EFFECTS OF STARVATION, SEPTICAEMIA AND CHRONIC ILLNESS ON THE GROWTH CARTILAGE PLATE AND METAPHYSIS OF THE IMMATURE RAT

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The effects of a short-lasting period of total starvation, and of pneumococcal septicaemia treated with penicillin, upon the skeletal development of the 25-day-old albino rat have been the subject of a recent experiment (Acheson & Macintyre, 1958; Macintyre, Acheson & Oldham, 1958). Daily records were taken of weight and length of the experimental animals and of their litter-mate controls, and assessments were made of skeletal maturity by radiographing the rats once a week. It was found that the traumatic episode, whether illness or starvation, caused an abrupt slowing of skeletal growth, but that the effect upon skeletal maturation was not so marked. The present paper describes the histological appearances of the tissues in the region of the growth cartilage plate of some of the animals which succumbed during the traumatic episode and of others from a similar experiment carried out more recently.

MATERIAL AND METHOD

Full details of the original experiments have already been published (Acheson & Macintyre, 1958), and a summary of the pertinent facts only will be given here.

Experiment I. Sixty-four albino rats, from eight litters, were used. Thirty-seven of them (seventeen males and twenty females) were inoculated intraperitoneally with a virulent strain of pneumococci at the age of 25 days, and the remaining twenty-seven animals were used as controls. Eighteen hours after inoculation treatment of the infected animals with penicillin was started, but only nine of the experimental group survived. Of the remainder, twenty died within 24 hr. of infection, four died on the third day, three on the fourth day and one on the eleventh day. In the majority of these cases of premature death the control animal was also killed. After death the fore-paw, hind-paw, radius, ulna, humerus, femur and tibia from the right side of the body, and the tail of each animal, were decalcified and sectioned for histological examination. The sections were stained with haematoxylin and eosin.

Experiment II. A study was made of forty rats from five litters. At the age of 27 days, thirty of them (fifteen males and fifteen females) were starved for 48 hr., and then, after 24 hr. *ad lib.* feeding, starved for a further 48 hr., so that they had no food for 4 out of 5 days. Four animals failed to survive the second period of starvation and their bones were decalcified, sectioned and stained in the same manner as was described for Exp. I.

Experiment III. In order to obtain fully calcified bone for sectioning, studies were made of a further group of eleven albino rats, aged 25–30 days, from three

litters; all of these animals were weighed daily for 4 days before they were exposed to illness or starvation to ensure that they were growing normally. Two animals were starved for 48 hr. and killed, together with a freely fed litter-mate control; two were starved for two 48 hr. periods, as described above, and killed with their control. Three were given intraperitoneal injection of virulent pneumococci (type III) but were not treated. Two of these died within 12 hr. of infection and the third was killed after 24 hr. This last group also had a litter-mate control which, as with the other animals, was killed with ether. The head of the humerus, and a few millimetres of the proximal end of the shafts, were dissected from each of the animals. Those from the right side of the body were decalcified, those from the left were sectioned in the fully calcified state. In each case the bone was first cut longitudinally until the sections showed the growth cartilage plate and metaphysis. Then the block was turned, and further sections made at right angles to the long axis of the bone. Some calcified sections were stained with cobalt nitrate, ammonium sulphate and haemalum, and some with haematoxylin and eosin; all the decalcified sections were stained with haematoxylin and eosin.

FINDINGS

The normal growth cartilage plate and metaphysis

The growth cartilage plate is a unipolar structure, that is to say, it grows in one direction only (Ring, 1955). The site of growth is in the reserve layer, where mitosis occurs, and this is situated in immediate relation to the bony epiphysis. As each new cell forms it pushes away its predecessor, thus forming columns of cartilage cells, first of increasing maturity and later of advancing degeneracy. The cells passing through this cycle make up the serial and columnar layers of the growth cartilage plate. The process of degeneration of the cartilage cells has two distinct characteristics: first the nucleus enlarges, disintegrates, and finally disappears, and secondly, the cell itself becomes vacuolated and greatly enlarged (Pl. 1, figs. 1, 4). As a consequence the vessels and osteoblasts of the metaphysis are invading a hollow scaffolding. The uprights of this scaffolding are pressed thin by the vacuolation of the cells between them, but maintain their pliability until their contact with the bone-forming tissue is imminent, when they become calcified lamellae (Pl. 1, fig. 2). The dominant cells at the metaphyseal margin are osteoblasts, which are marshalled in their thousands against the calcified lamellae, where they form bone (Pl. 1, fig. 3).

During rapid growth, which is characteristic of the healthy young animal, calcification does not penetrate far, and much of the cartilaginous matrix between the metaphysis and the reserve layer of the growth cartilage plate is uncalcified (Pl. 1, fig. 2). There is, however, an appreciable distance between the earliest new bone and the osteogenic elements which are most advanced into the cartilage. Capillaries can be traced between the delicate newly calcified lamellae, reaching up as far as the degenerate vacuolated cartilage cells (Pl. 1, fig. 3). Nowhere does this process of invasion appear to be held back or restricted; in fact the osteogenic tissues give the appearance of growing freely into empty spaces created by the degeneration of the cartilage (Pl. 1, fig. 3).

The growth cartilage plate and metaphysis in septicaemia and acute starvation

The changes in the normal pattern which occur in response to septicaemia and to starvation are similar, and will be described together. There is a pronounced decrease in the depth of the growth cartilage plate, which is mostly due to a reduction in the size of the columnar layer (Pl. 2, fig. 5; Pl. 3, fig. 8). Distended and degenerate cells are no longer to be seen at the metaphyseal margin, nor is the delicate intercellular matrix which characterizes normal growth any longer evident. As a consequence, the calcified cartilage, which penetrates as far as the serial layer of the plate, has lost its filigree appearance, and has become stout and thick (Pl. 3, fig. 9); calcification is also visible in many of the septae between the cells of the columnar layer. The effect of this increased penetration of calcification is that whereas in health only degenerate or empty cells are being surrounded by calcification, with slowed growth due to septicaemia or starvation, calcium salts are being laid down in a matrix which has not yet been pressed thin by vacuolation, and cartilage cells which only show the earliest evidence of degeneracy become enmeshed in a calcified network (Pl. 3, figs. 9, 10). In septicaemia these appearances manifest themselves within 24 hr. of the animal showing obvious signs of illness (Pl. 2, fig. 7).

Changes at the chondro-metaphyseal boundary, and in the metaphysis itself, are less dramatic and slower to develop. The line of demarcation between cartilage and newly forming bone is sharper than in health; and the new bone gradually comes nearer to the cartilage, and as this happens the number of osteoblasts becomes reduced (Pl. 2, fig. 6). In contrast the number of osteoclasts and chondroclasts increase, and many of these are to be seen at calcified intercellular septa which seem to act as barriers to free capillary and osteoblastic penetration of the cartilage (Pl. 3, fig. 11). The newly formed bony trabeculae are much thicker than in healthy animals of the same age, and frequently the transverse as well as the longitudinal septae become ossified (Pl. 2, fig. 6).

The growth cartilage plate and metaphysis in chronic illness

One male rat recovered from its initial septicaemia, but a few days later developed an otitis media from which it died aged 36 days, when its litter-mate control, also a male, was sacrificed. Throughout its illness the sick rat was fed on a full laboratory diet which was supplemented with milk given by hand from a dropper. Thus, the considerable interference which took place with its developmental processes cannot be ascribed to starvation in this case.

The growth cartilage plate was very narrow and inactive and a deep blue coloration with haematoxylin suggested extensive calcification (Pl. 4, figs. 12, 13), a suggestion which was supported by the radiographic appearances (Pl. 4, figs. 14, 15). The animal was dead for about 8 hr. before the bones were fixed, so that the changes in cell structure may, in part, be the result of post-mortem degeneration: nevertheless the general acellularity of the metaphysis is unlikely to be entirely due to this cause.

DISCUSSION

Measurements of the animals subjected to starvation or septicaemia had previously shown that growth stopped almost immediately after exposure to these adverse circumstances (Acheson & Macintyre, 1958). Histological studies now indicate that narrowing and increased calcification of the growth cartilage plate accompany the slowing of growth, and that *later* there is a decrease in the rate of osteogenesis in the metaphysis.

The thinning of the cartilage plate suggests that the normal balance between rates of cartilage growth and bone formation is disturbed, and that osteogenesis is, for a time at any rate, outstripping the provision of the cartilaginous scaffolding upon which the new bone is laid down. The altered pattern of calcification whereby calcium salts are deposited deeper and deeper along the interstitial matrix and through the septa of the growth cartilage plate (Pl. 2, fig. 7; Pl. 3, figs. 9, 10) is likewise explicable in terms of slowed cartilage growth and maturation. For whereas in health the distension and vacuolation of the cartilage cells causes the intercellular matrix to be pressed thin before calcification occurs (Pl. 1, figs. 2, 4), in the experimental animals extensive calcification precedes these changes and indeed seems to prevent them from occurring at all.

Osteogenesis continues fairly normally for a while and, as a result, new bone is brought up to the very margin of the cartilage, but then osteoblasts become fewer, and further osteogenesis only proceeds with the help of numerous chondroclasts, which permit capillary penetration by eroding the hardened cartilage.

Finally, however, if the general systemic disturbance continues, the osteoblasts vanish, and the whole process of skeletal development is brought almost to a halt.

These histological appearances in experimental animals are consistent with findings in the living child. Increase in stature is a measure of the chondroplasia in the tibiae, femora and the vertebrae; osteogenesis in the epiphyses can be studied in radiograms where it shows up as a series of shape changes in the shadow of the bony epiphysis (in this context it is usually called 'skeletal maturation') (Acheson, 1954, 1957). Study of these two processes has shown that when a child is sick, or when it lives in a poor home, increase in stature suffers a more serious setback than does skeletal maturation (Acheson & Hewitt, 1954; Hewitt, Westropp & Acheson, 1955; Falkner, 1958). Using similar radiographic methods it has been found that in the rat also longitudinal growth seems much more susceptible to interference than skeletal maturation (Acheson & Macintyre, 1958). Thus, the clinical and histological evidence go to support the suggestion already made by Park and his collaborator Follis (Follis & Park, 1952; Park, 1954) that chondroplasia and osteogenesis are dissociable. The nature and degree of dissociation would seem to depend upon the duration and severity of the adverse experience.

Pathogenesis of lines of increased density in radiographs of growing bones

Although Stettner (1920, 1921) and Harris (1926, 1931) both realized that a line of increased density in the radiogram of the metaphysis indicated that a child had suffered a period of arrested or slowed growth, Follis & Park (1952) were the first to suggest that a dissociation between chondroplasia and osteogenesis was the

immediate cause of such lines. They differentiate between a 'transverse stratum' of thickened bone, and a 'growth retardation lattice' of calcified cartilage, both of which are radio-opaque. The first, they believe, is due to continued osteoblastic activity when cartilage growth has slowed, the second to 'the continued growth of the cartilage' with 'osteoblastic and vascular failure' (Follis & Park, 1952). They state (*loc. cit.*) that 'transverse strata in bones may be the result of illnesses of a most temporary and relatively mild nature', whereas 'lattice formation is the result of a growth disturbance of a number of days or weeks' such as 'the severe pneumonias following whooping cough'. This hard and fast differentiation between the two is almost certainly artificial. The formation of a calcified lattice (the penetration of calcium salts deep into the cartilage) followed immediately upon systemic disturbance in the rats discussed in this paper; Harris (1933) commented upon similar changes in puppies which were starved for 72 hr. It is a little more than an exaggeration of the physiological calcification of cartilage which is an essential step in normal bone formation; and the thickened trabeculae illustrated in Pl. 2, fig. 6, and Pl. 3, fig. 11, are evidently the result of ossification occurring on the bulky cartilaginous matrix of the growth retardation lattice. These thickened trabeculae show up very clearly in the radiogram of the metaphysis as a dense shadow and, in animals which survived the systemic disturbance, radiographs taken after recovery revealed a classical 'line or arrested growth' in the diaphysis. In cases where the systemic disturbance is protracted and osteoblastic activity diminishes, the retardation lattice will have less and less bone formed on it, and eventually will itself become the principal reason for a dense shadow in an X-ray of the metaphysis.

It seems, however, that even in the most unfavourable conditions cartilage growth does not come to a *complete* halt. Study of serial radiograms of children in prolonged coma due to tuberculous meningitis show that a certain amount of new bone is still being formed at the metaphysis (Acheson, 1958, and unpublished data). In the experimental animal, Winters, Smith & Mendel (1927) and Quimby (1951) found that immature rats, whose weight was held constant for several weeks, continued to enlarge their skeletons a little, and Follis & Park (1952) observed some growth occurring in the ribs of chronically ill children, which post-mortem were found to have a pronounced 'growth retardation lattice'.

There is a considerable amount of evidence to suggest that the pars anterior of the pituitary gland undergoes atrophic structural changes during starvation which involve, in particular, the acidophil cells (Jackson, 1917; Meyer, 1917; Sedlezky, 1924; Stefko, 1927; Kylin, 1937) and that in such circumstances, there is some withdrawal of the somatotrophic and other hormones (Kylin, 1937; Werner, 1939; Mulinos & Pomerantz, 1940; Stephens, 1941; Vollmer, 1943). Furthermore, it has been shown that anterior pituitary extract, given as a supplement to normal feeding, after the starvation of young rats, improves the quality of recovery (Quimby, 1951; Fábry & Hrůza, 1956).

It is well known that normal cartilage growth cannot take place without adequate secretion of somatotrophic hormone (Asling, Simpson, Li & Evans, 1950, 1954; Ray, Simpson, Li, Asling & Evans, 1950; Ray, Asling, Walker, Simpson, Li & Evans, 1954; Simpson, Asling & Evans, 1950), so it may be postulated that the slowing of chondroplasia in the starved rat is due to the withdrawal of the somatotrophic

hormone, and that a similar mechanism is brought into action during septicaemia and other illness. The phenomenon may, in fact, be looked upon as an example of what Hubble (1957) has called endocrine homeostasis.

SUMMARY

The changes evoked by acute starvation, pneumococcal septicaemia or chronic otitis media, in the growth cartilage plates and metaphyses of immature rats are described. There appears to be immediate slowing of chondroplasia, with more extensive calcification of the cartilage than is normal, followed later by a reduction of osteoblastic activity. The pathogenesis of lines of arrested growth, often visible in the radiogram of the metaphysis of the growing child, is discussed in the light of these findings. It is suggested that withdrawal of the somatotrophic hormone of the anterior pituitary gland may initiate the changes in starvation, and possibly also during septicaemia and other illness.

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EXPLANATION OF PLATES

In the majority of the animals several bones were studied, but in any individual the appearances of growth cartilage and metaphysis were, at the age groups under consideration, remarkably consistent. Therefore all the sections illustrated (figs. 1–13) are from a single representative region, the proximal end of the humerus. The radiograms, however (figs. 14, 15), are of the lower limb and tail which, because of their size, are more suitable for illustration by this method than the humerus.

PLATE 1. Appearance in health

Fig. 1. Healthy female 29 days old. Note the depth of the cartilaginous growth plate. (Rat F. 4, H. & E.) ×70.

Fig. 2. Healthy male, 27 days old. Calcified cartilage, which is black in the photograph, has not penetrated very deeply into the plate. Note that the intercellular matrix has been pressed thin by vacuolation of the cartilage cells before calcification has occurred. (Rat BJ. 6, cobalt sulphide.) ×240.

Fig. 3. Same section as fig. 1. Note that, despite the intense osteoblastic activity, it is only towards the bottom of the photograph that much bone has been formed upon the calcified lamellae. (H. & E.) ×280.

Fig. 4. Transverse section from same block of tissue as illustrated in fig. 2. The degeneracy and vacuolation achieved by the cartilage cells before the matrix becomes calcified are again shown. (Cobalt sulphide and haemalum.) ×670.

PLATE 2. Appearance in septicaemia

Fig. 5. Male which died aged 28 days, 3 days after developing septicaemia. The growth cartilage is not so deep as that of the healthy litter-mate shown in fig. 1, and the greater part of this change has occurred in the columnar layer. (Rat F. 2, H. & E.) ×70.

Fig. 6. Same section as fig. 5. Compare with healthy animal shown in fig. 3 and note bone at margin of cartilage, thickened trabeculae with ossification of transverse septae, and decrease in number of osteoblasts. (H. & E.) ×280.

Fig. 7. Female aged 30 days, killed 24 hr. after an intraperitoneal injection of pneumococci. Compare with fig. 4 and note that the cartilage cells, which are at an early stage of degeneration, show little, if any, vacuolation; the calcified intercellular matrix is therefore thick. (Rat BK. 8, Cobalt sulphide and haemalum.) ×670.

PLATE 3. Appearance in acute starvation

Fig. 8. Female aged 30 days, starved 4 days out of 5. Compare with figs. 1 and 5 and note that there is again a pronounced decrease in depth of the growth cartilage. (Rat AJ. 7, H. & E.) ×70.

Fig. 9. Male aged 30 days, starved 4 days out of 5. In contrast to fig. 2, calcification extends for the entire depth of the columnar layer and reaches the reserve layer. The thickening of the calcified matrix is also seen. (Rat BH. 2, cobalt sulphide.) ×280.

Fig. 10. Female aged 30 days, starved 4 days out of 5. Thickening of calcified matrix is again shown. The cartilage cells are a little smaller and less degenerate than those in the animal which was only sick for 24 hr. (see fig. 7). (Rat BH. 3, cobalt sulphide and haemalum.) ×670.

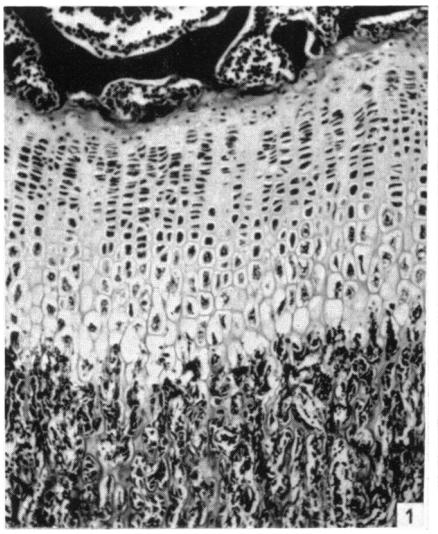
Fig. 11. Section shown in fig. 8. Bony trabeculae are thicker than those in the animal which had septicaemia for 3 days (fig. 6). Osteoclasts, however, seem to have caused erosion at the junction of metaphysis and cartilage, and numerous chondroclasts are also to be seen. There is very little osteoblastic activity. (H. & E.) ×280.

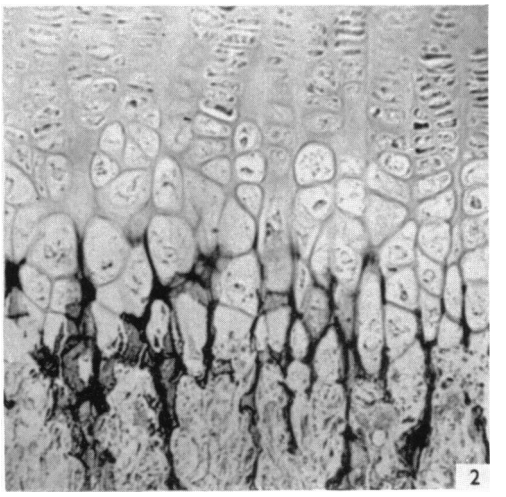
PLATE 4. Appearance in chronic illness

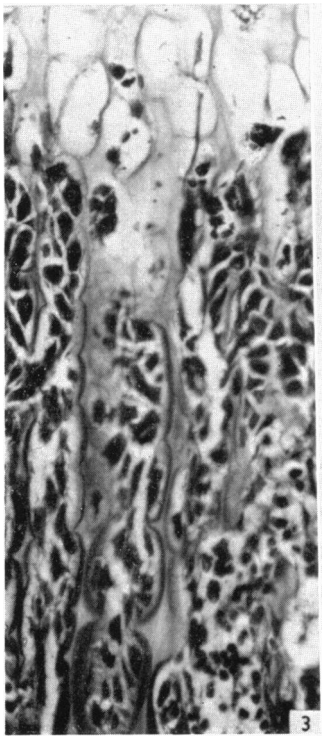
Fig. 12. Male aged 36 days, which died after suffering from otitis media for 7 days. The growth cartilage, which should be distinguished in this figure from the epiphyseal cartilage, shows considerable narrowing. (Rat K. 1, H. & E.) ×70.

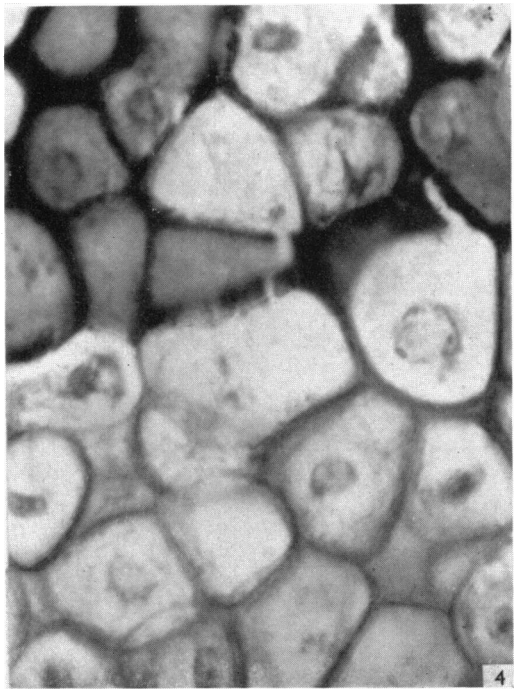
Fig. 13. Section shown in fig. 12. The metaphysis, the trabeculae of which are greatly thickened, consists of osteoid deposited on calcified cartilage matrix. The cellular changes in this section may be due to post-mortem degeneration. (H. & E.) ×280.

Figs. 14, 15. The lower limbs and tail, at death, of the animal shown in figs. 12 and 13, compared with those of its litter-mate control (rat K. 3), which was radiographed simultaneously. The points to note in the sick animal (fig. 15) include its smaller size; a dense shadow caused by calcification at the metaphyses of tibia, metatarsals, proximal phalanges, caudal vertebrae, ischia, etc.; narrowing of the growth cartilage plates; general osteoporosis and, at the top left corner, shadows cast by intestinal contents, supportive evidence that the animal continued to eat well till death. Below the proximal metaphysis of the tibia a 'line of arrested growth' is visible, which was formed during the original septicaemia.









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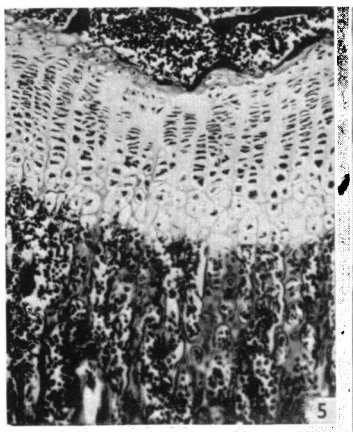
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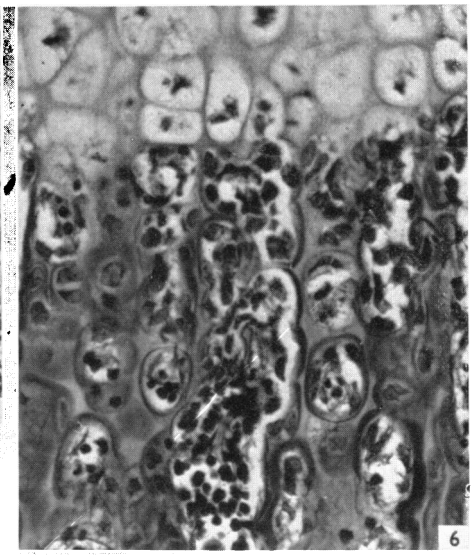
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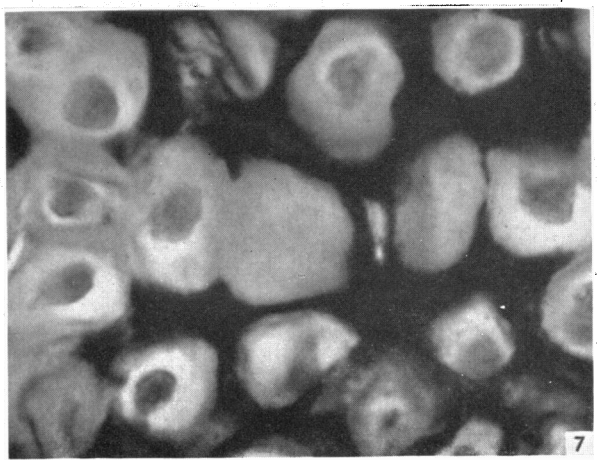
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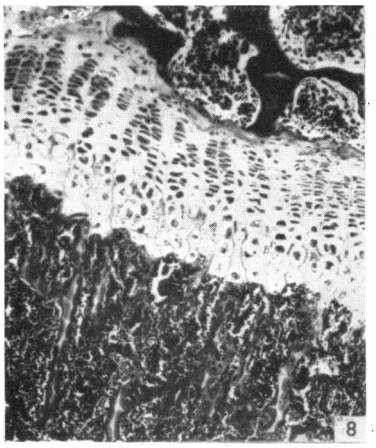
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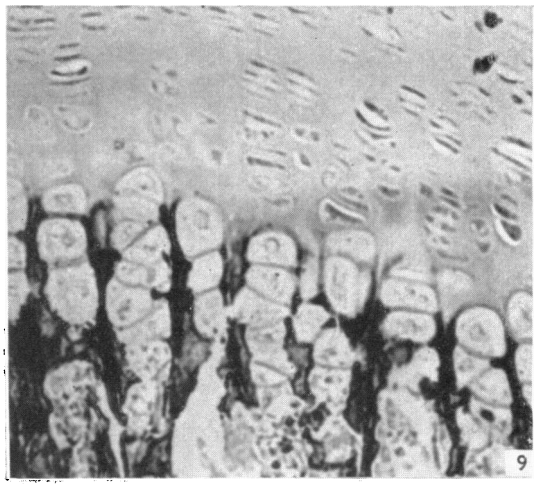
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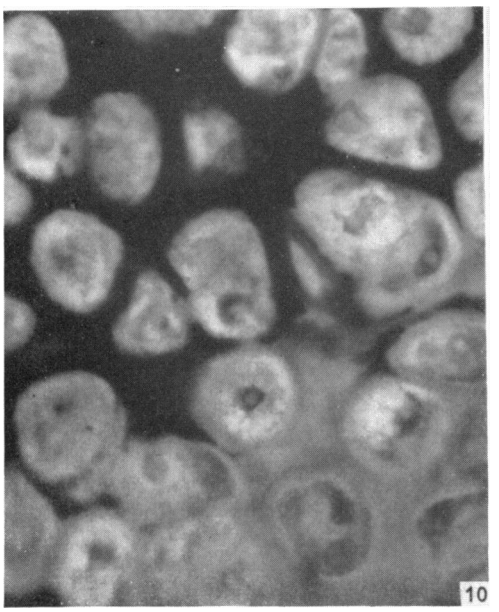
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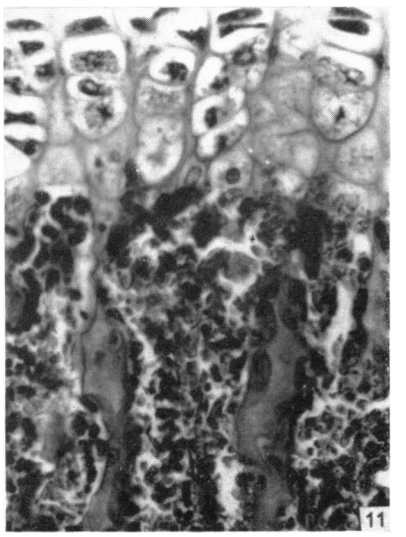
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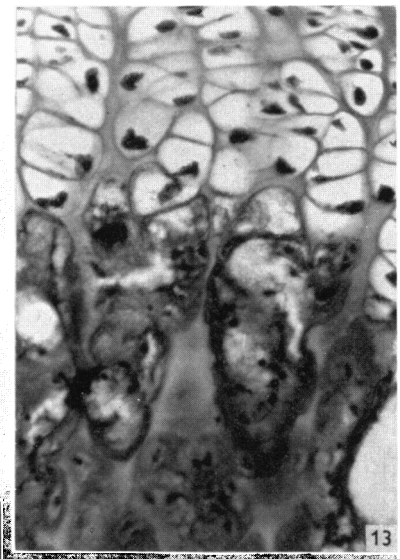
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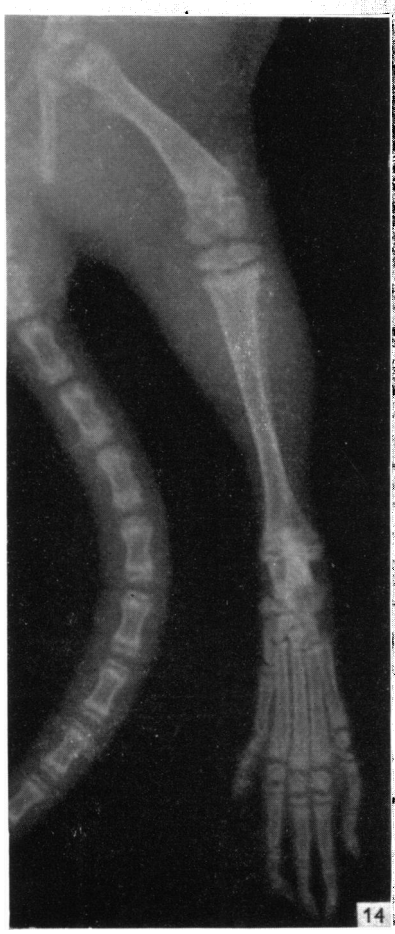
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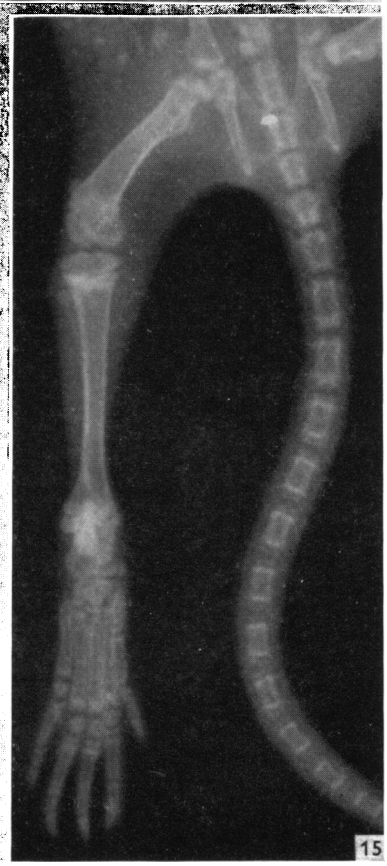
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