INTERMITTENT BONE CHANGES AND MULTIPLE CARTILAGE DEFECTS IN CHRONIC STRONTIUM RICKETS IN RATS

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In skeletal disease of man bone changes are demonstrably intermittent (King 1935; Gilmour 1947; Fairbank 1951; Follis and Park 1952; Dreizen, Currie, Gilley and Spies 1956; Shiels, Neuhauer and Bowman 1957) and have been induced by periodic administration of cortone or vitamin D (Storey 1958, 1960a). The present work shows that a continuous stimulus in rats also may give intermittent bone changes. Here, on giving strontium at a dosage which induces rickets in young rats, cartilage undergoes interrupted ossification shown by metaphysical lines. Moreover, multiple nodules of cartilage are sequestrated into the formed bone. A general account of the changes only is given here.

REVIEW OF LITERATURE ON STRONTIUM AND BONE CHANGES

Lehnerdt (1910) first demonstrated strontium-induced skeletal defects and later studies showed their rachitic nature (Shipley, Park, McCollum, Simmonds and Kinney 1922). This form of rickets is incurable by either normal or excess vitamin D administration (Sobel, Goldfarb and Kramer 1934); alkaline phosphatase activity is unchanged (Sobel, Cohen and Kramer 1935b). The defect may be due to preferential binding of Sr instead of Ca by a component of the cartilage matrix (Sobel 1954). With adequate dietary calcium, phosphorus and vitamin D, strontium induces metaphysical changes and lowers the percentage of ash in bone without a widened epiphysial cartilage (MacDonald, Nusbaum, Stearns, Ezmirlian, McArthur and Spain 1951; Follis 1956). Strontium has been advocated for the treatment of post-menopausal osteoporosis (Shorr and Carter 1947) and its usefulness confirmed (McCaslin and Janes 1959). The nature of the action of strontium is not clear: it might seem paradoxical that an element known to induce "rachitic" changes could also inhibit the development of osteoporosis.

EXPERIMENTAL PROCEDURES

Strontium carbonate was incorporated into Barastoc diet (a local proprietary food) and fed daily, together with water, to young (50–75 grammes) and adult (200–250 grammes) rats of both sexes. The diet contained approximately 1.5 per cent of calcium, 1.8 per cent of strontium and 0.90 per cent of phosphorus.

Animals were killed with ether at intervals during the first month and thereafter monthly for seven months. The skull, femur and tibia were dissected from the soft tissue, cut in section and fixed in 10 per cent formol saline.

Specimens of bone were decalcified in 5 per cent nitric acid and embedded in paraffin wax; selected bones were embedded without prior decalcification in polyester resin (Ueckert 1960). Sections cut at 7 μ were stained by both Ehrlich's and Weigert's haematoxylin stains. Selected sections were stained with: periodic acid-Schiff; Alcian blue; Schmorl's canaliculi stain; silver impregnation and Von Kossa's stain.

Identification of calcified tissues presenting little difficulty in undecalcified sections is described here to avoid needless repetition. Microradiographs of strontium-rachitic bone demonstrate that areas staining with haematoxylin, periodic acid-Schiff and Von Kossa's stain can with confidence be designated calcified. In decalcified sections Ehrlich's haematoxylin is equally reliable in detection of sites of previous calcification.
RESULTS

MACROSCOPIC APPEARANCES

Control rats (12)—In both young and old rats the long bones have an endochondral growth centre at each end (Fig. 1). This consists of a narrow epiphysial cartilage and a dense metaphysis merging into a narrow white bone shaft with a well-defined medullary cavity.

Strontium-treated rats (50). Young rats—At three weeks rats had a “rachitic” gait and subsequently some developed spinal kyphosis, bent tibiae and irregular white instead of orange enamel on anterior teeth. Although a few rats with extreme changes died the majority survived, became healthier, more active and slowly gained weight so that at seven months they were approximately two-thirds as heavy as controls. The most obvious changes occurred in the distal end of the femur and proximal end of the tibia. By the end of three weeks the epiphysial cartilage was grossly widened and the metaphysis was a mass of soft white tissue (Fig. 2). Subsequently endochondral ossification proceeded so that the cartilage plate, although irregular in outline, approached normal width again (Fig. 3).

After two months there was considerable variation; some bones were normal in form, others bent posteriorly and in yet others remodelling of the metaphysis was incomplete with marrow alternating between white transverse bands of tissue (Fig. 4).

After three months transverse bands were increased in number; the site of the original metaphysis still remained unchanged; in some bones discrete nodes of cartilage were present either partly or completely separated from the irregularly widened epiphysial cartilage (Fig. 5). The diaphysis was still hard and brittle.

After four to five months some bones were extremely bent, with transverse bands and small nodules of cartilage in the metaphysis; similar but less extensive changes were present after six months. By seven months in both tibia and femur the epiphysial plate was still slightly irregular and there was a wedge-shaped medially placed mass of white tissue. Remnants of transverse lines were seen in the marrow cavity (Fig. 6). The skull showed no change while the enamel of the incisor teeth was still white and pitted.

Adult rats—Changes were less severe and extensive in adult rats; after three months the first fine transverse bands had developed in the upper tibial metaphysis but not until five months was there slight widening of the epiphysial cartilage and a metaphysial wedge of tissue.

At seven months the bone shape was normal but on section the metaphysial wedge was larger and remnants of transverse bands still persisted (Fig. 7). The skull was unchanged but the enamel of incisor teeth was white and pitted.

MICROSCOPIC APPEARANCES

Control rats. Young rats—The epiphysial cartilage consists of longitudinally arranged columns of cartilage cells in homogeneous matrix which, in the hypertrophic zone, is calcified to the width of the last two to three cells. Alcian blue staining shows calcification to be associated with fine intercellular globules which accumulate until they hide the matrix. From the metaphysis vessels and cells grow along the resorbing cartilage columns; on persisting calcified cartilage cores bone matrix is laid down. Continued growth gives metaphysial trabeculae which are continuous with the bone shaft where remodelling gradually takes place until all traces of calcified cartilage are removed and lamellar bone remains. In the cranial vault, on margins of bones and sutures appositional growth occurs; here bone calcifies almost as quickly as it is laid down so that only fine osteoid seams are demonstrable. A few reversal lines are present in the bone.

Adult rats—In old rats differences are of degree only: the epiphysial plate and zone of calcification is narrow, metaphysial trabeculae shorter but wider and the remodelling zone less extensive. In the shaft and the skull Haversian systems and reversal lines are few.

Strontium-treated rats. Young rats. 1. Long bones: tibia and femur—After seven days calcification has ceased and both epiphysial cartilage and osteoid seams are wider than normal.
Figures 1 to 7—Effect of strontium diet—macroscopic appearances. Figure 1—Tibia of young control rat. (×2.) Figure 2—Tibia of young rat on strontium diet for three weeks. The epiphysial cartilage is widened and the metaphysis consists of osteoid tissue. Note the spontaneous "healing" of the lower part of the cartilage plate. (×2.) Figure 3—Tibia of young rat on strontium diet for four weeks. The epiphysial cartilage is slightly widened and a new metaphysis has formed separated from the original osteoid one by marrow cavity. A similar pattern is seen at both the proximal and distal ends of the bone. (×2.) Figure 4—Tibia of young rat on strontium diet for two months. A second dense transverse band of osteoid tissue is present in the shaft of the bone. (×2.) Figure 5—Tibia of young rat on strontium diet for three months. Towards the middle of the epiphysial plate a nodule of cartilage projects down into the metaphysis; here a number of transverse bands of osteoid tissue are prominent. (×6.) Figure 6—Tibia of young rat after seven months on the strontium diet. The epiphysial cartilage is of normal width and the middle of the metaphysis consists of an irregularly shaped wedge of osteoid tissue. (×2.) Figure 7—Tibia of adult rat after seven months on the strontium diet; a sharply defined wedge of osteoid tissue forms the middle of the metaphysis. Note the single thin transverse band in the tibia and the three dense ones in the upper end of the fibula. (×2.)
By fourteen days where the cartilage intercellular matrix fails to calcify the chondrocyte lacunae become flatter and some, but not all, contain cells. Vessels no longer grow regularly along chondrocyte columns but penetrate between zones of flattened hypertrophic cartilage to form large vascular tufts which together with connective tissue and macrophage cells are associated with removal of cartilage matrix. In the metaphysis osteoid tissue, lined by large osteoblasts, forms on calcified cartilage cores or on calcified bone margins.

After three weeks the epiphysial cartilage is extremely wide and circumscribed areas or transverse bands of matrix now calcify. This matrix may be resorbed completely by vascular connective tissue and replaced by osteoid material. Zones of shrunken chondrocyte capsules are not removed but become enased by osteoid tissue and subsequently calcified. The metaphysis now consists of a mass of osteoid tissue encasing a network of calcified cartilage in which transverse strata of compressed chondrocyte lacunae lie. By four weeks the cartilage plate is narrower and partly replaced by osteoid tissue. In some rapidly growing animals the metaphysis consists of as many as three distinct layers of osteoid tissue, separated by transverse strata of flattened hypertrophic zone, encasing longitudinally arranged calcified bones.
Calcification of cartilage matrix has occurred in the lateral aspects of the epiphysial plate with formation of a partly calcified bone shaft; in the middle of the epiphysial plate calcification has ceased and a longitudinally arranged band of osteoid forms part of the metaphysis. (Von Kossa, Erös, x 12.) Figure 11—Higher power of part of the metaphysis seen in Figure 10 showing endochondral ossification with calcified cartilage matrix and bone encased by osteoid tissue. Note the transverse band of calcified bone trabeculae between longitudinally arranged cartilage remnants in the metaphysis. (Von Kossa, Erös, x 60.)

cartilage cores. In other animals marrow separates the metaphysial osteoid tissue into transverse bands.

After two months the epiphysial cartilage is irregular in outline but in places endochondral ossification is now proceeding in a more regular manner. The metaphysis may consist of alternating transverse bands of different structure consisting of either irregular or more regular osteoid trabeculae encasing calcified cartilage core and bone; these alternating layers may be contiguous or separated into transverse bands by marrow (Figs. 8 and 9).

In all bones a dense osteoid mass marks the site of the metaphysis when strontium was first administered. Here small areas of diffuse calcification are present in osteoid tissue lined by small osteoblasts and a few osteoclasts confined to calcified bone margins. One bone examined shows different cartilage changes. In the middle of the epiphysial plate cartilage columns are no longer single, but arranged in groups and, in the hypertrophic zone, chondrocyte lacunae are larger and elliptical in shape. The cells are irregularly arranged, intercellular matrix is diminished in amount and, in contrast to nearby cartilage, fails to calcify. Metaphysial vessels instead of growing along chondrocyte columns run at random beneath the cartilage
FIG. 12
Photomicrograph of section of the tibia from a rat on strontium diet for three months. A sharply defined wedge-shaped area of osteoid tissue is present in the metaphysis. (Haematoxylin and eosin, ×16.)

FIG. 13
Photomicrograph of section of the tibia from a rat on strontium diet for three months showing the cartilage plate folded down into the localised osteoid wedge in the metaphysis. Chondrocyte lacunae in the fold area are larger and cartilage matrix has failed to calcify in the hypertrophic zone. Compare this area with the right hand side of the photograph where endochondral ossification proceeds with formation of a partly calcified metaphysis. (Periodic acid-Schiff, Tartrazine, ×100.)
plate and a longitudinal band of osteoid tissue forms in the middle of the metaphysis (Fig. 10). In the lateral aspects of the metaphysis cartilage matrix calcifies and, with subsequent endochondral ossification, becomes enclosed by osteoid tissue and divided into layers by transverse bands of calcified bone (Fig. 11).

After three months the epiphysial plate is still slightly widened and in the metaphysis are one or more sharply defined wedge-shaped masses or transverse bands of osteoid trabeculae in which calcified cartilage or bone is absent (Fig. 12). In some specimens a fold of cartilage projects into the metaphysis; chondrocytes in and adjoining these cartilage folds are no longer arranged in orderly columns nor is the matrix calcified. As the cartilage plate folds farther the central area forms a core of dense fibrous tissue from which radially placed cartilage columns grow; the proliferative zone of chondroblasts is situated in the middle and the hypertrophic chondrocytes peripherally (Fig. 13). Resorption of cartilage matrix and replacement with osteoid continues so that eventually the cartilage fold becomes separated from the epiphysial plate to form a nodule of cartilage enclosed, partially or completely by metaphysial osteoid tissue. Lateral to these localised cartilage plate defects calcification and

FIG. 14
Photomicrograph of metaphysial area from a rat on strontium diet showing two nodules of cartilage partly surrounded by osteoid trabeculae. The proliferative layer of cells is situated towards the middle, and cartilage columns grow out to the periphery of the nodules. (Periodic acid-Schiff, Tartrazine, × 60.)
endochondral ossification continue and a diaphysis still forms. A number of transverse osteoid bands remain in the marrow cavity and the site of the original metaphysis still consists largely of osteoid tissue which has undergone little remodelling.

Between the fourth and seventh month the epiphysial plate defects become increasingly complex and variable. These are described here in order of increasing severity, not chronologically, as the degree of change is related to the severity of the rachitic change in individual animals.

Slight changes—

The epiphysial plate is continuous but in the metaphysis a number of cartilage nodules of different sizes and shapes are present (Fig. 14). In one case a large nodule encroached on the posterior border of the diaphysis; in another cartilage remnants were on the external surface of the bone. Still others were in the middle of the bone near the mass of tissue marking the site of the original metaphysis. Some of these nodules are encased by osteoid tissue but others are free in the marrow cavity although remodelling still occurs around them. An occasional nodule is in the epiphysis.

Moderate changes—

The epiphysial plate is continuous but forms a series of folds involving both the epiphysis and metaphysis where nodules and fragments of cartilage are encased by osteoid tissue. In some small areas the bone supporting the cartilage plate may be perforated by columns of cells growing up into the epiphysis from the resting chondrocytes of the epiphysial cartilage.

Gross changes—

The epiphysial plate is no longer continuous and is either perforated by vessels or disrupted into fragments. Where the blood vessels perforate the epiphysial plate the adjoining cartilage is arranged in the form of nodules (Fig. 15). When the epiphysial plate is disrupted the lateral aspects of the cartilage remain connected to the shaft while the free ends bend up into the epiphysis leaving large nodules behind in the metaphysis (Fig. 16). In addition fragments form growing nodules, some within the epiphysis and others attached to the inner aspect of the articular cartilage.

Changes in the epiphysis are related to the degree of change in the epiphysial plate: nodules or areas of cartilage are not only derived from the epiphysial plate but also from the lateral aspect of the growing epiphysis. Cartilage forming from this site follows the pattern seen in the early stages of strontium rickets, that is to say, bands of cartilage matrix separated by marrow and bone trabeculae remain in the epiphysis. In animals with disruption of the cartilage plate the epiphysis is flatter than normal.

At seven months the amount of osteoid differs but in most animals the juxta-epiphysial wedge is still present. Silver impregnation reveals this osteoid tissue to be partly woven, partly lamellar in structure, and trabeculae are lined by small spindle cells and osteoclasts and osteoblasts are difficult to find; in the trabecular interstices fatty marrow predominates. This mass and other transverse osteoid bars, although reduced in content, persist as far down as the site of the original metaphysis. The shaft of the bone is now largely calcified and high power examination shows widened eccentric crescents or rings of osteoid lining margins of small vascular channels; reversal lines are not numerous but those between osteoid and calcified matrix are extremely wide and deeply stained with haematoxylin; under high magnification granules extend from the reversal line out into the surrounding uncalcified matrix (Figs. 17 and 18).

In the distal end of the tibia the degree of bone change is considerably less. In the femur, although not as extensive, changes closely follow the pattern described in the tibia.
FIG. 15
Photomicrograph of the tibia of a rat on strontium diet. The epiphysial plate is no longer continuous but consists of large nodules of cartilage in the area adjoining the metaphysial osteoid wedge. (Periodic acid-Schiff, Tartrazine, × 60.)

FIG. 16
Photomicrograph of a fragmented epiphysial plate. The metaphysial osteoid wedge no longer adjoins the epiphysial plate and one large nodule of cartilage is still connected to it; others are in the metaphysis and epiphysis. (Periodic acid-Schiff, Tartrazine, × 60.)
Some long bones are bent posteriorly at the site of the original metaphysis where a large osteoid callus has formed. This consists mainly of woven fibrous osteoid tissue containing small patches of calcification, particularly on the external margin of the callus where layers of appositional growth have partially mineralised.

![Figure 17](image1.jpg)  ![Figure 18](image2.jpg)

**Figure 17**—Photomicrograph of vascular canals in tibia of a control rat showing a central vessel with reversal lines in surrounding bone. (Ehrlich's haematoxylin and eosin, ×500.) **Figure 18**—Photomicrograph of vascular canals in tibia of a rat on a strontium diet for seven months. A deeply staining wide reversal line lies between calcified bone and osteoid lining vascular canals. (Ehrlich's haematoxylin and eosin, ×500.)

2. **Skull**—Sagittal section of the skull demonstrates changes especially at sites of appositional bone growth. By the end of the first month appositional and sutural growth areas are shown by a wide osteoid seam; within the bone where remodelling is taking place a faint scalloped reversal line indicates the junction of osteoid tissue and calcified bone. After three months osteoid seams are wider still and bone resorption diminished. At five months although the amount of demonstrable uncalcified bone has decreased detailed study shows that great variation exists in colouration of matrix from that of frank osteoid to mature lamellar bone in which osteocyte processes are detectable; such processes are not seen in osteoid or lightly stained "osteoid" tissue. By seven months the amount of uncalcified osteoid tissue is still further diminished; recently formed appositional layers of bone have few and only faintly staining reversal lines and small vascular canals are lined or obliterated by osteoid tissue.

**Adult rats.** 1. **Long bones: tibia and femur**—Bone changes follow the general pattern described in young rats but to a greatly reduced degree. Not until the third month does a localised defect develop in the epiphysial plate when a wedge of metaphysial osteoid trabeculae is demonstrable. By the end of the fifth month cartilage nodules form and are sequestrated into the metaphysis where masses of osteoid tissue and remnants of transverse band remain in the medullary cavity. After seven months the osteoid metaphysial wedge is larger and extends farther into the medullary cavity where cartilage nodules still persist.

In contrast to young animals the cartilage plate is never disrupted although folds are seen. Transverse bands and masses of osteoid tissue remain in the medullary cavity in contrast to the bone shaft which is largely calcified except for prominent osteoid margins around most vascular spaces (Fig. 19).

2. **Skull**—In the skull there is considerably less osteoid tissue at either appositional or sutural growth areas than in young rats.
DISCUSSION

Dietary strontium containing a high balanced calcium and phosphorus with adequate vitamin D first induces rachitic changes in young animals, but as they grow older a complex series of structural defects develops in bones. The changing nature of the process leaves little doubt that MacDonald and his colleagues (1951) who found little macroscopic sign of gross rickets and Follis (1956) who demonstrated metaphyseal osteoid formation without change in cartilage width observed but part of the developing lesion. The development of rachitic changes is due to a discrepancy between the rate of calcification and matrix formation and in the present experiments strontium clearly inhibited the calcification mechanism even in the presence of adequate calcium phosphorus and vitamin D. The nature of this inhibition is still under discussion for the theory of competitive mechanisms of Sobel (1954) has not been supported by tissue culture studies (Lengemann 1957). Despite this initial rachitic effect slow mineralisation continues although uncalcified osteoid tissue is still demonstrable as rats grow older. This is shown in cartilage and teeth and by the presence of a bone shaft largely mineralised during the experiment.

The healing of rachitic cartilage is associated with calcification of intercellular matrix and endochondral ossification, but in strontium rickets the bone matrix fails to calcify, the metaphysis consisting of osteoid tissue encasing cores of calcified cartilage. Mineralisation of this osteoid tissue and its subsequent remodelling is extremely slow in contrast to healing of rickets caused by lack of vitamin D (Baillie and Irving 1955). Such differences in rate of calcification of osteoid and cartilage tissue have been demonstrated in vitro (Lamm and Neuman 1958). Spontaneous healing of widened cartilage is known in naturally occurring rickets (Park 1939) but the mechanism is obscure and many factors have been implicated. For example change in diet, starvation or illness are important (McCollum, Simmonds, Shipley and Park 1922; Thomas, Howard and Connor 1957; Park 1954). In strontium rickets vitamin D is ineffective, dietary and serum calcium strontium and phosphorus remain relatively constant and animals were not starved; self-imposed restriction of food cannot be eliminated entirely but would seem unlikely as the majority of animals appeared well after the first few weeks on the diet. Recent observations suggest that a mechanism completely different from that operating in calcification of naturally occurring lesions is responsible for delayed mineralisation in strontium rickets. There is evidence that calcium can gradually accumulate replacing strontium at the site of calcification until mineralisation occurs (Sobel, Cohen and Kramer 1935a) and further, that overall discrimination in favour of calcium against strontium takes place in bone in vivo (Likins, Posner, Kunde and Craven 1959);
INTERMITTENT BONE CHANGES AND MULTIPLE CARTILAGE DEFECTS IN STRONTIUM RICKETS 205

Storey 1961) and in tissue culture (Lengemann 1957). Such a mechanism would be consistent with the present findings, particularly the intermittent nature of the calcification process.

The nature of the intermittent healing process in rickets is not simple as there are clearly two interdependent processes—growth and calcification—which can operate at different rates. Thus the growth rate may alter periodically while calcification continues slowly, or growth may be continuous with episodes of calcification of matrix. Finally the intermittent process may occur as the result of local alterations of tissue activity and structure not related to either general growth or calcification processes. Support for the generalised nature of the intermittent changes comes from both tibiae of the same animal; here the growth pattern in the bone is the same in each leg. Similarly when the distal and proximal metaphyses of the tibia are compared, though differences, usually in size of bands of osteoid, exist, the early pattern is similar. Detailed study of transverse bands in the metaphysis suggests that their formation is related to episodes of calcification of widened cartilage matrix but may also indicate alterations in growth rate for, when growth is fast trabeculae are longitudinal and when slow some are transverse (Follis and Park 1952, Park and Richter 1953). Comparison of endochondral and appositional growth sites reveals differences in overall pattern; most appositional sites show no clear evidence of intermittent growth or calcification activity. The only tissue where periodic calcification occurred was in growing dentine, such mineralisation lines being characteristic of the rachitic process in teeth (Kronfeld 1955).

Localised endochondral growth defects develop in the late stages of chronic strontium "rickets." These are associated with inhibition of calcification of part of the epiphyseal cartilage with subsequent alteration in rates of growth and developmental abnormalities; among these are wedge-shaped masses of osteoid tissue in the metaphysis, appearance of multiple cartilage nodules in the metaphysis, epiphysis and bone shaft and perforation and subsequent fragmentation of the epiphyseal plate. The localisation of these defects may be due to a number of factors. First, the shape of the wedge of osteoid tissue suggests local interruption of blood supply, for Trueta and Amato (1960) have shown this to result in wedge-shaped projections of cartilage in the metaphysis; however at no time did they observe wedge-shaped projections and in the present experiments there was no evidence of localised vascular defects. Secondly, as parts of the epiphyseal plate may calcify out of phase with the remainder, disturbance of the orderly sequence of endochondral growth could result in an abnormal distribution of stress with altered architecture of the part. Thirdly, an abnormal distribution of stress within the softened endochondral growth site may induce formation of masses of osteoid tissue of unusual structure beneath "weak areas" of the cartilage plate. Clearly further information is required before the nature of these defects can be decided.

Cartilage nodules have been reported in the metaphysis of children with long-standing rickets (Shipley, Park, McCollum and Simmonds 1922) and renal rickets (Mitchell 1930, McMaster 1935, Gilmour 1947, Müller and Sissons 1951). The present work demonstrates at least three ways in which abnormal cartilage inclusions in bone may occur. First, hypertrophic cells may remain in the metaphysis during development or healing of rickets; this is the common finding in experimental studies (Dodds and Cameron 1939). Secondly, folds may appear in the epiphyseal plate and with continued remodelling nodules of cartilage with a central zone of proliferating cells remain in the metaphysis or epiphysis. Finally, segments of cartilage may separate from the growing epiphyseal plate and form large nodules. While it is clear that small cartilage nodules form by "invagination" of the epiphyseal plate it is less obvious how large ones develop. Some form within the epiphyseal plate and, with further longitudinal bone growth, remain behind in the metaphysis; others probably develop from fragments of cartilage when part of the epiphyseal plate folds up into the epiphysis. Some bones contain multiple nodules of cartilage within the epiphysis and metaphysis with little discontinuity of the epiphyseal plate. This suggests that the epiphyseal plate can periodically
become deformed and restored to normal shape; further detailed study is required to test this supposition.

Abnormal cartilage masses also develop in cartilage dystrophies typified by multiple enchondromatosis and multiple exostosis. Although rickets may occasionally mimic one member of the group (Müller and Sissons 1951) they are considered to be related, not to defective calcification by itself but to anatomical disturbances of the growth process (Keith 1919, Jaffe 1943) and the abnormal cartilage derived from the epiphysial plate (Jaffe 1943, Fairbank 1951). Experimental studies have failed to clarify the position for transplanted epiphysial cartilage does not form exostoses while periosteal grafts may form cartilage nodules (Cohen and Lacroix 1955, Schneider 1956). In the present experiments changes, in some ways mimicking enchondromata, were seen but cartilage enclosed in the bone shaft did not form exostoses. This may be due to the relatively rapid maturation in rats for, by the time cartilage nodules are demonstrable, the growth rate of animals has slowed appreciably.

In strontium rickets uncalcified matrix persists for months in the medullary cavity, in fracture callus, around vascular channels in bone and primitive Haversian systems and only slowly calcifies. Thus further resorption is not often seen in these areas for osteoid tissue is resistant to resorption (Weinmann and Sicher 1955; Bloom, Domm, Nalbandov and Bloom 1958; Storey 1960b) and consequently remodelling of bone is inhibited to a greater or less extent. If a similar restriction of Haversian remodelling occurs in man then these results may be applicable to the understanding of the treatment of osteoporosis by strontium (Shorr and Carter 1947, McCaslin and Janes 1959).

SUMMARY

Continuous strontium administration first induces typical "rickets" in young rats receiving adequate calcium phosphorus and vitamin D but later the widened cartilage spontaneously calcifies intermittently leaving transverse bands consisting largely of osteoid tissue in the metaphysis; in addition to intermittent calcification bone changes indicate that skeletal growth is not uniformly progressive.

Subsequently areas of the epiphysial cartilage fail to calcify and localised defects develop; among these are wedge-shaped metaphysial osteoid tissue masses, "invagination" of the epiphysial plate to form multiple nodules of cartilage with proliferating cells in the middle and hypertrophic ones at the periphery, perforation and fragmentation of the epiphysial plate with formation of large cartilage nodules. Multiple cartilage nodules of different sizes appear in the epiphysis, metaphysis and bone shaft.

Most bone margins are lined by osteoid seams which only slowly calcify and concomitantly resorption is decreased so that the rate of remodelling of the skeleton is diminished. This type of process may help to explain the results of treatment of osteoporosis by strontium administration.

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INTERMITTENT BONE CHANGES AND MULTIPLE CARTILAGE DEFECTS IN STRONTIUM RICKETS


