

Regeneration of the Growth Plate

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Abstract. The occurrence of growth plate regeneration has been doubted. However, in 5 different series of experiments reported between 1950 and 1986 regeneration of injured parts of growth plates in long bones of rabbits and pigs could be demonstrated. The 1st series implied partial X-ray injury of growth plates in rabbits aged 3–6 weeks. The 2nd series implied autotransplantation of the head of the fibula in rabbits aged 10–21 days. The 3rd, 4th and 5th series implied transplantation of autologous fat grafts into provoked defects of growth plates in rabbits and pigs. The findings show that regeneration of a growth plate occurs when a part of it is injured in such a manner that a bone bridge is not formed between the epiphysis and the metaphysis. Regeneration of a plate is much faster in relation to the growth in length of the bone in the rabbit than in the pig.

The 1st and 2nd series suggest that regeneration takes place by interstitial proliferation of cells from the germinal layer of the uninjured parts of the plate. Signs of partial regeneration of growth plates have been seen in radiographs after operation for partial closure of growth plates in children.

Introduction

The sequels of mechanical trauma to the proximal growth plate of the tibia in rabbits and rats were studied by Banks and Compere (1941). They wrote the following: 'In each instance in which the epiphyseal plate was the focus of surgical attack, it was definitely shown, confirming previous reports by Haas, that this epiphyseal cartilage plate possesses no capacity for regeneration.'

Bidder (1873) was the first to call attention to the post-traumatic formation of a bony bridge between the epiphysis and the metaphysis in a tubular bone. Such a bridge causes mechanical impediment of growth and the resulting deformity depends on the size and the location of the bridge. Although Banks and Compere (1941) saw no regeneration of the epiphyseal plate after mechanical

trauma Langenskiöld and Edgren wrote the following in 1950: 'The experimental results show how the epiphyseal cartilage regenerates when it has been injured in such a manner that bony bridges do not develop between the epiphysis and the metaphysis.'

In a monograph based on a conference on the growth plate held in the West Indies in 1969 (Rang, 1969) nothing was mentioned about regeneration of the growth plate. In a monograph on 'Biology of Cartilage Cells' published by R.A. Stockwell in 1979 nothing can be read about regeneration of the cells of the epiphyseal plate. After transplantation of epiphyseal cartilage Obata (1914) and Heller (1914) observed primary necrosis of the centre of the cartilage followed by almost complete regeneration with hardly any disturbance of growth. However, the differing results of Haas (1919) and Banks and Compere (1941) seem to have

attracted more attention. At a search of later literature no reports considering regeneration of the growth plate were found other than our own.

In research laboratories in Helsinki regeneration of growth plates has been demonstrated in five different series of experiments. In addition definite signs of growth plate regeneration have been seen in radiographs taken after operations in children. As the possibility of regeneration of injured or resected parts of growth plates for decades seems to have been left unnoticed in the literature, publication of a summary of experimentally demonstrated facts concerning regeneration of the epiphyseal plate seems to be justified. The material presented in this article has been described in orthopaedic or surgical journals between the years 1950 and 1987. The series of experiments are reported here in chronological order.

Material and Methods

1st series (Langenskiöld and Edgren, 1950)

The experiments were performed in order to elucidate the pathogenesis of dyschondroplasia. – 23 rabbits aged 3–6 weeks were exposed to localized X-ray irradiation under rectal chloral hydrate anaesthesia. Parts of the distal epiphyseal cartilages of the radius and the ulna were irradiated through a slit in a lead diaphragm. Single doses of about 8000–20000 r were used. The bones were radiographed with varying intervals. The animals were sacrificed at times varying from 10 to 131 days after irradiation. The bones were fixed in formalin and decalcified in nitric acid. Sections were made in paraffin wax in the radio-ulnar plane and stained with haematoxylin.

2nd series (Heikel, 1960)

The experiments were performed in order to find a method of treatment of aplasia of the radius. – On 34 rabbits aged 10, 15 or 21 days 64 autotransplantations of the proximal part of the fibula to the site of the distal part of the radius or to the thigh were carried out under local Xylocain anaesthesia. The animals were sacrificed 2 to 40 days after the transplantation. The extremity in question was examined radiographically, fixed in formalin, decalcified, sectioned and stained with haematoxylin.

3rd series (Österman, 1972)

The experiments were made in order to develop details in the operative treatment of partial closure of the growth plates of long bones. – In 178 rabbits aged 3–6 weeks the distal growth plate of the femur was partially injured by a bone bridge provoking operation. When an epiphysometaphyseal bridge had formed and a growth disturbance had appeared (fig. 9a) then a corrective operation was performed. This operation implied removal of the bone bridge. In the resulting defect a free autologous fat transplant, heterologous cartilage or bone wax was implanted. The operations were performed under local Xylocain anaesthesia. The growth of the bone was followed by radiography and the animals were killed after a period varying from 2 to 150 days. The distal ends of the femora were fixed in formalin, decalcified in nitric acid or in 10 per cent EDTA, embedded in paraffin wax, cut in 7 μ thick sections which were stained with haematoxylin.

4th series (Langenskiöld and Österman, 1979, Experiments performed by Österman)

The experiments were made in order to develop details in the operative treatment of partial closure of growth plates of long bones. – Fig. 10 shows a schematic drawing illustrating how a cylinder including almost 2/3 of the epiphyseal plate was removed from the distal end of the femur of a rabbit aged 4 weeks. The operation was performed on both femora in a series of 38 animals under local Xylocain anaesthesia. In one femur the resulting cavity was filled with a free fat transplant, in the other femur the defect was left to be filled by a blood clot. The growth of the bone was followed by radiography. The femora were treated as in the 3rd series and cut in the sagittal plane.

5th series (Langenskiöld, Videman and Nevalainen, 1986)

The experiments were made in order to develop details in the operative treatment of partial closure of growth plates of long bones. – Pigs aged 3 to 4½ months were premedicated and anaesthesia was induced with intramuscular azaperone and intraperitoneal metomidate. In 14 legs in 9 pigs the proximal growth plate of the tibia was exposed and anterior to the medial collateral ligament a round defect of 5 to 6 mm diameter was made in the surface of the bone at the level of the growth plate. Half of the defect was on the epiphyseal side and the other half on the metaphyseal side of the plate. A round or oval cavity of 6 to 7 mm in diameter was then made in the medial condyle and filled with a free transplant of autologous subcutaneous fat. The growth of the bone was followed by radiography during periods varying from 13 to 285 days. The tibiae were deep frozen and later dissected, fixed in formalin, decalcified in formic acid and embedded in paraffin wax. Sections were made at 7 μ in frontal and sagittal planes and stained with alcian blue, haematoxylin and chlorantin red.

Results

1st series. X-ray irradiation of parts of growth plates in rabbits. Irradiated portions of growth plate cartilage persisted as obliquely situated foci in the metaphyses and were more slowly replaced by bone than normal cartilage. Microscopic examination showed that the injured portions of cartilage were pushed aside by the unirradiated cartilage growing into the irradiated area transversely in relation to the axis of the bone. In several experiments deformities and radiolucent foci appeared which showed similarity to those seen in dyschondroplasia. When one half of the distal growth plate of the radius had been irradiated then lagging behind of ossification could be demonstrated after 9 days (fig. 1a, 2). The unirradiated part of the plate continuing to grow, angular deformity progressed (fig. 1b, 1c). A part of the injured cartilage was left behind in the metaphysis. Another part of it was adhering to the bony plate of the epiphysis. Between these two portions of injured cartilage normal growing cartilage was regenerating (fig. 3). Fig. 4 shows a section of a radius of which 1/3 of the distal growth plate was irradiated 14 days before sacrifice of the animal. The injured part of the cartilage had

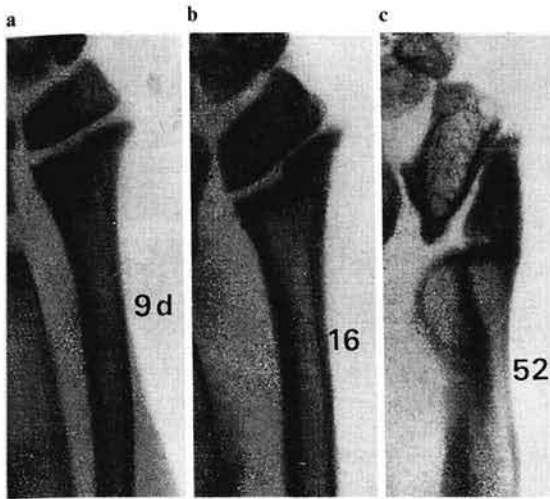


Fig. 1. From 1st series of experiments. Roentgenographs showing growth disturbance in the distal end of the radius of a rabbit after X-ray irradiation of the ulnar half of the epiphyseal plate. **a** 9 days after irradiation. **b** 16 days. **c** 52 days. (From Langenskiöld, A.: *Acta chir. Scand.* 105: 353–363 (1953).)

ruptured into two portions, one being left behind in the metaphysis, the other adhering to the epiphysis. The injured cells were pushed aside by normal cartilage regenerating into the irradiated area (fig. 4b). When a middle portion of the distal growth plate of the radius was irradiated then cartilage portions regenerating from two sides merged after 17 days (fig. 5).

2nd series. Transplantation of the fibular head in young rabbits.

Fig. 6 shows a schematic drawing illustrating the findings in sections of the transplanted heads of the fibulae. After 2 days (fig. 6a) it was seen that the cells of the central parts of the growth plates were severely injured from the lack of blood supply, the peripheral parts showing a normal appearance. After 7 days (fig. 6b) growth had continued from the normal peripheral parts of the plate the injured cells being partly left behind in the metaphysis and partly pressed together by normal growing cartilage bulging against the center of the plate from the periphery. After 14 days (fig. 6c) the plates had regenerated completely. Some unresorbed injured cartilage remained in the metaphysis. Fig. 7 shows a section of a fibular head from a rabbit killed 7 days after transplantation. The situation corresponds to what is schematically shown in fig. 6b. The plate was regenerating by interstitial growth. There was no perichondrium, no structure corresponding to the ossification groove of Ranvier where the plate was regenerating in a direction perpendicular to the axis of the bone. The regeneration seemed to take place by migration of cells from the

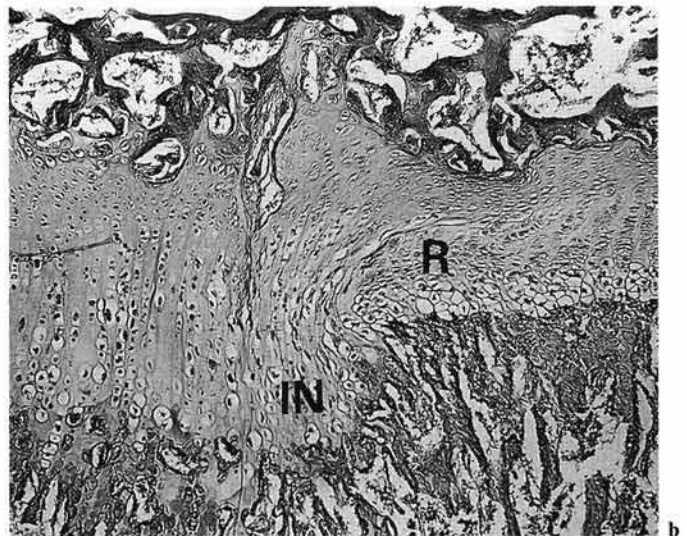
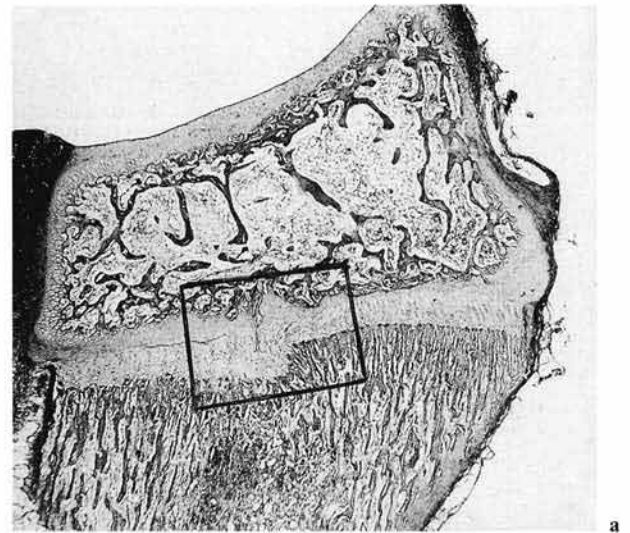


Fig. 2. **a** Photomicrograph corresponding to the state seen in fig. 1a. **b** Photomicrograph corresponding to the square area in a. Injured cartilage marked IN, regenerating cartilage marked R. **a** $\times 15$, **b** $\times 55$.

viable parts of the germinal cell layer. Fig. 8 is a section from a fibular head of a rabbit killed 14 days after transplantation. The plate had regenerated completely and some injured cartilage cells were seen unresorbed in the metaphysis.

3rd series. Experimentally provoked epiphyseometaphyseal bone bridges replaced with implants in rabbits age 3–6 weeks.

Within the first few days after implantation of fat, cartilage or bone wax in the defect produced by resection of the bone bridge the transplant occupied a defect in the

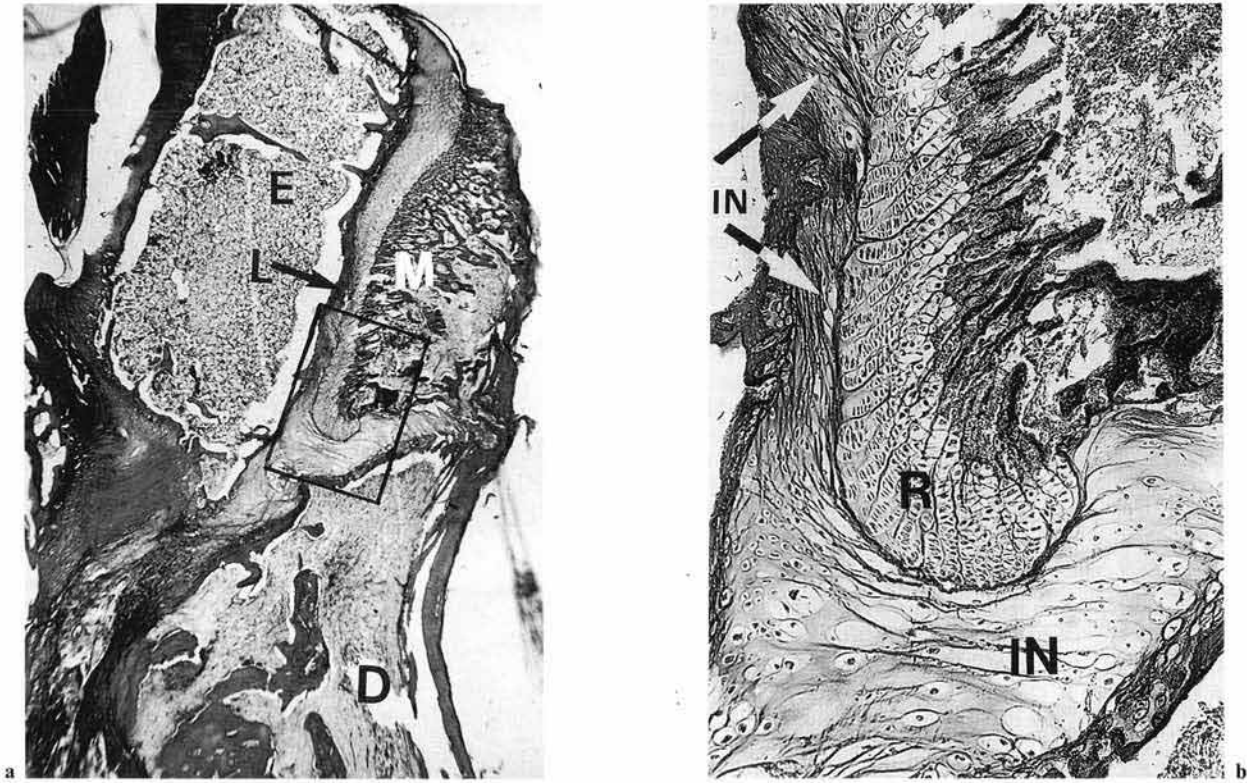


Fig. 3. **a** Photomicrograph corresponding to the state seen in fig. 1c. Epiphysis marked E, metaphysis M, diaphysis D. Borderline between injured and uninjured cartilage marked L (arrow). **b** Photomicrograph corresponding to the square area in a. Injured cartilage marked IN, regenerating cartilage marked R. **a** $\times 12$, **b** $\times 55$.

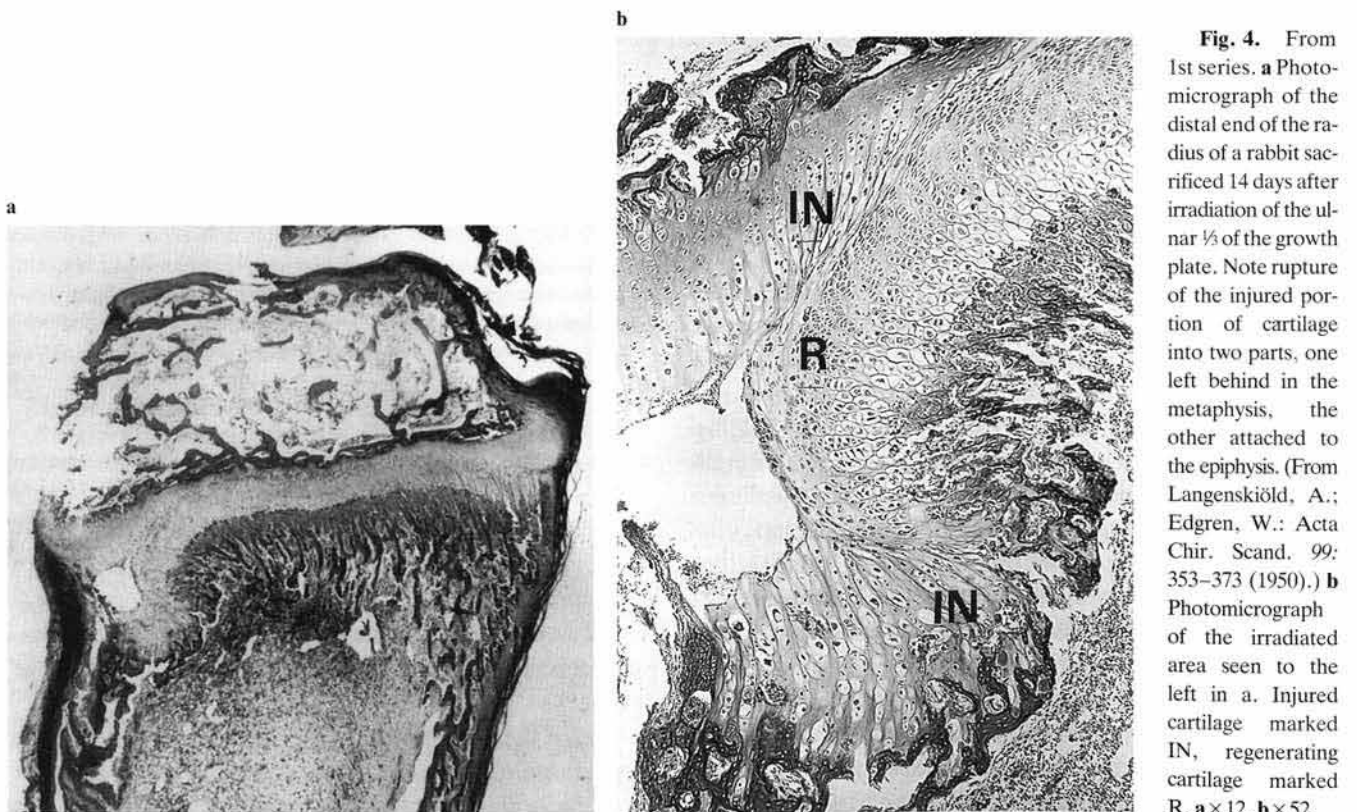


Fig. 4. From 1st series. **a** Photomicrograph of the distal end of the radius of a rabbit sacrificed 14 days after irradiation of the ulnar $\frac{1}{3}$ of the growth plate. Note rupture of the injured portion of cartilage into two parts, one left behind in the metaphysis, the other attached to the epiphysis. (From Langenskiöld, A.; Edgren, W.: *Acta Chir. Scand.* 99: 353-373 (1950).) **b** Photomicrograph of the irradiated area seen to the left in a. Injured cartilage marked IN, regenerating cartilage marked R. **a** $\times 12$, **b** $\times 52$.

Fig. 5. From 1st series. Photomicrograph of a part of the distal end of the radius of a rabbit sacrificed 17 days after irradiation of the middle part of the growth plate. Injured cartilage marked IN, regenerating cartilage marked R. Regenerating portions of cartilage had merged in the middle of the plate. $\times 55$. (From Langenskiöld, A.; Edgren, W.: *Acta Chir. Scand.* 99: 353–373 (1950).)

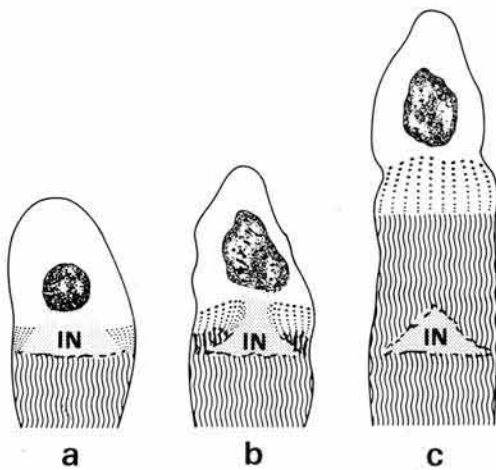
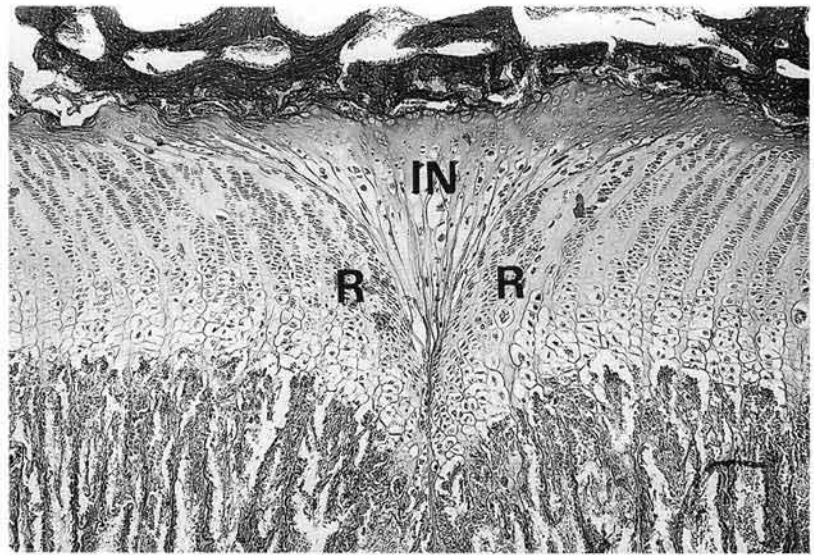


Fig. 6. From 2nd series. Schematic drawing showing regenerating cartilage replacing central parts of growth plate of rabbit fibular head injured from transplantation. **a** Situation two days after transplantation. Injured cartilage marked IN. **b** Situation 7 days after transplantation. Regenerating cartilage bulging from the periphery of the plate against the center, the injured cartilage being left behind in the metaphysis. **c** Situation 14 days after transplantation. Complete regeneration of growth plate. A vestige of the injured cartilage (IN) unresorbed in the metaphysis. (Modified from Heikel, 1960).

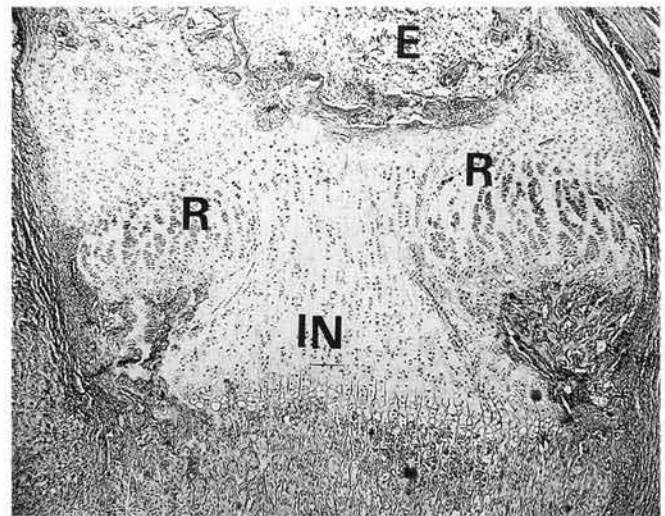


Fig. 7. From 2nd series. Photomicrograph of fibular head of rabbit sacrificed 7 days after autotransplantation to the thigh. Epiphysis marked E, injured cartilage IN, regenerating cartilage R. Compare with fig. 6b. $\times 40$.

epiphysis and the metaphysis. The implant was in contact with the resection surface of the growth plate (fig. 9b). In the second week after the implantation an ossification groove was reformed at the edge of the resected cartilaginous plate and regeneration of it in the direction of the defect could be seen (fig. 9c). In the course of later growth the plate was restored to its normal width, the transplant

or a vestige of it being often left as an obliquely situated focus in the periphery of the metaphysis (fig. 9d).

4th series. Removal of 2/3 of the distal femoral growth plate in rabbits and filling of the defect with a fat transplant (fig. 10).

One week after the implantation of fat in the defect the implant had not changed very much and there was no for-

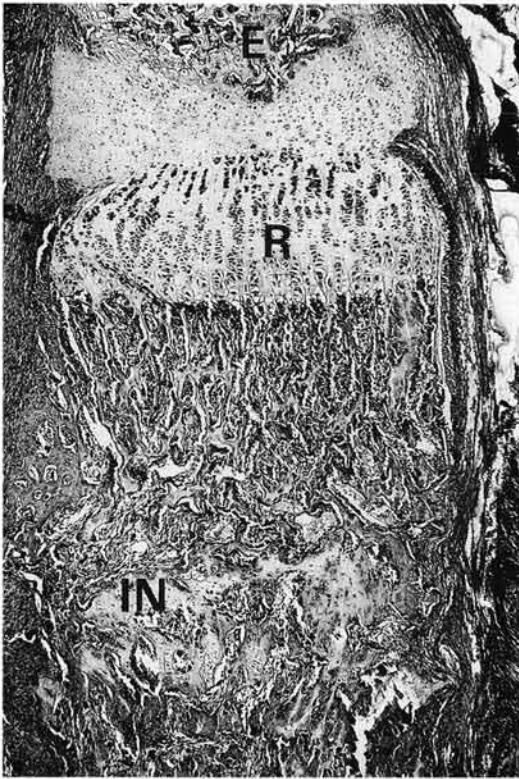


Fig. 8. From 2nd series. Photomicrograph of the fibular head of a rabbit sacrificed 14 days after autotransplantation to the site of the radius. Epiphysis marked E, regenerated cartilage R, vestige of injured cartilage IN. Compare with fig. 6c. $\times 35$.

mation of a bone bridge between the epiphysis and the metaphysis (fig. 11a). When no fat had been implanted in the defect it was filled by bone after a week and there was complete growth arrest. Four weeks after implantation of fat the implant had been left behind in the metaphysis and the growth plate had regenerated almost completely (fig. 11b). When no fat was implanted there was deformation of the end of the bone and complete growth arrest.

5th series. Implantation of fat grafts in provoked defects in the growth zone of the proximal end of the tibia in young pigs.

Radiographs taken immediately after operation showed the cavities as round or oval radiolucent areas (fig. 12a) which later became progressively elongated (fig. 12b). This was seen in all 14 tibiae. In 9 of 12 tibiae examined histologically the elongated cavities were completely filled by living adipose tissue intermingled with strands of connective tissue and blood vessels. In 3 legs small areas of necrotic fat was seen. The volume of the

cavities filled by adipose tissue had gradually increased in parallel with the growth in length of the bone even during 4 months. With continued growth the defect in the cartilaginous plate was gradually reduced by regeneration from the cut edge of the plate. Fig. 13a is a sagittal section of the bone radiographed in fig. 12b. Only partial regeneration of the growth plate was seen. Fig. 13b shows the region of the defect of the growth plate in fig. 13a in a greater magnification.

Signs of Partial Regeneration of Growth Plates Seen in Radiographs of Children after Operations (Langenskiöld, Österman and Valle, 1987)

The phenomenon of gradual reduction of defects of growth plates seen in radiographs of pigs as seen in fig. 12 was histologically shown to be due to partial regeneration of the cartilaginous plate (fig. 13). The same phenomenon of gradual reduction of such defects was seen in radiographs of several bones in children operated on for partial closure of a growth plate (fig. 14a–c). Fatty tissue can be identified by computerized tomography. Thus the CT scanner was expected to demonstrate the nature of the tissue in radiolucent metaphyseal areas enlarged after implantation of fat when epiphyseometaphyseal bone bridges had been resected. The density in Hounsfield Units in the enlarged cavities showed that the fat grafts had grown in size in parallel with postoperatively regained growth of the bone. Postoperative gradual diminution of the defect in the growth plate produced at operation could also be demonstrated in the series of CT pictures (fig. 14c, 15) as it could be in experiments in pigs.

Discussion

The findings in the 2nd series of experiments (fig. 7) suggest that regeneration of injured cells in the growth plate of a very young animal takes place by interstitial growth from a broad layer of germinal zone cells. It must be noted that between the injured cartilage cells and the cells bulging from the periphery there is no layer which could be called a perichondrium and no structure corresponding to the ossification groove of Ranvier. The findings are in accordance with the statement of Rigal (in Rang, 1969, p. 94): 'It is generally accepted that interstitial latitudinal growth occurs in the very young animal, when the germinal zone cells of the growth plate are adjacent to a largely cartilaginous epiphysis, as the tissues are plastic.'

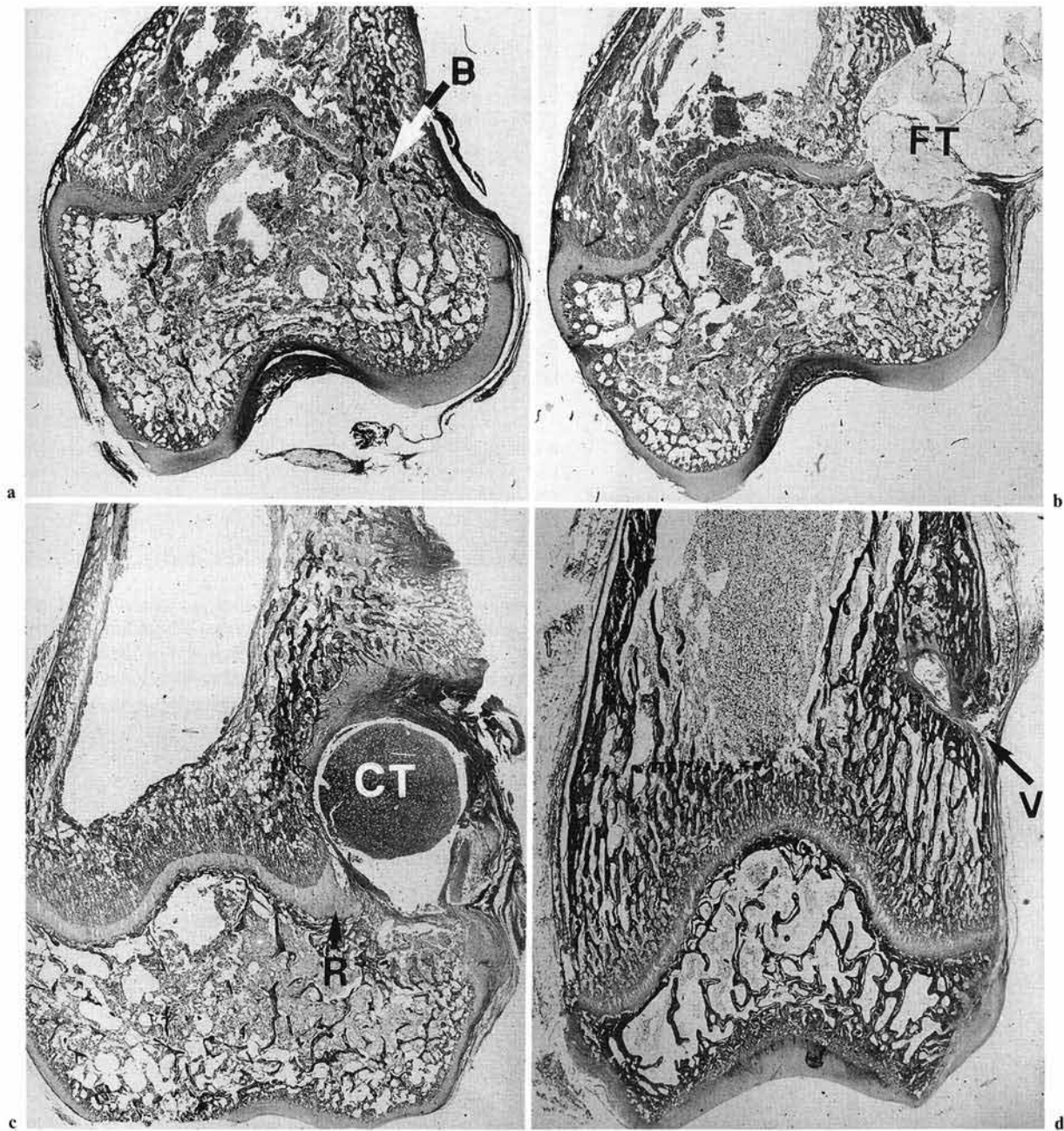


Fig. 9. From 3rd series. Photomicrographs of distal ends of rabbit femora. **a** Two weeks after provocation of epiphyseometaphyseal bone bridge (B, arrow) at the lateral edge of the growth plate. **b** 5 days after resection of bone bridge and its replacement with an autologous fat transplant (FT). **c** 15 days after bridge resection and implantation of a piece of cartilage from a pig. Transplant marked CT, regenerating cartilage R. **d** 84 days after bone bridge resection and implantation of cartilage from a pig. Complete regeneration of the growth plate. Vestige of cartilage marked V (arrow). **a** $\times 7$, **b** $\times 7$, **c** $\times 6.5$, **d** $\times 6.5$.

In the 1st series the histological findings also suggest that the cells replacing the injured part of the cartilaginous plate have migrated from the germinal zone in the uninjured part. In these sections (fig. 2–5) there is no perichondrium and no structure resembling the ossification groove

of Ranvier between the injured cells and the cartilage bulging from the uninjured layer of germinal cells. Also this finding is in accordance with Rigal's studies of normal growth of the epiphyseal plate (in Rang, 1969): 'Although the germinal cells later become adjacent to a rigid epiphys-

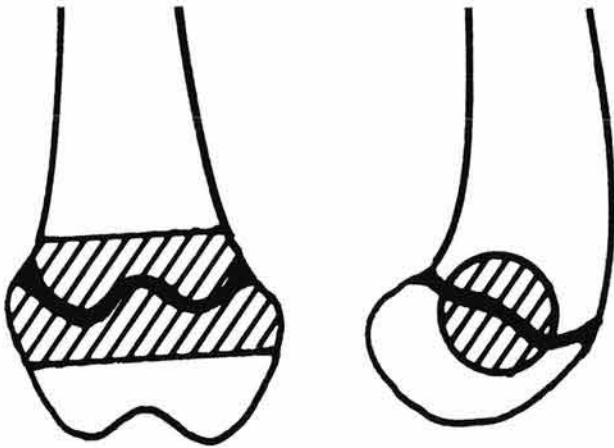


Fig. 10. From 4th series. Schematic drawing showing how a cylinder including about $\frac{2}{3}$ of the growth plate was removed by means of a trephine from the distal end of the femur in rabbits.

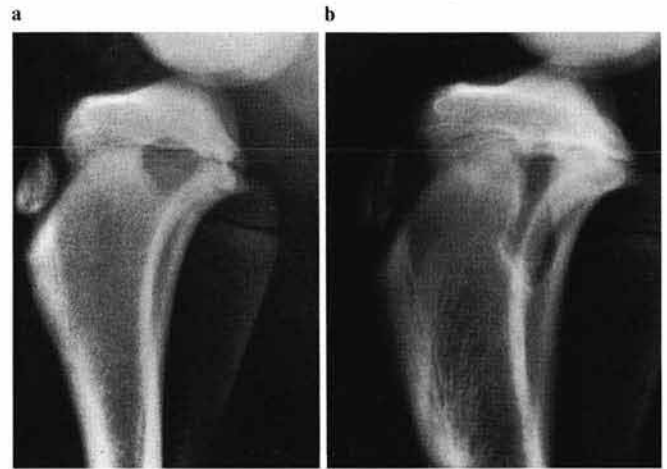


Fig. 12. From 5th series. Side view radiographs of a tibia of a pig. **a** Picture taken immediately after implantation of a piece of fat in a round cavity made in the growth zone. **b** Picture of the same tibia as in **a**, four months after operation. Note elongation of the cavity and diminution of the defect in the growth plate with proceeding growth in length of the bone.

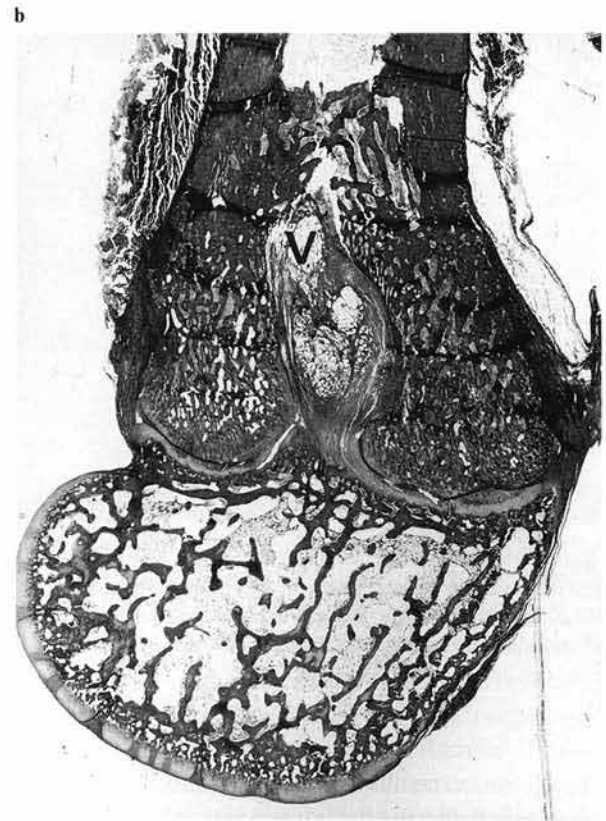
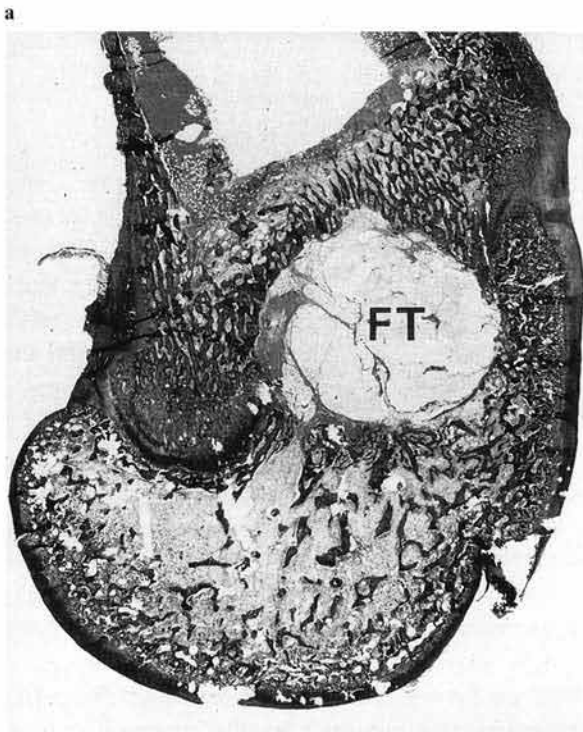


Fig. 11. From 4th series. Photomicrographs of sagittal sections of rabbit femora. **a** One week after resection shown schematically in fig. 10 and implantation of a fat transplant (FT) in the defect. No bone bridge formation. **b** Four weeks after resection according to fig. 10 and fat implantation. Almost complete regeneration of the growth plate. Vestige of fat transplant marked V. **a** $\times 6.5$, **b** $\times 6.5$

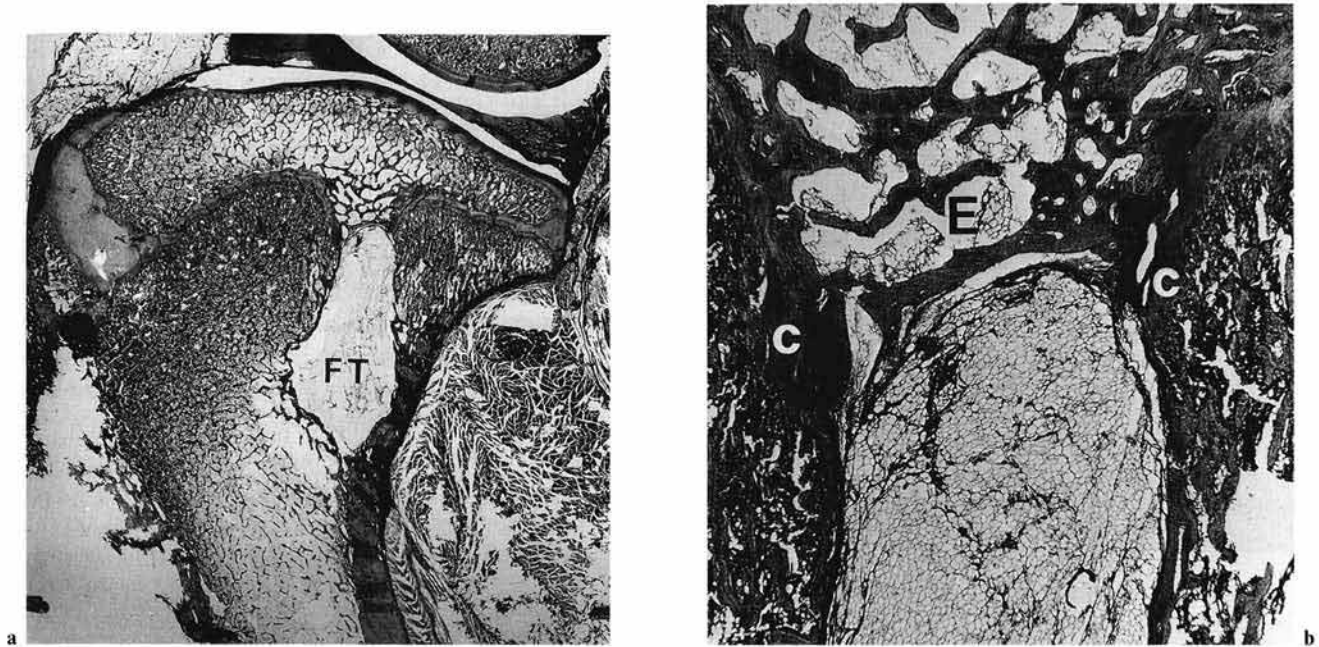


Fig. 13. **a** Photomicrograph of a sagittal section of the tibia seen in fig. 12b as it was immediately before sacrifice of the pig. Note that the cross-section of the implantation area (FT) is greater than the cross-section of the fat containing cavity at the new level of the growth plate, a phenomenon resulting from partial regeneration of the cartilaginous plate. **b** Photomicrograph of the proximal end of the elongated fat transplant. Epiphysis marked E, edges of cartilage at the defect in the plate marked c. **a** $\times 2.5$, **b** $\times 15$.

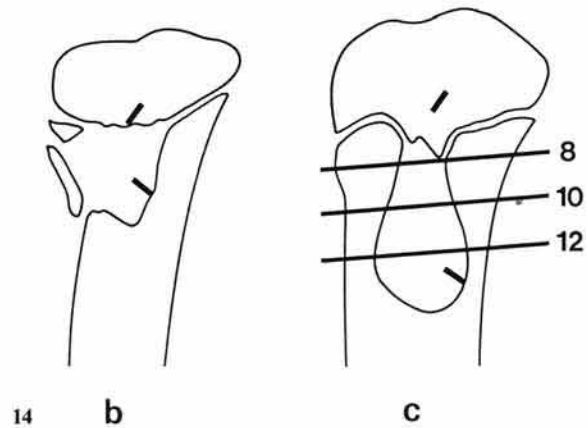


Fig. 14. **a** Side view radiograph taken of the tibia of a boy aged 11 years, 3 years after resection of a centrally situated bone bridge and implantation of fat. Silver clips were implanted at operation in the epiphysis and the metaphysis. Note that the width of the elongated cavity is larger in the implantation area close to the metaphyseal silver clip than close to the new position of the growth plate. **b** Contour drawing of a side view tomograph taken of the same tibia one week after operation. **c** Contour drawing corresponding to the radiograph seen in **a** and showing the levels 8, 10 and 12 of the computed tomography scans seen in fig. 15.

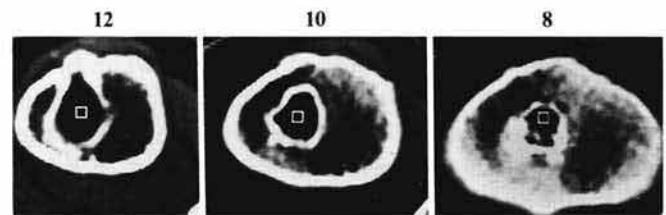


Fig. 15. Computed tomography scans of the tibia seen in fig. 14c taken on the same day as the radiograph seen in fig. 14a. The levels of the scans 8, 10 and 12 are seen in fig. 14c. Note the gradual diminution of the diameter of the cavity with proceeding growth in length of the bone during 3 years after operation.

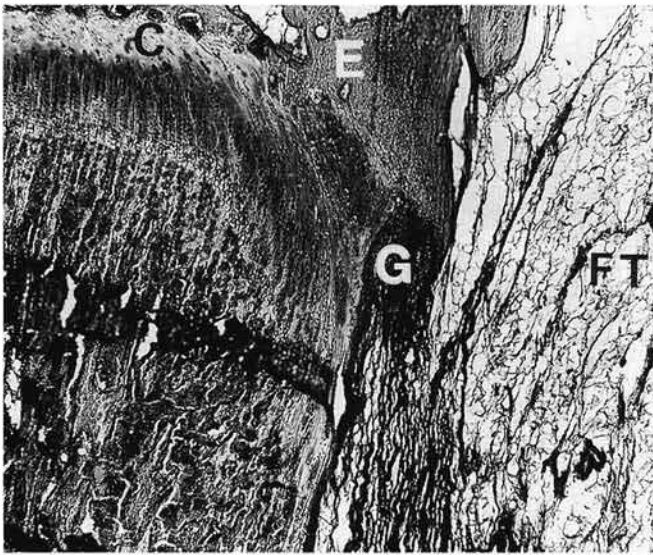


Fig. 16. Photomicrograph of the edge of the regenerating growth plate from a section of the same tibia as seen in fig. 13. Germinal zone of growth plate marked C, epiphysis marked E, fat transplant marked FT and ossification groove of Ranvier marked G. $\times 30$.

al base plate, cartilage retains its plasticity; even at this stage interstitial latitudinal growth continues.'

In the series 3–5 in which a defect of a growth plate has been filled up by a free fat transplant and not by injured cartilage as in series 1 and 2 the diminution of the defect in the plate has been accompanied by the appearance of a structure resembling an ossification groove of Ranvier between the cut edge of the plate and the elongating transplant of adipose tissue (fig. 16). Although the series 3–5 do demonstrate regeneration of the growth plate they do not tell anything about the much discussed question whether a growth plate normally grows in diameter by interstitial or appositional growth.

Series 1 and 2, although being examples of regeneration and not of normal growth, speak in favour of the idea that the epiphyseal plate normally grows in width by interstitial growth in the germinal cell layer of the plate. According to Lacroix (1951) the epiphyseal plate grows in width by appositional growth as a function of chondrocytes of the perichondrial ring. Contrary to the widespread opinion of Lacroix (1951) studies by means of ^3H -thymidine (Rigal, 1962, 1969; Mielke, 1974; Shapiro et al., 1977) and colchicine (Hert, 1972) have suggested that latitudinal growth of the plate takes place by interstitial proliferation of cartilage cells. Hert (1972) wrote: 'The results of the

study provide grounds for rejecting the hypothesis of appositional growth of the epiphyseal plate from perichondrium.' Mielke (1974) wrote: 'One must agree therefore with the conclusions of Rigal ('62) and Hert ('72) that epiphyseal cartilage increases in transverse diameter by interstitial growth.'

Although the question as to the mechanism of growth in width of the epiphyseal plate seems to have been settled, the question as to the histogenesis of the cells of the ossification groove of Ranvier is still unanswered (Shapiro et al., 1977). Ranvier (1889) wrote: The cells forming the periosteal bone probably originate in cells of the cartilage, which are released with their fibres and follow them. The bone thus grows in thickness at the expense of a material furnished by the cartilaginous tissue.

Ranvier's (1889) views were supported by Dahl (1936), Policard (1941) and Langenskiöld and Edgren (1950). Their views were not accepted by Lacroix (1951) whose views have dominated in chapters on the subject in textbooks and in general reviews.

The final proof of the histogenesis of the cells of the ossification groove of Ranvier will possibly give us the key to the understanding of the pathogenesis of some diseases affecting the growth zones of long bones in man.

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