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Vegetative and mechanical bone growth

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INTRODUCTION

In order to better understand some of the conditions met with in growing children, with reference to the growth of bone, I have attempted to examine some of the literature dealing with this problem. I have studied the subject to better acquaint myself with the physiological aspects of bone growth, that I might therefore better understand the pathological conditions as they arise in the various diseases of growing individuals, and that have their affect on growing bone.

I hope that the material brought forth may be of some benefit to the reader, and that a better comprehension of the problem be gained. I have not attempted to completely cover all the writings and findings of the many authors, but I have put down the theories and observations that seem to me to be the most widely accepted and the best proved.

I have included a study of the embryology of the various bones as I think that such a study is necessary as a starting point, or origin, of the subject matter of my thesis. Also I have included the histology as the reader must know the elements dealt with in order to understand their derivation.

There are many diseases that affect the bones directly or indirectly during the different periods of most rapid growth, that is, during the intrauterine or embryo stage, the period immediately following birth, and the third period during the years shortly before and during puberty. In addition to this, there are abnormal conditions that affect their growth during the periods mentioned above and at other times. These bone diseases and abnormal growth conditions I have not attempted to discuss except where such a discussion might be advantageous to better understand the material presented, as a paper on any of these conditions would require an almost endless search in medical literature. I leave such a study for other students, dealing here only with the physiological growth of bone.

During the process of growth, bone may be laid down either in membrane or in cartilage. At birth the human body contains about 270 bony masses, some of which fuse during infancy, but from then until puberty, due to the appearance of epiphysis and the bones of the carpus and tarsus, there is a more or less steady increase in number until at puberty. At this time there are about 350 bony masses to be found, the number further increasing even beyond the second decade of life. Thereafter, fusions of the different masses bring about a reduction to the

final adult number of 206, the reduction often not being completed until well into middle life. (1)

The above bones go to form the axial skeleton, (the skull, vertebrae, ribs, and sternum) and the appendicular skeleton, (the pectoral and pelvic girdles, and the limb bones). There may be some variation from the anatomical discriptions of the bones, but fundamentally there is very little variation from one individual to another. (1) Also, the growth of the same bone or sets of bones may vary considerably from one individual to another bringing about differences in appearances that may be a racial rather than an abnormal characteristic, but still not varying to any considerable degree fundamentally. The growth of the bone as bone only is discussed in this thesis.

I have further discussed growth of bone from a vegetative point of view, that is, when the growth energy of the bone matrix proliferates the bone tissue required for bone growth at the periosteal and enchondral growth zones and later absorbes what has become unnecessary from the marrow cavity; and from a mechanical point of view, or, when the bone grows as a result of mechanical work performed by the extension into space of processes of absorption and apposition. (19)

The fundamental cause of skeletal growth is not definitely known, although there are many theories, but there is much of it inherited in the germ plasm from the parents, and can be altered but little. Many things enter into and influence this growth, such as, mechanical forces resulting from muscular and gravity pull, diseases which slow or increase the growth of bone, endocrine glands, and nutrition.

I have discussed only briefly several of the above phases, using some of the data and conclusions that are quite generally accepted. Many experiments have been carried out, some of which are extremely ingenious. I have inserted a few of these that I think are particularly enlightening, and I have written the conclusions formed by the authors.

This thesis deals with the influence of the endocrines on bone growth only briefly. From the material accumulated, I find that not a great deal is known about this particular phase of the problem, but I have put down a few of the facts most generally accepted. Some of these are only observed findings, the actual cause not known, however, others have been proved as valid.

EMBROLOGY

To discuss the embryology of bone we must start from that type of diffuse mesoderm known as the mesenchyme. The mesoderm is inserted between the outer ectoderm and the inner entoderm forming three germ layers, which are seen in the hollowed out gastrula stage of the developing embryo. This third germ layer, mesoderm, is first seen following or even overlapping the gastrula stage. At this time a primitive streak appears on the blastoderm which is a thickened band continuous with the surface ectoderm. On the under side of the primitive streak tissue proliferates cells, the mesoderm, which spreads laterally and caudally. This single sheet of mesoderm, thus, formed, lies between the other two germ layers and soon devides into two layers, the outer layer of which is called the somatic layer and the inner, the splanchnic layer. These form the Coelomic cavity.

The mesenchyme is a spongy meshwork composed of branching cells whose processes do not anastomose, but just touch each other. Between these cells the spaces are filled with a coagulable fluid, or ground substance, that is called the matrix.

The cartilage that is formed, and from which the cartilage bones are later formed, begins as early as the fifth week to develop with the enlargement and

differentiation of mesenchymal cells into a compact cellular tissue called pre-cartilage, with the matrix and cells filling the intercellular spaces. The cartilage grows both internally and peripherally. Internal growth goes on from the division of cartilage cells. Peripherally growth proceeds by the mitotic activity of the connective tissue sheath, known as the perichondrium, the inner cells of which become cartilage cells and are added to the outside of the matrix already present.

Bone begins to appear about the seventh week of foetal life, some of them as in the flat bones of the face and cranial vault, are developed directly within, and are preceded by, mesenchymal or connective tissue. Other bones, as in the long bones of the extremities and ribs, the pectoral and pelvic girdle bones, as well as the vertebrae are preceded by a earlier cartilage skeleton, and ossification develops in this. The actual process of histogenesis, however, is the same in both types.

In the membrane bone, or the mesenchymal bone there are one or more points where ossification begins. In each bone this process starts with the appearance of cells called osteoblasts, which deposit bone matrix in the form of spicules that unite and spread radially in all directions, as trabeculae, in the bone. Thus the spicule

grows in thickness and in length by the laying down of the bone matrix. Some of the cells, however, become enmeshed and are lodged in spaces called lacunae.

Later on, as this spongy plate is thus forming, the mesenchyme next to the surface forms into a fibrous membrane, termed the periosteum. The osteoblasts on the inner surface of this limiting membrane lay down parallel plates of compact bone and this process is called periosteal ossification. Thus we have a spongy mass of bone, the diploe, between the inner and outer tables of compact bone.

Osteoclasts in the form of large multinuclear cells form on the surface of the bone matrix, and at the same time there is reabsorption of much of the bone already developed, which is then replaced in varying degrees as the bone grows and assumes its adult form. These osteoclasts are said by some men to be responsible for the absorption of the bone, but there is no definite evidence that such is the case. Osteoclasts are to some extent composed of fused osteoblasts and freed bone cells.

The plates and trabeculae of the bone are arranged so that a minimum of material is used to gain maximum strength in conformity with the stresses and strains encountered.

Cartilage bone is developed from the transitory cartilage model, which precedes the bone, being more or less the shape of the bone to be formed. The cartilage is first destroyed, in a manner later described, before true ossification proceeds. Ossification goes on within the eroded cartilage, as intracartilagenous or endochondral formation, and proceeds peripherally beneath the perichondrium (later periosteum) as perichondral or periosteal formation.

In the endochondral formation, the cartilage cells enlarge, become arranged in radial rows, and in addition, some calcium salts are deposited in the matrix. The cells and calcified matrix then are absorbed and disappear, forming the primodial marrow cavities. The osteoblasts deposit matrix at many points, the matrix being first deposited directly upon the spicules of cartilage which have escaped destruction; hence endochondral bone is characteristically spongy. In a progressive manner the hitherto intact regions of cartilage also undergo invasion, destruction and replacement until eventually the entire cartilage is superseded by spongy (cancellous) bone.

In the embryonic development of the vertebrae the sclerotomic mesenchyme comes to lie in paired segmental

masses alongside the notochord, separated from similar masses before and behind, by the intersegmental arteries. Each sclerotome differentiates into a compact caudal portion and a less dense cranial half. The denser caudal part of each sclerotome mass presently unites with the looser cranial half of the sclerotome next to it, and behind it, to form the substance of the definitive vertebrae. From the dense half (now cranial) dorsal extensions pass upward around the neural tube to constitute the vertebral arch, and paired ventrolateral outgrowths make up the costal processes, or forerunners of the ribs.

Following this blastemal stage, centers of chondrification appear in the seventh week. There are two centers in the vertebral body and one in each half of the vertebral arch, also one appears in each costal process. These four centers enlarge and fuse into one solid cartilaginous vertebra. A single, rather than a paired center exists in the body of a vertebra and one in each half of it's arch, but the full union of these parts is not completed until several years after birth. At about the seventeenth year secondary centers arise in the cartilage, still covering the cranial and caudal ends of the vertebral body, and resolve it into the

disc-like bony epiphyses. These plates, peculiar to mammals, unite with the rest of the vertebra at about the twentieth year.

The ribs develop from the costal processes which grow out from the primitive vertebral mass. These processes transform into cartilage and the original union of a costal process with a vertebra is replaced by a joint. A center of ossification appears near the future angle of each rib even before the vertebral centers develop; but the distal ends of the long thoracic ribs always remain cartilaginous. At about the time of puberty two epiphyseal centers appear in the tubercle and one appears in the head.

The sternum develops from a pair of mesenchymal bands which can be identified in human embryos of a full six weeks. These lie ventrolaterally in the body wall and at first have no connection either with the ribs or with each other. Following the prompt attachment of the ribs the paired sternal bars unite progressively in a cephalocaudal direction. About the ninth week the union is complete and ossification centers arise, usually, bilaterally.

The skull arises from a mass of mesenchyme first noted about the fifth or sixth week, enveloping the cranial end of the notochord and extending cephally into the

nasal region. Laterally it expands into wings which grow upward to enclose the neural tube. During the seventh week chondrification begins mesially in the future occipital and sphenoidal regions, then spreads laterally and dorsally and into the nose. The chondrocranium is thus confined to the base of the skull and somewhat to the branchial arches, whereas the sides, roof and face are of membranous origin. Ossification of the chondrocranium begins in the third month.

The occipital bone is ossified from four centers appearing at right angles about the foramen magnum. From the ventral center comes the basilar part; from the lateral centers, the lateral parts with the condyles; and from the dorsal center, the squamous part below the superior nuchal line. Above this line the remaining squamous area is of membranous origin.

There are ten principal centers of ossification in the cartilage of the sphenoid bone. These are found:

1-2. In each ala parva,

3-4. In each ala magna,

5-6. In the corpus between the alae parvae,

7-8. In the corpus between the alae magnae,

9-10. In each lingula.

Intramembranous bone forms the orbital and temporal portion of each ala magna and the mesial laminae of each pterygoid process.

The ethmoid bone is made up of a mesial mass extending from the sphenoid to the tip of the nasal process, and of paired masses which lie laterally to the olfactory sacs. The terminal part of the mesial mass persists as the cartilaginous nasal septum, while ossification of the upper portion produces the perpendicular plate and the crista galli of the septum. The lateral masses ossify first into the ethmoidal labyrinths and then the ethmoidal cells and the nasal conchae differentiate.

In the petrous portion and mastoid portions of the temporal bone, three or more centers of ossification in the periotic capsule unite into a single center to form the above. The squamosal and tympanic portions are of intramembranous origin, while the styloid process originates from the proximal end of the second branchial arch.

The rest of the bones of the skull are of intramembranous origin, each of the parietals originate from single centers, but the frontals each from paired centers.

From the first branchial arch the upper maxillary and the lower mandibular processes arise. The maxilla and palate bones arise in membrane, each palate develops a single center of ossification, and each maxilla forms two centers: one of which is in the portion bearing the incisor teeth, the other to the remainder. The mandible arises from membrane bone with two centers of ossification, one in each of its two halves.

The appendicular skeleton, consisting of the pelvic and pectoral girdles and the appendages, form directly from the unsegmented somatic mesenchyme.

The clavicle is the first bone in the skeleton to completely ossify and arises from two centers of ossification which appear on the shaft in embryos 15 mm. long. It is indefinite whether this bone is intracartilaginous or intramembranous in origin.

The scapula arises as a single plate with two centers of ossification and several later epiphyseal centers. An early primary center forms the body and the spine. The other, after birth, gives rise to the coracoid process.

The humerus, radius and ulna all ossify from a single primary center in the diaphysis and epiphyseal center at each end.

Each carpal bone ossifies from a single center as do the metacarpals and the phalanges.

The hip bone arises from three centers of ossification and gradually shapes into the dorsal illium, the ventral ischium, and the cranial pubis. These three parts join in a cup shaped depression, the acetabulum, which later receives the head of the femur.

The bones of the lower extremities develop and ossify in much the same manner, as do the corresponding bones of the upper extremity. (1)

HISTOLOGY

When examined by the naked eye, bone is seen to have either a spongy or a compact structure. The spongy framework is make up of crossing bars and plates of various thicknesses and shapes. These are branching with one another, and partially surround spaces filled with bone marrow. Compact bone appears as a continous, hard, white mass in which no spaces can be distinguished macroscopically. Both spongy and compact bone have the same histological elements. A microscopic study of bone shows the presence of cells in the lacunae (bone cell cavities) surrounded by interstitial substance and connected by anastomosing processes which lie in canaliculi. The cells consist of protoplasm and a nucleus and they completely fill the lacunae in which they occur. The shape of the cell corresponds exactly with that of the lacunae and in the thin bones is usually irregular and roughly rounded, or oval. On the surface of the cell body are many fine projections which enter the corresponding hollows of the wall of the cavity. From these hollows arise numerous thin canalicules, the bone canalicules, which penetrate the hard interstitial substance in all directions. They branch abundantly and anastomose with one another, form a network. In this manner they connect all of the

star-shaped lacunae into a continous system of cavities.

The interstitial substance of fresh bone has a hidden, fibrillar structure similiar to that of the interstitial substance found in hyaline cartilage. The fibers are closely associated, separate fibers, which are sometimes gathered into small bundles 3 to 5 microns thick. These are the osteocollagenous fibers and are united by a special binding substance.

A specialized, thin layer of the interstitial substance directly adjoins the lacunae and the canalicules and form a capsule for them. This layer does not contain fibrils and is quite homogeneous and differs from the rest of the interstitial substance by its greater resistance to various destructive influences.

The mass of the bone tissue is usually striated, that is, its elements are arranged in thin, closely adjoining layers which are called lamellae or bone plates. These are the simplest architectural units of the bone and vary from 6.7 microns to 9 microns in thickness.

The lacunae with their enclosed cells and canalicules and the fibrils of the interstitial substance are arranged in a definite fashion in the lamellae. The lacunae usually have flat, oval shapes resembling the seeds of a melon. Their size varies from 22 to 52 microns in length, from 6 to 14 microns in width, and from 4 to 9 microns in thickness. Their broad surfaces are parallel

to the surface of the lamellae and their long diameters are all arranged in the same direction. This direction depends upon that of the fibrils of the interstitial substance.

The bone canalicules project from any point in the wall of a lacunae, not only from its broad surface but from its edges as well.

The bundles of osteocollagenous fibrils of the interstitial substance of the lamellae run between the bone cavities and canaliculies. They to, have a very regular, parallel arrangement. Their direction is always the same as that of the long diameter of the bone cavities.

Spongy bone varies in its microscopical appearance in different parts of the skeleton. It may consist of:

1. tubes, with a compact or perforated wall,
2. hollow globes,
3. narrow or wide lamellae,
4. massive, more or less regularly cylindrical bars or rods.

According to the predominance of one or the other of these formations, one may distinguish a spongiosa, tubulosa, globosa, lamellosa, or trabeculosa.

In microscopical section of soongy substance all of its parts prove to be striated. They consist of a varying number of closely adjoining lamellae which have either a granular or a striated appearance depending on the direction of the fibrils and the lacunae. On cross-sections of the spongiosa tubulosa the cylindrical cavities are surrounded by concentric layers of lamellae; they have been regarded as typical Haversian canals with very wide lumens and very thin walls

In the compact bone substance the complex, regular arrangement of the lamellae is closely connected with the blood supply. Most of the blood vessels are so thin that they are invisible to the naked eye. With the microscope it is seen that the compact substance of the diaphysis is penetrated by thin, branching, and anastomosing canals 22 to 110 microns wide. These are for the most part directed along the length of the bone so that on cross-section they appear as round openings, and in longitudinal section as long slits. These are the Haversian canals; which live bone has and contains blood vessels with some connective tissue. The Haversian systems, as the units are named, are composed of the Haversian canals surrounded by systems of concentrically arranged plates or lamellae. The number of lamellae varies from 4 to 20 or even more. The separate lamellae of the Haversian

system are ring-shaped in cross-section.

There are usually two types of plates which alternate in cross-sections of the Haversian system. Under the microscope one type appears as fine dots and their lacunae are seen to be cut along their short diameter. This appearance is due to the fact that the fibrils and also the lacunae have a longitudinal direction more or less parallel to the axis of the Haversian canal and are here cut perpendicularly. The other type of lamellae is shining and fibrillar and its bone cavities are cut along their long diameters. Such plates contain fibrils and cavities which are arranged more or less circularly about the axis of the Haversian canal. The lamellae of the first type are usually thicker than those of the second type.

The direction of the fibrils in the Haversian lamellae alternate in successive plates. The alternation of perfectly longitudinal and circular lamellae occurs very seldom. More frequently this arrangement is only approximated and the fibrils in all the lamellae run spirally to the axis of the Haversian canal. This arrangement of the fibrillar structure of the Haversian lamellae in alternating crossing spirals, as well as the striation of the bone substance in general, have a great

mechanical significance. They assure a maximal degree of rigidity with regard to pressure, binding and expansion, with the least weight for a given mass of bone.

The irregular, angular spaces which remain between the Haversian systems, are filled with the interstitial or ground lamellae. These systems also consist of layers of alternating lamellae with fibrils oriented in various ways. They are scattered in separate, sharply outlined regions which do not show any regularity in their relationship to one another. The direction of the lamellae within them varies greatly.

Finally, on the external surface of the compact substance and on the internal surface which forms the wall of the bone marrow cavity are the basic lamellae; these vary in number and are arranged parallel to the surface of the bone. Penetrating these systems and opening on the free surface of the bone or in the bone-marrow cavity are the Volkmann canals which are often quite wide. Like the Haversian canals, they, too, contain blood vessels during life, but they do not possess walls of concentrically arranged plates that belong to the Haversian canals. In the interior of the compact mass they pass directly over into the Haversian canals.

All of these various systems of lamellae in the compact substance appear very sharply outlined in sections, due to the presence between them of well pronounced, bright cementing lines. These are cross sections of the thin layers of solid binding substance.

Sharpey's, or perforating fibers, as collagenous bundles of varying thickness, pass from the periosteum through the systems of lamellae in various directions. They are encountered in the external basic and intermediate layers which develop by periosteal ossification.

With the exception of the joint surfaces, bone is covered everywhere by the periosteum, a special, dense connective tissue layer. In adults this consists of two layers which are not sharply separated from each other. The external layer is composed of closely adjoining, thick, mainly longitudinal, collagenous bundles, and a few, but thick elastic fibers and of fibroblasts. This external layer is a layer of dense connective tissue which contains blood vessels. The deeper layer, adjacent to the bone, is composed of thinner, loosely arranged collagenous bundles; they curve archlike and form the Sharpey's fibers which enter the bone. This layer also contains a network of thin elastic fibers and spindle-shaped and star-shaped fibroblasts. Blood vessels extend from the external layer through this deep layer

from which they pass via Volkmann's canals to the Haversian canals. (20).

VEGATATIVE BONE GROWTH

Throughout the life-cycle of cartilage, the cartilage lives, grows, and decays, without a blood supply or demonstrable nerve supply.

Although it is known that cartilage proliferates from the undifferentiated embryonic mesenchyme as described previously in the discussion of embryology, the multiplication of cartilage cells had not been observed until Evans and Swezy developed a method of studying growth and nutrition of cartilage. Small portions of fresh tissue were fixed in Allen's modification of Bouin's fliud at 38 degrees centigrade for 15-30 minutes. After embedding in paraffin, serial sections 8 microns thick were stained with iron haematozylin without counter stain. Excess stain was removed with 70 percent alcohol. The sections were mounted and veiwed under high power and with a 400 watt lamp. This displays mitotic figures in cartilage. (13).

It has been observed that the mitotic figures in the serial sections of the ends of long bones of human embryos, are arranged roughly in an annulus, with no mitotic figures occurring in the center of the mass. In any direction from the mitotic annulus the cells become more mature, and the senescent cells are seen to

be more crowded, and the conditions of nutrition more difficult.

Cartilage being a typical vegatative tissue in which cells continue to proliferate in a matrix relatively devoid of blood vessels, the tissue juice furnishes nutriment. Characteristic is the specific limit of growth. The cartilaginous epiphysis reachs a certain size and the cells near the center can not acquire the necessary nutriment and fluid to maintain life; the area of active mitosis being limited to the annulus at some distance from the periphery, thus the size of the bone following is limited and explains the order and pattern of the calcification and ossification in embryo, foetus, and child. This is explained as the area in the cell available for the absorption of tissue juice increases as the square of the linear dimension, whereas the bulk increases as the cube.

The cells in the zone of minimum advantage from the point of nutrition, therefore, undergo senescent changes. The cell nuclei become smaller, they stain less definitely, the cell shrinks and coincidently calcification begins in the matrix. This process accounts for the calcification of the cartilaginous epiphysis and how the limit of growth is reached. The colony of cells begin to die at the core, the process being quite well regulated

within the limits.

The site of calcification in the cartilaginous mass of the epiphysis, as in the cartilaginous shape of the long bones in the early embryo, is at the center of the mass of cartilage, where overcrowding of the cells from the nutritional point of view is maximal. On the other hand, the site of calcification is about the older cells of the epiphysial plate or growth cartilage and is limited to a band or plaque, as distinct from a core, which is removed as far as possible from the zone of proliferation and is continuous with the bony diaphysis.

The lymph flow is arranged so that the epiphysial and diaphysial territories have no anastomoses. Thus cartilage cells in proximity to the diaphysis cannot absorb enough nourishment from the diaphysis to maintain life. They become senescent, degenerate and calcify.

Thus the process of senescence leads to accumulation of 'dead' calcified cartilage, and as a 'foreign' body is removed by the host, the calcified cartilage is attacked by young actively growing capillaries from the adjoining marrow cavity and a process as of aseptic inflammation goes on. In the embryo the cartilaginous shaft which undergoes calcification is attacked by an irruption of blood vessels from the vascular perichondrium

which itself lays down ectochondral bone. The calcified cartilage is eroded by the capilaries, and ectochondral bone is deposited. Two tissues are layed down which preserve to the maximum the power of differentiation, live bone and marrow.

On passing from the portion of the mitotic annulus which borders on the shaft of the bone, we transverse a zone of cartilage in which the progressive ageing cells are arranged in a series or in columns and arrive at a zone of senescent cartilage cells in which calcification of the matrix is the main feature. The calcification of the matrix has a fundamental pattern consisting of well-developed longitudinal trabeculae between the successive cells in any given column. By a process of aseptic inflammation senescent calcified cartilage is replaced by bone. The pattern of bony trabeculae is already predetermined by the pattern of the calcified cartilage matrix. One out of three longitudinal trabeculae and six out of seven transverse trabeculae of the calcified cartilage matrix persists and becomes converted into bone. (13).

The most suitable method of the study of conceptions pertaining to the significance of the cellular elements for the process of ossification is from the artificial growth of tissue. This method makes it possible to study the morphology, physiology, and genesis of the

individual types of cells participating in the process of ossification.

Dolschansky's experiment with cultures of bony tissue and periosteum has somewhat a different result from that obtained by most authors and seems to have an important significance.

The material he used consisted of the frontal bone of a chick embryo. This bone is made up of thin, practically transparent plates. After it was removed from the embryo, the bony plates with the corresponding periosteum were cut into small quadrangular sections. These were places in plasma and extract and grown artificially according to the usual methods. For microscopic studies cultures were fixed with formalin, Zenker-formol, Carnoy's fluid, and stained with henatoxylin, Giemsa solution, and azur-eosin. The demonstration of calcium was carried out by the method of Kossa. The series of sections of the cultures were prepared according to the method of Maximow. For the vital staining anus-green B and neutral-red were used.

The results obtained were as follows: Not all bony fragments underwent proliferation. A considerable number snowed no trace of increase in the number of cells, and the bony platelets seemed to be dead in the plasma. In some of the cultures, however, there could be observed a growth of long, very narrow cells, presenting the typical

form of fibroblasts, and identical with those that were described by Policard, and Wjereszinsky. After 48 hours the fragments became surrounded by a layer of spindle-shaped, fine fibroblasts, the cellular nuclei of which showed clear contours. The cells had an oval form and 2-3 chromatic inclusions, and were homogeneous.

These cells must be considered as a product of proliferation from the peripheral layer of periosteum. Besides fibroblasts, there may be found in such cultures also round cells, apparently of a hematogenous origin, which are limited in number, undergo liquifaction, and disappear after a short time. For a certain length of time some of the cultures, however, may show some variations. The layer of osteoblasts of the periosteum and cellular bony elements under-went development, causing the zone of fibroblasts to disappear completely or become displaced toward the periphery. From the deep periosteal layers and from the bone plates themselves there occured a growth of other elements which were also responsible for part of the displacement. These cells grow inthe form of dense layers, which at times suggest epithelial membranes. A culture of this type can hardly be mistaken for a usual fibroblast culture.

On sections this process can be easily followed up. From the bony plates or from the periosteal layers immediately surrounding them, there began a proliferation

of small roumd cells which have a basophilic plasma and a round nucleus, and which resemble the usual osteoblasts or osteocytes of the chick embryo. This proliferation progresses rapidly. Following the entrance into the plasma coagulum, the cells undergo definite changes. They may become flattened and may assume a typical epitheloid appearance. The emigrated cells next become distinctly demarcated and arranged in the form of a membrane, at the same time they become flattened and may assume a polygonal form. The protoplasm is highly basophilic and is granular, the granules being of variable size; with the nucleus situated centrally, as a small, round, body rich in chromatin.

In some cultures the mode of development of the emigrated cells is somewhat different. Without showing any change in the external form of the protoplasmic body, there appear thin, thread-like plasmatic processes: these processes later lead to the development of a network , consisting of small round cells connected with each other by fine plasma fibrils this network suggests the bone cells.

These two types of proliferation of the periosteal and bony cultures are only rarely observed in a pure form; practically always the picture is dominated by another

form of proliferation, consisting in a mesenchyme-like growth of cells.

Cells of this type have a fibroblast-like appearance: their protoplasm is basophilic and granulated: the nucleus is oval, containing 2-3 nucleoli and occasionally one of the cells contains 2 or more nuclei. The protoplasmic granulations vary from fine, dust-like, to massive granules. Occasionally the protoplasm contains granular inclusions of considerable size and consistency, and are included in the cellular body and surrounded by a transparent area.

Nothing definite can be stated in reference to the nature of these granules. It is reasonable to assume that calcium compounds have to be dealt with, as stated by Frattin and others, who are unable to demonstrate calcium in the osteoblast granules. Only the large inclusions having a transparent area give a positive reaction.

Besides the nucleus, there are also found vacuolar structures, which at times may reach the size of the nucleus. The vacuole is definitely separated from the cytoplasm and contains a structureless substance.

The chondriosome consists of 2 plump rods and a few discrete granules. Neutral-red granules were numerous.

The proliferating bony and periosteal cells show a considerable activity, frequently giving rise to pseudopodia of various types. Occasionally there may be found

outside of the zone of growth separated cells situated singly in the plasma, and having an ameboid shape. Such cells may also show a phagocytic activity. The intensity of the proliferation of the bony and periosteal cultures is quite pronounced.

The cultures retain their appearance even after a number of passages with the typical bony and periosteal cells persist. Also the other characteristic strains are retained, however, the cells of the epithelioid character and the branched cells do not remain in vitro for any length of time and disappear after 3-4 passages. Since numerous transitional forms of epithelioid cells to cells of the mesenchymal type are found, it is reasonable to assume that both are variations in form of the same type of cell.

The bony plate introduced into the culture becomes gradually destroyed with the loss of substance, which takes place extremely slowly. The class of cells, however, that have an osteoclactic activity cannot be demonstrated. Not a single culture was found to demonstrate the formation of bony tissue. (9).

Bones begin to appear about the seventh week of foetal life, with the bone matrix being deposited through the activity of specialized connective tissue cells,

named osteoblasts or bone-formers. There is formed a soft preosseus tissue, made up chiefly of fibrillae which becomes impregnated with a deposit of lime salts.

The deposition of calcium in the normal development of bone is a function of living cells. It is in constrast to the process following pathological lesions in which the deposits are the result of the physical precipitation of calcium in the dead or injured tissues.

The first sign of ossification in normal embryo cartilage is enlargement of the cartilage cells at the ends of the long bones and their arrangement into columns. The next stage is the formation of groups of cells between which there is formed a substantial branching trabecular network which later becomes the most heavily calcified area. The matrix between the cells first stains more deeply, and then small granules appear around the periphery of the lacunae of the cartilage cells and gradually increase until the matrix becomes a solid mass.

Calcification of the epiphyses begins in the center, the process being the same as that found in the short irregular bones. There is first an increase in vascularization and in the amount of matrix between the cells. The cells then group themselves into clusters, and around the periphery of each cell small granules are deposited.

The deposit takes place first around the cells nearest the blood vessels, the blood vessels not penetrating the central part of the cartilage until it begins to calcify, entering the calcified mass by erosion, and the true ossification proceeds along the vessels. Flat bones, such as those of the skull, may calcify without the presence of blood vessels in the cartilage, in other respects they develop in the same way as other parts of the skeleton.

Membrane bones are produced by numerous layers of cells on the surface of the fibrous sheets which serve as a framework, with calcification proceeding from the surface to the center of the sheet. The bone-forming cells exude the calcium salts into the matrix, where they precipitate, giving the bone its hardness.

In all cases of calcification of cartilage, calcium appears first in the form of granules, the granules becoming embedded in the matrix immediately outside the cell capsule, and the calcium salts appearing before the blood vessels are present in the calcified area. The calcium salts do not appear, however, until the cartilage cells have become enlarged and grouped.

Wells has shown that 85 percent of the calcium in bone is in the form of phosphate and 15 percent in the

form of carbonate. Bergeim's experiments showed that in rachitic rats calcium and phosphorus are both lost in the feces, whereas in normal rats these elements are absorbed. Other experiments have shown that all tissues which utilize phosphates possess a ferment called "phosphatase" which will produce inorganic phosphates from organic phosphoric esters. Eden found large amounts of calcium in the callus of healing fractures before any callus was visible in the roentgenogram, it being evident in a form bound to protein. Injections of calcium salts into the site of a fracture have been known to hasten healing.

The formation of clam shells and egg shells is another evidence of the secretive power of the living cell in the production of calcification. The shell of bird's eggs is composed almost entirely of calcium and is secreted by the shell gland, a modified part of the genital tract. This secretion is an undeniable cellular activity causing calcification. In experiments on young mice in which blue dye was injected and the developing teeth examined, Blotevogel, found the dye not only in the cells before the dentine and enamel were formed but also in the calcified tooth. The influence of some of the ductless glands on bone formation, notably in

acromegaly and cretinism, is further evidence that the bone growth and calcification is an activity of the living cell rather than a physical precipitation.

Calcium is secreted to form hard structures by six types of cells, three epithelial cells and three connective tissue cells. The epitheial cells are:

1. The ameloblast, which builds the enamel of the teeth.
2. The epithelium of the bird's shell gland.
3. The epithelium of the mussel shells.

The connective tissue cells are:

1. The odontoblast, which builds dentine in the teeth.
2. The cartilage.
3. The osteoblast and bone corpuscle. (26).

On close examination the osteoblast is seen to have a nucleus that is large and contains relatively coarse chromatin particles and large nucleoli. The protoplasm of the osteoblasts according to some authors has a granular structure, according to others it is reticulofibrillar; these appearances are probably due to the type of reagent used. The cell further contains numerous, thread-like mitochondria, vacuoles of probably secretory character and, near the nucleus, a pale attraction sphere

with a typical diplosome. The osteoblast has a diameter of from 15 to 20 microns.

The bone lamellae in the older, central portions of the center of ossification increase in size as the interstitial substance is being formed and spreading at the periphery. The resulting increase in mass is undoubtedly the result of the activity of the osteoblasts that lie as a continuous layer more or less, on the surface of the lamellae. The osteoblasts gradually move to the exterior of the mass as successive layers are added. However some of the osteoblasts are caught by gradually being included, one by one, within the substance as somewhat smaller, more angular cells. These are the first real bone cells or osteocytes and come to lie in the lacunae. Thus they are formed from osteoblasts which persist as bone cells.

The osteoblasts not caught continue at the periphery laying down bone substance and, with the gradual thickening of the substance in layers, they move away from the cells caught. The osteoblasts thus remain as a continuous layer even though some of them become included in the bony mass as bone cells. The number is kept constant by the addition of cells from the connective tissue layer surrounding it. As the osteoblasts are connected by

processes that pass between them as well as to the osteocytes, it can be seen why they are star-shaped, and how their processes penetrate the bone substance in all directions, connect the cells and form the canalicules. In this manner it can be easily seen how the Haversian system is brought about, with its various parts as described in the histology section, preceding this one.

Thus we see in the above discussion, that there is an evolution, in the vegetative growth of bone, from a primitive multicellular colony of cartilage to the more recent, highly vascularized adult bone and marrow. The processes of hypertrophy, hyperplasia, degeneration, inflammation, metaplasia, heterotopia can be studied in the narrow epiphiseal zone where the vegetative bone growth, herein described, takes place. We can study further absorption and deposition of the alkaline earths, absorption and deposition and remodeling of the bony trabeculae, all taking place on the framework of the calcified matrix of senescent cartilage, all studied in terms of osteoclast and osteoblasts, and the latter finally becoming the true bone cells.

MECHANICAL BONE GROWTH

While the vegetative processes of absorption and apposition are very thoroughly discussed in the text-books of anatomy and developmental history, and their finest histological detains shown, there is practically nothing about the mechanical function of growing bone in the medical literature studied; and yet this mechanical function of growing bone is of just as great importance in the physiology and pathology of bone as the vegetative bone growth.

A good picture of the mechanical work of growing bone can be gained only where bone construction, particularly the construction of the spongy bone architecture, is taking place; that is, at the enchondral zones of growth; for at the periosteal grow zones there is hardly anything that can be called a true construction of bone. At these zones the growth of bone is chiefly vegetative, as the vegetative growth energy of the periosteum adds one layer of bone to another, leaving free only the necessary canals for the nerves and vessels. At the enchondral zones of growth the bone at first grows vegetatively too, but is transformed by the mechanical work of the enchondral growth zones into spongy bone, so that this is chiefly known as "growth", that

is, increase in size and change in form of the growing bone, is brought about much more rapidly and extensively than by the compact apposition of the periosteum.

The mechanical work of the enchondral growth zones is brought about primarily by the marrow cells. They are to a certain extent the borers of the growing bone which, like the boring machines used in building tunnels, grow into the proliferated and calcified epiphyseal cartilage and tunnel through it in various directions, forming marrow cavities. The marrow cells in this way make it possible for the true bone builders, the osteoblasts, and other cells, to wall the tunnels of the epiphyseal cartilage with young bone tissue so that a spongy bone construction is built up in place of the cartilage that is destroyed.

This mechanical work of spongy bone construction is of course accompanied by the vegetative processes of marrow cell proliferation, vessel budding, proliferation of bone tissue, etc. But the decisive point in spongy bone construction is not so much these vegetative processes themselves and their quantitative course, but rather the rapidity and direction of their extension into space; for the rapidity of spongy bone growth depends on the rapidity of this extension, and its structure and form, on

their direction.

Spongy bone growth is much more a result of mechanical than of vegetative growth; this must be kept clearly in mind in order to understand the physiology and pathology of bone growth.

The epiphyseal cartilage is by no means passive in the mechanical work of spongy bone construction. It is not an organ that proliferates bone tissue, this is accomplished solely by the osteogenic zones of the bone itself, the original derivatives of the perichondrium, but it fulfills other functions that are important in spongy bone structure. In the first place by its growth and the formation of columns of cartilage cells it regulates the rapidity and direction of the formation of marrow spaces. The formation of marrow spaces in the cartilage can of course not take place any more rapidly than the cartilage itself grows, and the longitudinal cartilage cell columns form tracts that can readily be opened up in the calcified cartilage and offer comparatively the least resistance to the penetration of the marrow spaces. So the proliferating and calcifying epiphyseal cartilage is the chief regulator of the rapidity and direction of spongy bone growth.

The epiphyseal cartilage also accomplishes another

important function without which the mechanical work of spongy bone construction could not be accomplished. It furnishes the soft spongy bone framework a firm support until it has attained its physiological solidity and firmness by calcification.

Enchondral bone growth can only be understood by bearing in mind that all bone tissue, as shown by Pommer, is originally deposited in a non-calcified condition and that the construction of spongy bone from this osteoid tissue on the free surface of the bone would be a mechanical impossibility; for the osteoid trabeculae and buttresses would immediately yield to the physiological growth pressure on them, because in every growing organism the parts exercise mutual pressure on each other, and there is a comparatively high growth pressure on the spongy growth zones because of their rapid growth.

These processes of enchondral bone growth must be considered with the eye of the architect in order to understand them and to realize that for the building up of spongy bone architecture from the calcium-free osteoid tissue it required supports which cannot be dispensed with until the soft osteoid tissue has become transformed into firm calcified bone. This support is furnished by the proliferating epiphyseal cartilage,

and by its calcification it makes it possible for the bone framework, that is developing in it and under its protection, to harden into solid bone rapidly and almost instantaneously at the critical moment at which the cartilage calcium is dissolved by the formation of marrow spaces and the cartilage proliferation destroyed. Not until calcium is absorbed is the success of spongy bone construction assured, the cartilage supports can be dispensed with and the mechanical work of enchondral bone construction can progress into the next zone of ossification of the cartilage which in the meantime has proliferated further and calcified. The epiphyseal cartilage is a very important factor in the mechanical work of the spongy bone construction, and though spongy bone construction takes place without the cartilage in some parts of the skeleton, for instance the flat bones of the skull, it must be remembered that even here the formation of the diploe does not take place in the soft connective tissue of the suture lines, but only after this has become sclerotic by the preparatory absorption of calcium. It is shown, therefore, that the same mechanical conditions are fulfilled here as in the parts of the skeleton that are formed from epiphyseal cartilage.

It is hoped that in this discussion it has been

shown that bone growth and bone construction are two different things. A study of some pathological conditions that have been observed in bone may serve to make a sharper distinction than has heretofore been made between the vegetative and mechanical work of growing bone, or between the vegetative and mechanical work of growing bone, or between the disturbances of bone growth and disturbances of bone construction. The disturbances of enchondral bone growth that are the most frequent and practically the most important, act not on the vegetative but on the mechanical work of growing bone. They are, consequently, not true disturbances which do not involve the proliferative or absorptive capacity of the bone matrix at all or involve it only secondarily. This is true for the most part of the disturbances of growth after injuries and diseases of the epiphyseal cartilage. It is true without exception of all defects of growth that are caused mechanically and is also true of rachitic disturbances of growth. It is believed that not only the pathogenesis but also the anatomical and clinical pictures of these disturbances of growth will be made much clearer by making a strict differentiation between vegetative and mechanical work in the growth of bone.

Among the injuries or diseases of bone cartilage are

the ones that are of primary interest, or the ones in which the growth of the cartilage comes to a standstill prematurely but the bone matrix itself is not injured or diseased. For the premature standstill of cartilage growth must necessarily bring about a standstill in the mechanical work of enchondral bone construction but with the matrix intact.

Vegetative bone growth at the boundaries between the cartilage and bone does not come to a standstill but is entirely physiological in amount. It is thought that a particularly striking example of the above is chondrodystrophic dwarfism, particularly the hyperplastic form of it described by Kaufmann, in which not only are the ends of the diaphysis of the long bones dilated into a club-shape by an apparent excess of bone formation, but the periosteal growth in diameter seems to be excessive. He thinks that great care must be exercised in making a diagnosis in the growing skeleton of hyperphasia or hypoplasia of bone, or of hypertrophy or atrophy, particularly in those disturbances of growth that do not act on vegetative bone growth but on the mechanical work of growing bone. For in these conditions, as long as the bone matrix is intact, there is neither more or less proliferation or absorption than mormal. The swellings of the ends of the diaphysis in chondrodystrophic dwarfs are not

vegetative disturbances of bone growth, not pathological new-growths of bone tissue, but physiological amounts of tissue that have accumulated at the bone-cartilage boundary because of the standstill in the growth of the cartilage and the standstill in enchondral bone construction caused by it. The situation is about like that at a building site where the stones have been collected and heaped but the building cannot for some reason go on.

The excessive growth in diameter of the long bones is not due to a pathologically increased apposition on the part of the periosteum, but is also due to purely mechanical causes, because with the loss of spongy bone construction and the resulting decrease in growth in length of the long bones the periosteum also very quickly loses its physiologic longitudinal tension, about like a rubber tube that has been stretched and then released, and as periosteal apposition takes place in physiological amount it must increase in thickness as it decreases in length. This can be seen in any long bone as soon as its growth in length is interfered with, either in rickets or in experimental shortening of the long bones.

Chondrodystrophic dwarfism shows with special clearness the effects of loss of the mechanical work of growing bone and its sequels of enchondral and periosteal growth

and shows what an important factor the mechanical work of growing bone is in the normal growth in length of the skeleton and how little purely vegetative bone growth can accomplish in this direction. On account of the swelling of the ends of the diaphyses and the increased diameter of the long bones, fetal chondrodystrophia is often confused with fetal rickets. But in chondrodystrophy the assimilation of calcium takes place promply and there is no pathological softness of the bone. On the contrary these bones are excessively hard and sclerotic because in place of the spongy ends of the diaphyses there are more or less compact masses of calcified bone and these masses finally fill the whole marrow cavity. A bone develops that resenbles the "marbled bone" described by Albers-Schonberg and it is believed that this marbled bone and many obscure cases of diffuse osteosclerosis are really only bones whose zones of proliferation have remained active but whose mechanical work for some reason or other came to a standstill prematurely.

What is seen in gross in fetal chondrodystrophy and related diseases (chondrodystrophia, thyreopriva, myxedema, etc.) is repeated in miniature in the local injuries and diseases of epiphyseal cartilage but here not in such a pure form for, on account of the close

anatomical relations of cartilage and bone, local injuries or diseases of the epiphyseal cartilage are generally accompanied by injury or disease of the bone itself, so that vegetative disturbances of the bone matrix complicates the anatomical and clinical picture more or less.

Among the defects of growth due to mechanical causes are those due to the upright position of the body, the so-called deformities from weight-bearing, curvatures of the spinal column, genu valgum, flat-foot, etc., are of interest on account of their frequency and practical importance and because there is still a great deal of dispute about their pathogenesis.

The upright position of the body makes no difference at all in vegetative bone growth; for an intact bone matrix will not proliferate or absorb any more or any less bone in an upright position than in a horizontal one. But for the mechanical work of growing bone the upright position beyond doubt means an increase of work, at least for the enchondral growth zones that have to bear the weight of the body in the upright position. For the simplest mechanical and dynamic reasons it seems to be inconceivable that the penetration of the marrow spaces, the tunnelling of the cartilage, etc., should take place as rapidly in the upright position as in the

horizontal one, any more than it seems possible that a boat could move as rapidly against the current as with it, or one of the boring machines in tunnel construction, work as rapidly in hard stone as in soft earth.

The clinical fact that children grow in height faster when they are sick in bed may be due to this; possibly we would all be taller if we spent the years of growth in bed. That cannot be controlled for lack of objects of comparison, but such comparisons can be made when the action on the growth zones is not symmetrical, as in the fatigue positions, when instead of using the fatigued muscles to maintain the upright position, demands are made on the joints of the spinal column, the lower extremity, etc., as in kyphotic or scoliotic fatigue positions, found in school children.

In any scoliolic spinal column it is easy to see that the spongy growth in height of the body of the vertebra takes place more slowly on the side on which less weight is borne, and it is equally easy to see that this asymmetry of growth is not at all vegetative; for in proportion as the body of the vertebra on the side on which the most weight is borne remains lower, its spongy structure becomes more compact and it encreases in breadth as it decreases in height.

These are not vegetative disturbances of bone growth, not "vital reactions of growing bone to changed static demands," for there is no more or no less absorption and proliferation than normal, but they are purely mechanical or dynamic disturbances of rapidity or direction of growth, from which all the other changes in the scoliotic spinal column or thorax are derived according to mechanical and dynamic laws.

Another danger point in the upright position for the mechanical work of bone growth lies at the proximal end of the tibia, in which, because of its great growth energy, the processes of bone construction take place with particular rapidity and therefore they react with a special sensitiveness to unsymmetrical pressure from weight.

In the fatigue position the knee-joint is forced into an extreme valgus position by the weight of the body so that the whole weight of the body rests on the lateral part of the joint of the tibia, so that spongy growth of the bone here takes place under increased pressure and on the median side under decreased pressure. The growth of such a tibia as compared with a normal one shows that the pathological pressure and traction tensions do not act on the epiphyses but on the enchondral growth zones of the end of the diaphysis.

The processes of growth at this point offer the best point of action for these pathological tensions, and it is easy to see that the changed direction of growth of the end of the diaphysis is explained by the purely mechanical or dynamic impairment of these processes of growth. It is only the resultant of the physiological direction of growth on the one hand and the pathological tensions of pressure and traction on the other, according to the law of the parallelogram of forces. And it is this changed direction of growth of the diaphysis that secondarily displaces the epiphysis into its valgus position.

The third danger point in the upright position is the spongy growth of the talus and calcaneus at the enchondral growth zones of the upper and lower ankle joints, which are also forced into a valgus position by the weight of the body in the fatigue position, so that the asymmetrical growth is brought about just as it is in the scoliotic spinal column and so pes-valgus develops.

A fourth danger point lies at the epiphyseal junction of the neck of the femur. But this is less threatened by the upright position of the body than the other points for the very simple reason that the epiphyseal

line of the neck of the femur in the upright position is not horizontal but inclined to the horizontal at an angle of about 45 degrees, so that the spongy growth of the neck of the femur contributes much more to the growth in breadth of the hips than to the growth in length of the lower extremity. It is only in the position of extreme abduction of the hip joint that is sometimes assumed by farm workers or in the squatting position of the orientals, that the upright position may become dangerous for the growth of the neck of the femur by muscle fatigue, and deviate this growth in the direction of coxa vara or coxa valga.

The fact that these various disturbances are mechanical or dynamic and not caused by vegetative disturbances of bone growth is also shown beyond doubt in animal experiments, when for instance, the hind leg of a young animal is put in plaster in an artificial genu valgum position and the growth of the plaster side compared with that of the free extremity. The animal drags such a plastered extremity in a position of extreme abduction so it is put entirely out of commission by the plaster; after a comparatively short period the proximal end of the tibia shows the same disturbances of growth as in static genu valgum in man.

The effect of this simple animal experiment is compared to the effect of currents of a ship. The ship's speed is increased by currents in the same direction, slowed by ones in the opposite direction, and deviated to one side by lateral ones in accordance with the law of the parallelogram of forces. In the same way the formation of the marrow spaces in the epiphyseal cartilage is influenced by tensions of pressure and traction which act with or against it or at a tangent to it. This animal experiment also shows that the temporary, discontinous action of pathological tensions such as those in fatigue positions may injure bone growth in the same way as the continuous action in the animal experiment. The rapidity and direction of bone growth does not depend on whether the action is continuous or discontinuous, but on how frequently it is repeated and how intense it is. In a three day ship journey it does not make any difference whether contrary winds slow the course for one whole day of the three or for 8 hours on each of the three days; and the same thing is true of the mechanical work of growing bone.

Of course there may be defects of growth in the spinal column and other parts of the skeleton from various causes, for instance congenital anomalies, trauma,

pathological softness of the bone, etc., and these may be increased by weight-bearing, but they are not true deformities from weight-bearing. True weight-bearing deformities are only essential disturbances of growth that take place under the influence of the upright position of the body in a skeleton that is normal, anatomically well-formed, physiologically able to bear weight and pressure, but only still plastic with the plasticity of growth; and it is thought that the great majority of curvatures of the spine, genu valgum and flatfoot and the more unusual curvatures of the neck of the femur are weight-bearing deformities in this sense. There is also a phylogenetic factor involved.

The spinal column with its 24 joints is an excellent organ of locomotion for the four-footed animal, but with its 24 enchondral zones of growth it is not an ideal organ for bearing weight, at least not during the growth period; and something similiar is true of the lower extremity. So the skeleton, so far as the mechanical work of enchondral bone construction is concerned, has adapted poorly or not at all to the upright position of man. The skeletal musculature has to compensate for the dangers that threaten spongy bone construction from the upright position and while a strong musculature may be able to

accomplish this it cannot be accomplished by a poorly developed or defectively innervated musculature such as is often seen in school children and young workmen.

It is particularly important to make this distinction between vegetative growth and mechanical construction of bone in rickets. For the disturbances in rickets does not act on vegetative bone growth but on mechanical bone construction. The interruption or delay of physiological calcification is a matter of indifference for vegetative bone growth; for it does not change the amount of proliferation or absorption of the normal bone matrix. But the normal time course of calcification is of greatest importance for the mechanical work of the spongy bone construction for any delay in calcification subjects the spongy bone framework before it has had time to solidify to the physiological growth pressure that acts on the zones of growth and therefore for purely mechanical reasons must lead to more or less collapse of the spongy bone structure.

In addition to this mechanical action there is the dynamic action of physiological growth pressure on the spatial extension of the formation of marrow spaces and tunneling of bone. For how can the marrow cells accomplish their mechanical work of tunneling and cartilage

with physiological rapidity under the action of physiological growth pressure when the spongy growth zones remain soft and their growth pressure sinks far below its physiological value, so the vis a tergo is lost that forces marrow space formation into the calcified cartilage? In proportion to the falling growth pressure of spongy bone growth zones the spatial penetration of marrow space formation is slowed, just as in making a tunnel the penetration of the boring machines are slowed when their hydralic or other driving force becomes defective for any reason and they are acting under half pressure.

It is only this mechanical or dynamic explanation that makes the anatomical effect of rickets clear. It explains why the manifestations first become evident at the bone-cartilage boundary where the mechanical work of spongy bone construction is going on most intensely and it explains why the ends of the diaphysis that have the greatest growth energy show these manifestations sooner than, and to a greater extent than the ones that grow more slowly. It is because of their more rapid growth that there is a greater physiological growth pressure on them. Vegetative growth is not interfered with, however the growth in length is, the bone becomes

denser, as on the more compressed side of the scoliotic spinal column, and the bone that is formed finds a way out in the direction of least resistance, so there is increased growth in breadth with decreased growth in length. As the rickets continue the periosteum loses its normal longitudinal tension and deposits cortical lamellae which are decreased in length and increased in thickness. But as these individual lamellae remain soft and with the increase in their diameter moves farther and farther from each other, the lateral pressure which the individual lamellae exercise on each other gradually decreases and so at the surface the compact structure loosens to a more spongy one, consequently on cross-section the lamellar structure of the bone cortex is much more evident than in normal bone, as layers of compact bone alternate with ones of a more spongy structure.

These facts also explain the changes at the bone-cartilage zone, the broadening of the zone of cartilage proliferation and the irregularity of the ossification line. These changes at the bone-cartilage boundary are by no means specific for rickets but may be seen anywhere that spongy bone construction has to struggle with pathological pressure and traction tensions, as shown in the different weight-bearing deformities

(scoliosis, coxa vara, genu valgum, etc.).

There is another error that is commonly made in rickets, namely that of considering the anatomical effects of the rachitic growth disturbance as being due to mechanical factors resulting from the use of the skeleton - weight-bearing pressure, muscle traction, air pressure etc., but this is not the case. These factors bring about the known rachitic deformities such as curvatures of the spinal column, deformities of the thorax, extremities, etc., but they are not responsible for the rachitic disturbance of growth in length of growth as such. They are not responsible for the decreased growth in length of the long bones, their increased growth in circumference, the swelling of the epiphyses, the changes at the bone-cartilage boundary, the increase in physiological curvatures and spontaneous fractures. These are due only to physiological growth pressure acting on the spongy growth zones that have remained soft. These rachitic disturbances of growth would doubtless occur in the same way if the rachitic skeleton were put out of commission during growth.

The effect on the periosteum has already been discussed. The marrow tissue and the circulation of the bone are also involved in the collapse of the spongy bone

construction and many of the clinical symptoms of rickets are probably due to this fact. (19).

Each pair of bones differs in the relative amounts of longitudinal growth taking place at the two ends of a given pair. Digby measured this amount by measuring from the nutrient artery opening to the ends of the given bone, Hatcher measured from the transverse lines formed by administering phosphorus to an individual, and from lines of arrested growth formed by a former illness and seen in radiographic studies of the given bone, to the ends of the bone. Digby gives the following figures calculated by his method:

Name of bone.	Proximal end.	Distal end
Femur	5 inches	11 inches
Tibia	$7\frac{1}{2}$ "	5 "
Fibula	$7\frac{1}{2}$ "	5 "
Humerus	$9\frac{1}{2}$ "	$2\frac{1}{2}$ "
Radius	2 "	6 "
Ulna	$1\frac{3}{4}$ "	$5\frac{1}{2}$ "

Hatchers calculations were as follows:

Femur	21 percent	79 percent
Tibia	56 "	44 "
Fibula	Approximately the same as the tibia	
Humerus	84 percent	16 percent
Radius and Ulna	18 "	82 "

From these figures as from many other experiments it can be seen that in these long bones the growth is greater toward the elbow and the knee joints. Knowledge of the growth of such long bones was first noted by Stephen Hales in 1747. He drilled holes in the shaft of the tibia of a growing chicken and made similiar observations. He said that the growth in length of the long bones is accomplished by the deposition of new bone at the extremities of the given bone. (22).

Bisgard made similiar experiments using goats in his experiments. To measure growth the bones were marked with steel shots placed in drill holes in the shafts when the goats were 2 to 5 days old, Roentgenograms were taken at the start of the experiment, and throughout the course of the experiment, a period of about twelve to eighteen months. Thus the growth could be measured from the shot to the ends of the bones to determine the amount of growth, all films were made with a precisely constant technic. The average percentages for each bone and the actual measurements were as follows:

Bone	Number of animals used in each experiment	Average Growth in mm.		Average Proportion of growth in percent	
		Proximal end	Distal end	Proximal end	Distal end
Humerus	4	51	11	82.0	18.0
Radius	3	11	32	25.5	74.5
Ulna	4	20	72	18.8	81.2
Femur	3	29	52	35.8	64.2
Tibia	3	64	53	54.8	45.2

The conclusions arrived at from these experiments by Bisgard were:

1. All longitudinal growth of long bones, both prenatal and postnatal, takes place at the ends. Length is gained from the deposition of layers of new bone between the end of the diaphysis and the epiphyseal cartilage and between the articular cartilage and the epiphysis.
2. The proportion of longitudinal growth from the two ends of a long bone is unequal. The disproportion is greater for growth occurring after birth.
3. The rate of growth remains constant during the first four months and then progresses at half of its former rate. The epiphyseal

cartilage, giving lesser increment, is the first to ossify and close.

4. The proportion of growth from each end of each long bone, as determined by actual measurements, is recorded. When converted into percentages these proportions are almost identical to those obtained by the method of Digby. We deduce, therefore, that the measurements of proportionate growth for human long bones as determined by Digby are accurate.
5. Growth arrest lines can be produced in the bones of a fetus by feeding phosphorus to the mother. (5).

ENDOCRINE GLANDS AND BONE GROWTH

Of recent years the function of the endocrine gland system has held the attention of many men in research, though little has been accepted as the final fact in regard to the influence they have on the various organs and tissues of the body.

In the problem of bone growth and the part played by these glands it is quite generally accepted that the hypophysis, the gonads, the thyroid, and the parathyroids have some influence on bone growth, either directly or indirectly.

The hyperfunction of the hypophysis when occuring in growing individuals, is known to cause gigantism, with the overgrowth of bone in particular, and to cause delayed closure of epiphyseal lines before normal growth is complete. If hyperfunction of the gland occurs following closure of the epiphyseal lines and after the adult stage is reached, there is the condition of acromegaly seen. Here there is widening and thickening of the hands and feet; thickening of the bones of the skull, which is most noticable in the frontal bones, and causing enlargement of the head; and a general enlargement of all of the skeleton.

Experiments have been done that have more or less proved the above. Putnam, caused acromegaly in adult dogs by injecting extract of the anterior portion of the pituitary gland.

Also when a tumor destroys the anterior portion of the gland, before closure of the epiphyseal lines, there is delayed closure and pituitary dwarfism. Removal of the hypoohysis in young animals causes dwarfism, and feeding these animals with anterior pituitary extract caused them to grow again.

When there is an eosinophilic adenoma of the hypophysis, with the resulting increase of anterior pituitary extract, acromegaly follows in adults, and gigantism in younger persons.

The part played by the gonads is less well known in their influence on bone growth. However it has been seen that hypofunction or castration of animals results in a delayed closure of the epiphyseal lines, and an increased longitudinal growth of the long bones beyond their usual span.

Hypofunction of the thyroid is seen in cretins, with a condition of dwarfism resulting during the normal growth period. There is persistance of open epiphyseal lines after the normal growth period is passed.

Evans believes that the thyroid affects the growth of bone only indirectly through its action on the anterior lobe of the pituitary gland. A hypofunction of the thyroid depresses the pituitary function resulting in cretinic dwarfism. Hyperfunction of the throid seems to have little if any influence on bone growth. (22).

Buelbring experimented on young parathyroprival rats, and rats treated with parathormone. Normally there was no increase in retention when the content of calcium was increased in the diet. After parathyroidectomy there was at first increased retention of calcium and phosphorus with every kind of diet, but this increase abated after some time. The administeration of Para-thormone reduces the retention of phosphorus and calcium. Calcium deficiency in the bones of normal animals is the result of both of a calcium-poor and calcium-rich diet. The phosphorus content of the bones is reduced by a calcium-rich diet and increased by a calcium-poor one, so that the quotient $\frac{Ca}{P}$ after a calcium-poor diet is lowered and after a calcium-rich diet is raised.

As a result of parathyroidectomy a deficient deposit of calcium occurs in the bones, which leads to increased calcium impoverishment within the first two weeks, but beyond this period, the deficiency grows less distinct.

This deficiency is greatly reduced by the administration of greater quantities of calcium; but with a calcium-poor diet is not so great as that of controls.

Para-thor-mone reduced the phosphorus and calcium content of the bones and all the more so with excess intake of calcium the effect of para-thor-mone is less intense, in fact, in this case the chemical composition of the bones approaches normal.

She found further that histological examination after a parathyroidectomy shows reduced bone metabolism but a marked degree of the latter after para-thor-mone treatment. At first this hormonic effect is reinforced by simultaneous maximum administration of calcium, manifesting itself in increased bone destruction, which can be seen in the increased absoption by masses of osteoclastic giant cells. The doses of para-thor-mone when large, subordinate the effect of the calcium. After long treatment with large doses there developed in the bones changes which have all of the ear-marks of ostitis fibrosa. (6).

SUMMARY

In the study and writing on the growth of bone, it is quite evident from the material presented that the processes taking place simultaneously of vegetative and mechanical bone growth, are necessary to one another in order that the final adult form of normal bones be attained from the starting point of the original mesenchymal tissue which first becomes evident in the gastrula stage of the embryo.

I have gained a much better understanding of the problem myself from my study, and I hope that anyone who may read this thesis may also gain a little better comprehension of it. I have discovered that there are some parts of the process that seem to be quite well understood and agreed upon, but there are also some phases that have as yet not been accepted and are only theories. I have attempted to bring out the phases that seem to be generally considered as fact by most of the authors, and have tried to illustrate these by clinical references, and experiments.

Perhaps some of the pathology met with in clinical work where bone is involved, may be better appreciated by myself and the reader, if the physiology is first

known and kept in mind. For, an upset in some phase of the physiological normal growth of bone brings about various pathological states that become manifest depending on the phase or phases disturbed. These upsets may be embryonic, nutritional, vascular, neurogenic, or catabolic in nature, depending on when, how, and why they take place.

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