasser (1940) reported a 50 year-old woman with a gradual onset of pain and deafness in the ear and a seropurulent discharge. She had transitory facial paralysis. Freund and Ripp (1941) reported a case of a 7 week-old infant with a "lump" in the groin. Enlargement of the cervical, axillary, and mediastinal nodes followed at 5 months. Exophthalmos and diabetes insipidus were present throughout the disease, the skull plates being clear at 7 months but revealing multiple extensive defects at 11 months.

Pulmonary fibrosis occurs rarely in this disease and suggests that it is of long standing. Currens and Popp (1943) reported such findings. A diagnosis of tuberculosis has been made in many cases.
LABORATORY FINDINGS - The laboratory findings are neither consistent nor characteristic. Most studies are normal. There may be slight leucocytosis, but this does not always occur. Eosinophilia has been noted only occasionally, and mostly has not been more than from 1 to 6% which can be considered within normal and upper normal limits. (Sleeper - 1951).

In Farber's (1941) series of 10 cases of eosinophilic granuloma followed over a period of 3 to ten years, there was an eosinophilia in one patient of 6%, and a significant elevation of total blood fat in one half of the cases.

All other laboratory studies are essentially negative.

ORAL FINDINGS - Oral characteristics of eosinophilic granuloma in the jaws are due to the anatomy of the structures involved, the presence of teeth, and to the ever-present multitude of bacteria in the mouth which predispose to secondary infection.

It occurs most frequently in the mandible, and in the maxilla only in connection with attacks on the mandible. (Holst, Husted and Pindborg - 1952).

In several cases it has been the localisation in the jaws that has led to the diagnosis of eosinophilic granuloma. Unlike most skull defects the eosinophilic jaw bone granuloma shows symptoms at
an early stage. In 1948 Conran reported eosinophilic granuloma of bone in the mandible without other lesions.

The oral symptoms seen to follow a typical pattern. Patients complain of sore mouth, loose teeth, fetid breath, pus from the mouth, pain and swelling of the jaws, sore gums, an unpleasant taste in the mouth and swollen gingivae. Many patients have loose teeth extracted and the sockets fail to heal (Sleeper – 1951). The condition may look like a chronic periodontal disorder. Resorption of bone and gingivae may be so extensive that the root surfaces of the teeth are exposed. (Peracchio – 1958)

Holst, Husted and Pindborg – (1952) state that the destructive process is more extensive than in a periodontal disease. It commences at first in the bone marrow of the jaws, and thereupon it attacks the osseous part of the paradentium, which soon is completely destroyed. The size of the granulomas varies, sometimes most of the mandible is affected.

The pathologic process commences in the bone marrow and thereafter it attacks the periodontal tissue. Gradually the periodontal structure is replaced completely by granulation tissue and on the roots more or less clear resorptions are noticeable. (Holst, Husted and Pindborg – 1952). Wassmund and Anders (1932) consider it possible that the pulp can be attacked by contiguity. However, it was Skorpil (1946) and Mezl and Skorpil (1947) who first showed the occurrence of the eosinophilic bone granuloma in the pulp in the form of small foci.

To the author’s knowledge nobody has proved eosinophilic granulomas in the pulp connective tissue itself; only in the apical foramen an accumulation like an abscess of eosinophilic leucocytes has been ascertained (Holst, Husted & Pindborg – 1952)

Nesbitt (1955) reported a case of eosinophilic granuloma in bone of the maxilla and mandible of a four year-old boy. Vincents infection was superimposed, with painful severe ulcerations in the
Teeth were exfoliated and mobile.

Cox (1946) reported 3 cases of eosinophilic granuloma in which the oral symptoms were first signs of something wrong. Kruger, Prickerman and Pugh (1949) reported dental lesions characterised by a rapid destruction of alveolar bone with no gross evidence of inflammation. Salman and Darlington (1945) reported puffy gingivae and tooth mobility. They called the lesion eosinophilic granuloma.

Wellensick (1946), Conran (1948) and Kauffman (1948) each reported eosinophilic granuloma involving the jaws. Diagnosis was made on biopsy. In these cases the symptoms of loose teeth, inflamed gingivae, pain, swelling, and foetid breath prevailed. Bailey and Freis (1944) reported Bell's palsy complicating involvement of the jaws, ribs, vertebrae and skull. Talley (1948), Schroff (1948) and Straus (1948) also described oral involvement with eosinophilic granuloma.

Shira (1953) states that oral manifestations of Letterer-Siwe disease originate in the bone marrow and an area of bone destruction becomes evident and has the same appearance as the lesion in any other bone. As it progresses, the cortex may be thinned from within and finally, perforated. The rapidly proliferating histiocytes may then involve the soft tissue and on occasion reach such proportions as to cover the teeth completely. Soft tissue involvement is manifested by a rapidly proliferating tumour mass that is soft, friable, reddish-purple in colour and gelatinous in consistency.

In Hand-Schuller-Christian disease, lesions in the jaws seem to have a predilection for the bone below the tooth germs. Oral lesions in this disease have been described as consisting of a necrotising gingivitis and large cystlike lesions in the bone of the jaws below the tooth germs cause displacement, loosening, and finally exfoliation of the teeth. These lesions contain the characteristic granulation tissue, mostly with foam cells. (Stahl & Robertson - 1955)
Sleeper (1951) reported 62% of 30 cases with either chief complaints or concomitant complaints referable to the oral cavity. These include "soreness and loosening of teeth, sore gums, pus extruding from around the teeth, sore mouth, premature loss of teeth, transitory facial paralysis or extensive gingival haemorrhages". The mucosal lesions which, upon microscopic examination, revealed the histologic pattern peculiar to histiocytosis X have been described clinically as ulcerated, necrotic, and hyperplastic. (Schroff - 1948; Sleeper - 1951; Stahl & Robertson - 1955), and may be distributed over the gingiva, tongue and palate.

In patients with obscure, persistent jaw pain without apparent clinical cause, dental x-rays may reveal areas of bone rarefaction apart from the tooth apices. When the granulomatous areas are more closely associated with the tooth apices, they may be mistaken for cysts. The contents of these lesions have a fatty appearance and consistency which permit ready differentiation from the common dental granuloma. As a rule, pulp vitality readings are within the normal ranges of values (Burket - 1957). Krogh - 1951) reported a case where teeth lost their vitality.

X-Ray FINDINGS - The appearances of bones affected with eosinophilic granuloma do not differ greatly from those seen in Letterer-Siwe disease and Hand-Schuller-Christian disease. (Shira - 1953). The defects appear as round oval, or very irregular radiolucent areas which have a sharp, clear margin without any inflammatory changes at the edge. In extensive involvement of the skull the arrangement may resemble the map of a continent, for which reason the effect is spoken of as geographic skull (Thoma - 1954). The lesions involve the inner table of the skull more than the outer table. They are sharply defined with no primary bone reaction except perhaps in the healing stages. (Sleeper - 1951).
The x-ray examination must include all bones, especially the pelvis and ribs. An x-ray picture of the lungs may show a diffuse infiltration with miliary nodules (Schüller - 1939). The lesions in bone show cortical erosion on the medullary side and thickening of the cortex on the periosteal side. They vary in size from 1 - 4 cm. There is no osteoporosis of the surrounding bone. They may expand or erode the cortex as the lesion grows, and a pathological fracture may occasionally be had (Bailey & Freis - 1944; Sleeper - 1951). The destruction of bone is infiltrative rather than invasive. The cortex may be decreased in thickness as the lesion grows, and may sometimes become perforated and, occasionally expanded. (Sleeper - 1951; Shira - 1953).

In the jaws the areas have the appearance of large cysts, but they are found in the apical part of the partly formed normal teeth in which locations cysts do not form.

The resorption of the alveolar bone may simulate advanced periodontosis. Crowns of unerupted or erupted teeth may seem to float in air; sometimes a large number of the deciduous and permanent teeth are exfoliated. (Thoma - 1954). The laterally spreading lesion in the subapical area may involve several teeth, but solitary and multiple lesions in the mandible, and more rarely in the maxilla, are common. (Thoma - 1954). Solitary lesions are well illustrated by Schroff (1948). Talley (1948) and Kruger, Prickman, and Pugh (1949) reported cases with progressive alveolar resorption. Other authors as Bailey and Freis (1944), Kauffman (1948), Cox (1946), Salman and Darlington (1945), Conran (1948), Wellensick (1946) and Thoma (1943) described lesions as areas of rarefaction, cystlike areas, destruction of alveolar bone, questionable cysts or tumours and bone destruction at the site of the tooth extraction. One or all of these characteristics may be present in the same individual.
In patients who have been treated with x-ray, there may be areas of bone sclerosis due to osteoblastic activity or repair. The healing process starts on the borders of the defects, the borders become illdefined, and the defects shrink by concentric formation of new bone seen in serial x-ray pictures. The healing process may be combined with hyperostosis, the new bone being thicker, denser and sclerosed, especially in the bones of the skull in the anterior and middle fossae. The x-ray appearance of this sclerosis is very similar to the picture of Albers-Schonberg's disease. (Schuller - 1939).

HISTOPATHOLOGY - Histiocytosis X may show considerable variation microscopically. It is believed that the primary disturbance is a proliferation of connective tissue and cells of the reticulo-endothelial system, forming granulomas containing large numbers of histiocytes. (Shira - 1953). These histiocytes are usually spread out in sheets, are pale-staining, and 10-20μ long (Holst, Husted and Pindborg - 1952). They have large, pale nuclei which may be either oval reniform, lobed and sometimes vacuolised and an abundance of cytoplasm which is either coarsely granular, definitely vacuolated, or frankly "foamy" in character. These cells are phagocytes. Frequently present in the large mononuclear cells are fragments of eosinophils or polymorphonuclear leucocytes, bits of intact bone, or unrecognisable debris. (Thoma - 1954). Interspersed and superimposed upon these are usually a large number of eosinophils, often in clumps or diffusely scattered. Eosinophilic myelocytes may be present. Others which are not eosinophilic may be seen, and may, at first, suggest myelocytic myeloma (Thoma - 1954). Plasma cells, their nuclei showing a "spoke-wheel" arrangement, are occasionally seen. Either the foci of eosinophils or masses of large mononuclear cells may dominate the picture. Multinucleated giant cells and foci of lymphocytes
may be present, and central areas of necrosis sometimes evident (Sleeper -1951). The stroma is fairly vascular. Dedolph (1957) states that the presence of eosinophils is variable, and they are not considered necessary for the diagnosis of eosinophilic granuloma.

Later in the disease process eosinophils are no longer present. Now large mononuclear cells, most of which are vacuolated, represent the most common cell found, and fibroblastic ingrowth is evident. A little later stage of this same process may show complete vacuolization of the large mononuclear cells — which may now be called lipophages — giving an appearance typical of the "foam" cells of xanthoma. In a still later stage of the disease the entire granulomatous process is replaced by connective tissue, which in turn will be transformed into bone.

Cahn (1955) states that from a diagnostic standpoint of Hand-Schuller-Christian disease, it is not necessary to find the so-called "foam" cells or lipophages in this tissue. These cells simply represent histiocytes that have taken up cholesterol esters which have formed as secondary degenerative changes in older lesions. Foam cells are found in many conditions attacking bone. One sees them in fibrous dysplasia, in chronic osteomyelitis, and occasionally in tumours.

To recapitulate, the early fresh lesions are characterized by histiocytes and variable numbers of eosinophils, while older lesions show lipidization and fibrosis. While multinucleated giant cells are not prominent features of histiocytosis X tissue, it is not thought that any significance need be placed on their presence. One frequently finds giant cells in granulomatous tissue and these represent a syncytium of histiocytes, phagocytic in action, possibly to remove cellular debris, haemorrhage, or some remnant of necrotic bone. (Cahn, 1955).
The varying findings of histiocytes, "foam" cells, eosinophilic leucocytes, giant cells, necrosis and fibrosis represent different stages of the granulomatous process. (Holst, Hustad & Pinborg - 1952).

DIAGNOSIS - Diagnosis of histiocytosis X is made from clinical observations, biopsy of the soft tissue of osseous lesions, and the x-ray. When unusual radiolucent areas which are associated with vital teeth or are apart from the apex of the tooth are noted in the jaws, the possibility of histiocytosis X should be considered. The granulomatous masses in the jaws offer favourable sites at which to obtain material for biopsy studies. It would seem desirable to include oral mucosal lesions as an important diagnostic sign, as these may precede the subsequent contiguouse bony lesions (Ross et al - 1956). Schuller ( 1939) regards hyperostotic changes of the skull in the x-ray, corresponding to the healing of the granulomatous process in the bone, as of some diagnostic value. However, accurate diagnosis requires biopsy of the lesion (Sleeper - 1951) and Peracchio - 1958). Laboratory studies are of no significance. When an eosinophilia is present, it is not diagnostic (Sleeper - 1951).

DIFFERENTIAL DIAGNOSIS - In a differential diagnosis, one must consider:

1). Multiple myeloma
2). Inflammatory lesions
3). Solitary bone cysts
4). Blastomyecosis
5). Osteogenic sarcoma
6). Giant cell tumour
7). Fibrous & Chondro dysplasias
8). Paget's disease.

(Schuller - 1939; Brayshaw & Orban - 1953; Sleeper - 1951).
In the jaws, cysts and periodontitis may be simulated. A biopsy is indicated to determine the exact nature of the lesion.

TREATMENT - Unfortunately it seems not to be generally recognised that diffuse pleural and interstitial pulmonary infiltration, leading eventually to fibrosis, honeycombing of the lungs, and episodes of spontaneous pneumothorax, is a rather common hallmark of chronic disseminated histiocytosis x (S-C), at least in adults (Lichtenstein - 1953). It may be pointed out that even in relatively serious, progressive cases presenting diabetes insipidus and/or extensive pulmonary infiltration as their major problem it is often possible by alert and well-conceived clinical management to ward off a fatal outcome for some time and occasionally to induce a remission. Such management is concerned mainly with abatement of skeletal foci through the use of adequate roentgen therapy, general supportive measures, prevention and control of potentially serious infections (especially pulmonary) by the judicious use of antibiotics, and amelioration of diabetes insipidus by the use of B-hypophamine (pitressin) or irradiation.

Dealy and Sosman (1956) state that the responses to ionizing irradiation of the lesions of Land-Schüller-Christian disease and eosinophilic granuloma of bone are as similar as one might expect them to be on the basis of current concepts, regarding their etiological and histopathologic interrelationships. They state that little experience has been accumulated in the therapy of the Letterer-Siwe variant.

The demonstration of the radio-responsiveness of these granulomatous lesions came somewhat by accident in 1928, when irradiation was given empirically to a lesion which responded dramatically to x-ray therapy.
Dealy & Sosman (1956) go on to say that small doses of x-ray, using a 200 to 250 kilovolt beam with medium filtration, can be relied upon to produce regression and healing of accessible lesions in most instances. Lesions of the skin, mucous membranes, subcutaneous tissues, lesions in and about the pituitary fossa and of the extradural space elsewhere, and lesions in bone that can be precisely localised with diagnostic x-ray films respond in gratifying fashion to doses of 600 to 900 r delivered in from one to three weeks. Lesions in the maxilla and mandible about the tooth roots respond no differently from lesions in bone elsewhere.

There is no evidence to indicate that larger doses will do a better job; rather, prompt recurrence may be encountered following augmented doses. Inasmuch as the problem of recurrence is one to be reckoned with, the case is strong in favour of the more moderate and lower doses, with treatment as required.

The visceral lesions, such as those in the lungs, have not responded as well to x-ray therapy and occasionally they seem to have been aggravated by it. (Dealy & Sosman - 1956). This may simply reflect the fact that gross involvement of these structures implies a progression of the disease into a more malignant phase, or that the type of stroma available for good healing reaction is inadequate.

Since it is estimated that some 30% of the cases will progress to involvement of other bones or general dissemination in the natural history of the disease, therapy should be instituted as soon as biopsy verification is obtained. X-ray therapy has no effect upon the underlying nature of the disease, and while spontaneous remissions may occur, perhaps the most that can be hoped for is a stemming of the progress of the disease.
Holst, Rusted and Pindborg (1952), referring to eosinophilic granuloma, state that irradiation will give immediate relief to pain, and that complete healing of bone defects, after radiologic treatment, has been observed after five to nine months.

In eosinophilic granuloma of bone, the nature of the growth cannot be determined accurately except by biopsy; it would seem that where possible, an excision biopsy would be indicated. This, in many cases, is sufficient to effect a cure, but x-ray therapy may be combined with it where it is felt necessary. In cases where there is more extensive involvement, simple biopsy where possible, to determine the nature of the lesion, and x-ray therapy would be the treatment of choice. Spontaneous disappearance of the bone lesions, especially after pathological fracture, has been reported.

In the mouth with histiocytosis, Ross et al. (1956) prescribe palliative periodontal therapy in favourable situations in order to provide maximum comfort for the patient. They state that such procedures as splinting teeth, scaling teeth, and limited occlusal equilibration will delay the problem of incomplete healing following extractions and the accompanying problem of tooth replacement on mucosal surfaces poorly adapted physiologically for the increased burden. Burket (1957) advises the removal of loose teeth and the establishment of good oral hygiene before deep x-ray therapy is administered.

Prognosis - The impression seems to prevail that the seriousness of the malady (histiocytosis x) is directly related to the age of the patient and that the younger the patient the graver is the outlook. The age factor alone is not necessarily a reliable guide to prognosis. Lichtenstein (1953) has observed a case of relatively mild eosinophilic granuloma of bone (localised histiocytosis x) in an infant only fourteen months of age; on the other hand the prognosis is not nec-
essarily favourable in older patients. There is now evidence to indicate that subacute disseminated histiocytosis X (L-S) does not occur exclusively in infants or young children, but has its adult counterpart (Lichtenstein - 1953). Shira (1953) states that a true case of Letterer-Siwe disease is refractory to all treatment and runs a rapidly fatal course.

Although eosinophilic granuloma is a benign phase healing completely with proper treatment, nevertheless the prognosis should be guarded, since the possibility of its developing into the chronic disseminated histiocytosis X (H-C) with involvement of other bones and structures must be considered.

The prognosis of this phase varies with the extent of involvement of various structures. If the liver, lungs, or brain are involved, the prognosis is graver. Since many of these cases have spontaneous remissions, and, since many of them may be either cured or held under control, if not too far advanced, the prognosis is far better than for almost any malignant neoplasm. (Sleeper - 1951).

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