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## CALVÉ PERTHES DISEASE

*With special reference to histological observations*

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Accepted 17.iv.73

Histological examination of cases of human Calvé Perthes disease *in vivo* has been described previously by Perthes (1913), Plemister (1921), Riedel (1922), Ferguson & Howorth (1934), Haythorn (1949), Jonsäter (1953), Ponseti (1956) and Mizuno et al. 1966). A brief summary of the conclusions drawn from the studies available is that necrosis of both bone and bone marrow may be found in the earlier stages of the disease, whereas in later stages there are regenerative changes with development of more or less irregular bone masses. Crushing of the trabeculae has been reported previously, but this is particularly mentioned in cases where biopsy was obtained by curettage (Haythorn 1949) or bone puncture (Jonsäter 1953, Ponseti 1956). It cannot be excluded that such crushing is, in fact, a result which is an artificial product.

The present study comprises a small group of patients with Calvé Perthes disease treated with subtrochanteric or intertrochanteric osteotomy. The operations were combined with opening the hip joints and, as carefully as possible under the control of the eye, removing a thin wedge from the anterior surface of the femoral head, consisting of the articular cartilage and a small part of the ossification centre. Biopsies were taken at various stages of the disease ranging from early in the initial stage to late in the fragmentation stage.

### MATERIAL AND METHODS

The material originates from 13 patients (11 boys and 2 girls) with radiologically verified Calvé Perthes disease. Seven of the cases were bilateral, three right-sided and three left-sided. Treatment consisted of subtrochanteric or intertrochanteric osteotomy of the femur. In three of the cases an adjustment of the position of the femoral head in the acetabulum was performed simultaneously, in order to obtain

Figure 1. Diagram showing that biopsy is taken as a wedge of the articular cartilage, including part of the ossification centre.



better contact. Osteotomy was performed on both sides in one of the seven bilateral cases. The age of the patients at the time of operation ranged from  $3\frac{3}{12}$  years to  $8\frac{9}{12}$  years, average 5.2 years.

In six cases arthrography was made in connection with the operation before the hip joint was opened. After opening the joint the macroscopical appearance of the head was evaluated and a photograph taken. Furthermore, assessment was made of any changes in the capsule and synovial membrane, and in six cases biopsy specimens were obtained from those sources. The biopsy material from the head was taken with a fine chisel, a wedge-shaped flake a few millimetres in breadth being taken from the anterior of the head. This contained both the articular cartilage and a small part of the ossification centre (Figure 1).

Before the operation labelling was made with Ledermycin, the patients being given two injections of 150 mg intramuscularly for two days twice with an interval of 14 days. The last injection was given 24 hours before the operation.

In addition to the 14 biopsies from patients with Calvé Perthes disease, biopsy material taken at autopsy from three children between the ages of 4 and 5 years was available as control material.

#### *Preparation:*

Immediately after the biopsy specimen was taken, the preparation was fixed in 10 per cent formalin alcohol. When large enough, the specimen was divided into two pieces, each containing a small part of the ossification centre. Preparations for histology were prepared from the one part after prior decalcification. After embedding in paraffin, sections with a thickness of  $5-10\ \mu$  were cut, and staining was made with haematoxylin-eosin and toluidine blue. The other part, which was available only if the specimen was big enough, was embedded in methyl-methacrylate without prior decalcification, after which the preparations were cut and ground down to a thickness of  $50\ \mu$ . These latter preparations were used for examining the result of labelling with Ledermycin using fluorescence microscopy and microradiographical examinations. Machlett A. E. G. X-ray tube (Carl Drenck) was used and the pictures were taken at a distance of 50 cm using 10 m.Amp. and 12 Kv.

The biopsy specimens from the capsule and synovial membrane were embedded in paraffin, cut into sections with a thickness of  $5-10\ \mu$ , and stained with haematoxylin-eosin.

Table 1. Radiographical, microscopical and macroscopical findings.

Case No.	Age (years)	Sex	Side	X-ray stage	Macroscopy	Histology
<i>Stage I.</i>						
1	6 <sup>9</sup> / <sub>12</sub>	m.	r.	Sclerosis, slight flattening of head	Normal	Cartilage with slight proliferation in the basal part, scattered necrosis of the bone and new bone with osteoblasts
2	3 <sup>3</sup> / <sub>12</sub>	m.	r.	Sclerosis, slight flattening	Normal	Cartilage with slight proliferation in the basal part, bone trabeculae with osteoblasts, no necrosis
3	8	m.	l.	Sclerosis, normal contour	Normal	Pronounced proliferation of the cartilage, thick bone trabeculae with necrosis in the central part and new bone with osteoblasts, islands of cartilage
4	4 <sup>5</sup> / <sub>12</sub>	m.	r.	Slight sclerosis, slight flattening	Normal	Pronounced proliferation of cartilage, thick bone formation with islands of cartilage
5	4 <sup>4</sup> / <sub>12</sub>	m.	l.	Sclerosis, flattening and fragmentation anteriorly	Normal	Scattered proliferation of the basal part of cartilage, islands of cartilage in the bone, no necrosis
<i>Stage II.</i>						
6	3 <sup>3</sup> / <sub>12</sub>	m.	l.	Sclerosis, marked flattening	Normal	Cartilage with scattered proliferation in the basal part, bone nucleus cannot be assessed
7	3 <sup>6</sup> / <sub>12</sub>	m.	r.	Sclerosis, marked flattening	Normal	Marked proliferation of the cartilage, endochondral ossification and osteoblastic apposition, big islands of cartilage
8	4	m.	l.	Sclerosis, marked flattening	Normal	Slight proliferation of cartilage, bone trabeculae without changes
9	4 <sup>5</sup> / <sub>12</sub>	m.	l.	Pronounced sclerosis and flattening	Head slightly flattened	Marked proliferation of the cartilage, thick irregular bone trabeculae with islands of cartilage

Table 1. Continued.

Case No.	Age (years)	Sex	Side	X-ray stage	Macroscopy	Histology
<i>Stage III.</i>						
10	3 <sup>3</sup> / <sub>12</sub>	f.	l.	Marked flattening, sclerosis and fragmentation	Head slightly flattened	Slight proliferation of the cartilage, bone nucleus cannot be assessed
11	6 <sup>4</sup> / <sub>12</sub>	m.	l.	Marked flattening, sclerosis and fragmentation	Normal	Marked proliferation of the cartilage, big islands of cartilage in the bone
12	6 <sup>9</sup> / <sub>12</sub>	m.	r.	Sclerosis, flattening and marked fragmentation	Head slightly flattened	Slight proliferation of the cartilage, thick irregular bone trabeculae
13	8 <sup>9</sup> / <sub>12</sub>	m.	r.	Marked flattening and fragmentation	Head mushroom-shaped	Cartilage proliferation more regular than previously, marked thickening of the bone with islands of cartilage
14	7	f.	l.	Slight flattening, scattered sclerosis	Normal	Cartilage irregular but without richness of cells and mitosis, bone trabeculae without changes

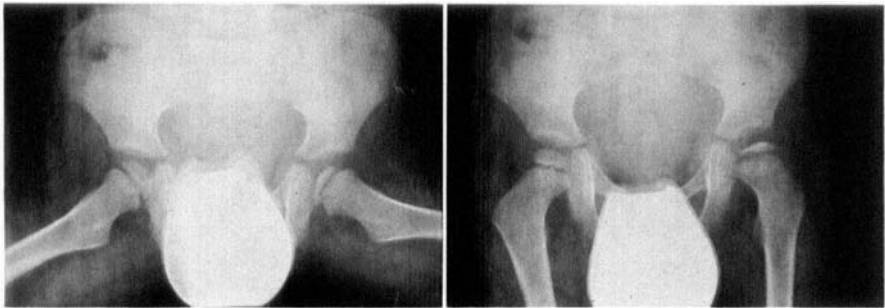
## RESULTS

Table 1 shows that 5 of the biopsy specimens originated from the initial stages, 4 from the intermediate stages, and 5 from the late stages of the disease. The stages were assessed on the basis of pre-operation radiographs. There was moderate sclerosis and slight flattening of the ossification centre in the early stages. In the intermediate stages, the sclerosis and flattening were more pronounced, and in the late stages fragmentation was also seen (Figures 2, 3 and 4).

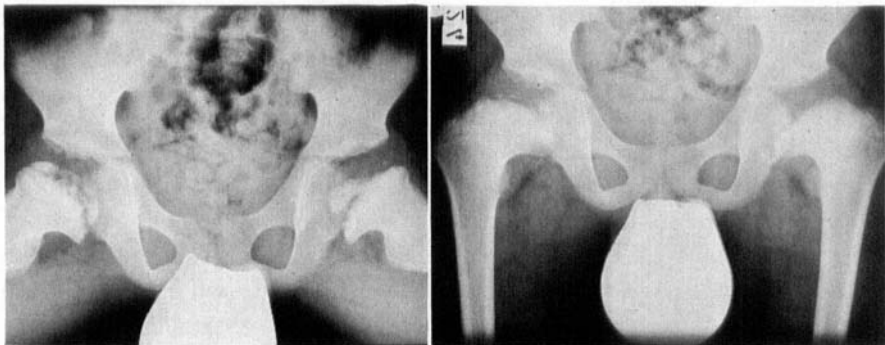
In 6 cases (Nos. 4, 7, 8, 9, 12 and 13), where arthrography was performed in connection with the operation, it was found that the cartilage contour of the femoral head was almost normal, despite the pronounced flattening of the ossification centre seen on the radiograph (Figure 6). Only in one case (No. 13) was there flattening and broadening of the contour (Figure 5). This was a late neglected case in which the femoral head was also found by gross inspection to be markedly deformed (mushroom-shaped). As will be seen from Table 1, the femoral head was normal macroscopically in the majority of the cases as regards



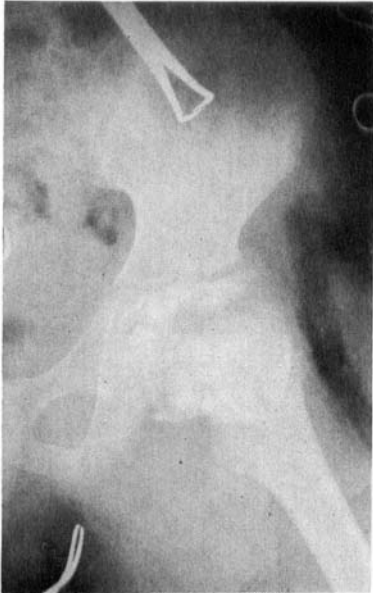
*Figure 2. Radiograph from Case No. 5, left-sided Calvé Perthes with sclerosis, showing flattening and fragmentation at the anterior of the ossification centre.*



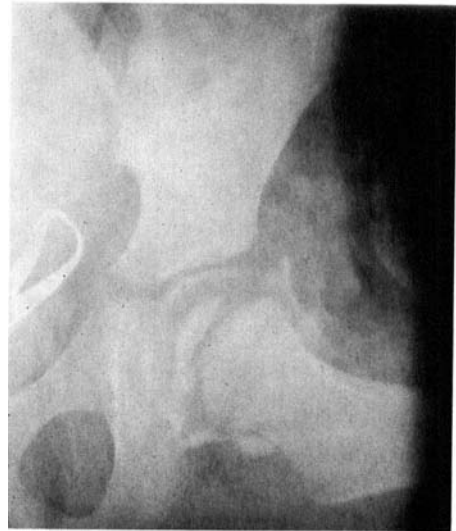
*Figure 3. Radiograph from Cases Nos. 4 and 9, bilateral Calvé Perthes, showing at right side stage I slight sclerosis and flattening of the ossification centre, at left side stage II-III pronounced sclerosis and flattening.*



*Figure 4. Radiograph from Case No. 13, bilateral Calvé Perthes, showing on both sides marked flattening, sclerosis and fragmentation of the ossification centre.*



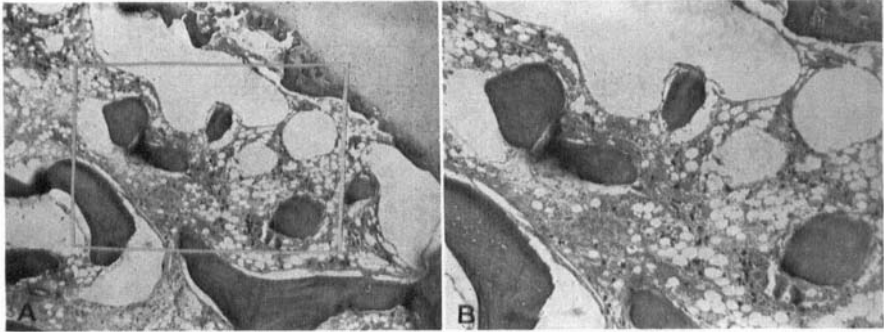
*Figure 5. Arthrography from Case No. 13, left side, showing some flattening of the contour of the femoral head.*



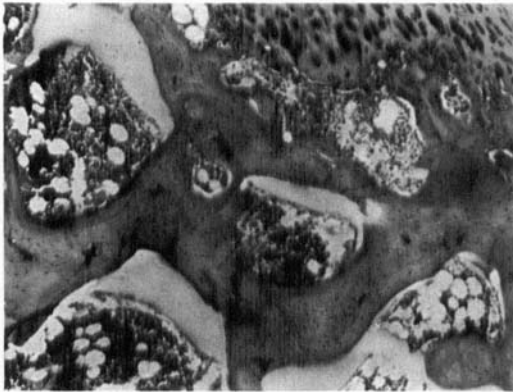
*Figure 6. Arthrography from Case No. 9, showing that, in spite of marked flattening of the ossification centre, the contour is normal.*

the form and appearance of the cartilage. There was only slight flattening of the head in 3 instances, which were cases in a quite late stage of the disease. In 3 cases there was slightly increased anteversion of the head. There was nothing special to be seen at the acetabulum in any of the cases.

In no case was an increase in the synovial fluid observed when the hip joint was opened. In 4 cases there was some thickening of the joint capsule but the synovial membrane was always considered to be normal. Histological examination of the 6 biopsies from capsule and synovial membrane showed slight hyperaemia in 3 cases but otherwise nothing abnormal. When 2 of the biopsies were taken from the femoral



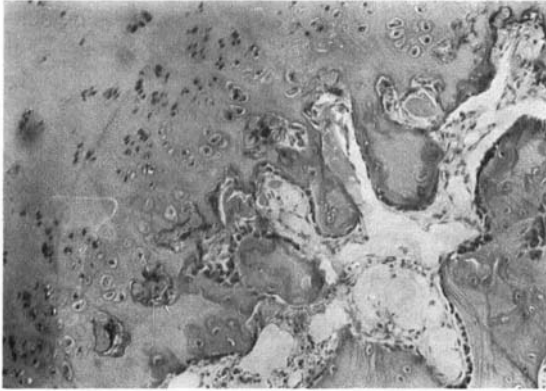
*Figure 7. From Case No. 1: Cartilage with slight proliferation in the basal part and necrosis of the bone can be seen. Haematoxylin-eosin, magnification 20 × (A) and 36 × (B).*



*Figure 8. From Case No. 4: Proliferation of the cartilage, thick bone trabeculae with small islands of cartilage. Haematoxylin-eosin, magnification 36 ×.*

head it was noticed that the cartilage was very thick and the line of demarcation with the ossification centre irregular. These were cases in the early stages. Measurement of the thickness of the cartilage in the histological preparations confirmed that this was thicker in the early stages than in the normal material.

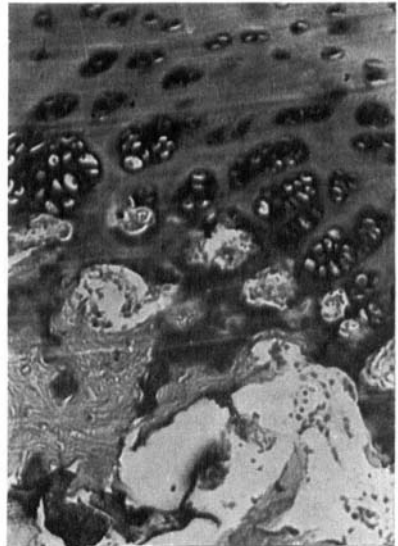
Evaluation of the histological preparations showed that in the early stages there was only one case where marked necrosis of the bone trabeculae could be seen (No. 1, Figure 7). In the other preparations from the early stages there were signs of regenerative processes in progress. There was newly developed bone with osteoblastic apposition. The articular cartilage was thickened but was normal in the superficial



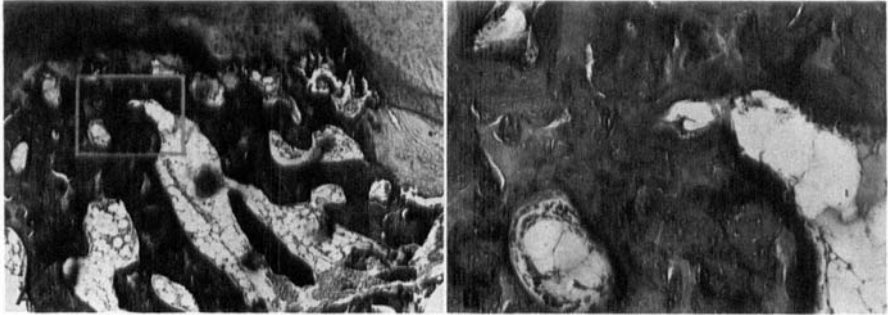
*Figure 9. From Case No. 7: Marked proliferation of the cartilage, osteoblastic apposition and islands of cartilage. Haematoxylin-eosin, magnification 80  $\times$ .*

layer. Basally there were signs of slight irregular proliferation (Figure 8). There was no evidence of inflammation.

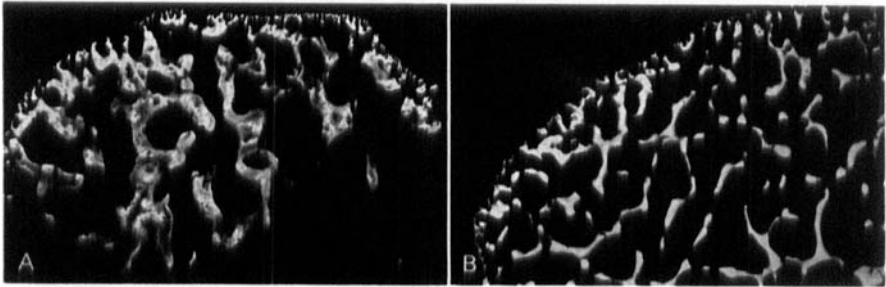
In the intermediate stages also the articular cartilage was thick with pronounced proliferation basally. At that stage there was no bone necrosis anywhere but considerable newly developed bone, and the trabeculae were often thickened and somewhat irregular. This thickening of the bone trabeculae was presumed to correspond to the sclerosis seen on the radiograph. Osteoblastic apposition on the bone trabeculae



*Figure 10. From Case No. 9: Marked proliferation of the cartilage with clusters. Haematoxylin-eosin, magnification 80  $\times$ .*



*Figure 11. From Case No. 13: Proliferation of the basal part of the cartilage more regular, marked thickening of the bone trabeculae with islands of cartilage. Haematoxylin-eosin, magnification 20 × (A) and 80 × (B).*



*Figure 12. Microradiograph (A) from Case No. 6, child aged 3<sup>3</sup>/<sub>12</sub> years, and (B) from normal child aged 3<sup>11</sup>/<sub>12</sub>, showing thick bone trabeculae and new bone formation as compared with normal case. Magnification 20 ×.*

was seen clearly at this stage, together with islands of cartilage in the trabeculae (Figures 9 and 10).

In the late stages further islands of cartilage could be seen, presumably corresponding to the fragmentation seen on the radiograph. The cartilage was more normal basally and did not show marked irregular proliferation (Figure 11). In one case (No. 14), where the femoral head was remodelled, the thickness of the cartilage was somewhat irregular and there was less cell activity in the basal layer, but the bone showed no changes.

In none of the preparations at the different stages was there sign of collapse or crushing of the bone trabeculae.

Assessment of the preparations labelled with Ledermycin showed, as could be expected, that the uptake was greatest subchondrally, suggesting increased activity. However, on account of the small amount

of bone available, the material was not suitable for further evaluation.

The microradiographical examinations were also affected by the small amount of bone available. However, it was evident that, as compared with the normal material, there was a marked thickening of the bone trabeculae and that these consisted mainly of newly developed bone (Figure 12). No change could be demonstrated in the thickness of the calcified zone.

#### DISCUSSION AND CONCLUSIONS

In 1913 Perthes described the histological findings in Calvé Perthes disease on the basis of a biopsy specimen from a 7-year-old boy (fragmentation stage). He emphasized that this was primarily a disease which takes place inside the epiphysis, since, in contrast to arthritis deformans, the articular cartilage was found to be normal. Based on radiographical studies, he considered that the epiphysis was flattened because of reduced resistance in the bone nucleus. The arthrographs taken in the present study illustrate that there are no changes in the contour of the head before late in the course of the disease.

On the basis of biopsy material taken by curettage, Haythorn (1949) reported the finding of areas with collapse of the bone tissue, and Jonsäter (1953), using fine needle biopsy, mentioned crushing of the trabeculae. In the present study, however, there was no sign of collapse or crushing, and thus it is possible that the changes described may have been an artificial product that occurred during the actual taking of the biopsy material.

As regards the aetiology of the disease, Perthes (1913) suggested that it might be a nutritional disturbance via the artery which supplies the region. This is in accordance with the histological findings in the early stages of the disease, since there would appear to be agreement that necrosis of both bone and bone marrow may be demonstrated (Haythorn 1949, Jonsäter 1953, Ponseti 1956, Mizuno 1966).

In the present study clear signs of necrosis were found in only one of the early stages, in contrast to Jonsäter (1953) who found necrosis in all the stages. The infrequent finding of necrosis may be due to the fact that the cases were not from early in the initial stage.

Experimental studies on dogs (Mizuno et al. 1966) have shown that various forms of vascular interruption of the blood supply to the femoral head produce changes resembling those found in Calvé Perthes disease, with partial or total necrosis. By examination of dogs with

Calvé Perthes, Hulth et al. (1962) demonstrated marked bone necrosis histologically and observed a decreased blood supply to the head by means of microangiography. The basic work of Trueta (1957) on the vascular supply during the growth period reported the most interesting finding that the supply of blood to the femoral head is particularly poor in the 4–5 year-age group, i.e. the “Calvé Perthes age”.

It can be seen by comparing the histological and radiographical findings that the thick bone trabeculae found early in the regeneration stages are the explanation of the sclerosis seen on the radiographs, whereas the islands of cartilage in the bone trabeculae in the late stage can account for the fragmentation.

The islands of cartilage were already mentioned by Perthes (1913). He contended that these were connected with the articular cartilage or that they were new formations of cartilage or incomplete ossification. The islands of cartilage found in the present study are considered to be an indication of endochondral ossification. Furthermore, some of the smaller islands situated subchondrally may originate from the proliferating cartilage and may be a result of the cutting technique. In several of the preparations there was a little thread-like connection to the articular cartilage.

The articular cartilage is always quite normal on the surface (Perthes 1913) but basally there is pronounced proliferation, particularly in the intermediate stages (Jonsäter 1953, Ponseti 1956).

The presence of changes deeper in the head and in the metaphysis cannot be elucidated on the basis of the present study. However, both Ponseti (1956) and Mattner (1968) extended their biopsy to go through the epiphyseal plate and found no changes, and particularly no necrosis metaphyseally.

No signs of epiphysitis as described by Phemister (1921) nor any fibrous degeneration (Riedel 1922) were found in the present study.

The principal conclusion is that signs of collapse or crushing of the trabeculae in the ossification centre of the femoral head could not be observed in any of the stages of the Calvé Perthes disease. All the findings were presumed to be irregularly changed ossification processes as a consequence of temporary necrosis and/or arrest of the normal growth of the bone nucleus, whereas the cartilage model of the head seems to be increased more or less normally. Thus a deformity in the late stage seems to be caused by irregular ossification of cartilage that was not previously ossified.

From the point of view of treatment, it would thus be logical to

adjust the position of the femoral head in order to ensure good contact with the acetabular wall so that a spherical form can be developed during re-ossification. This would seem to be more important than treatment aimed primarily at relieving the weight.

#### SUMMARY

Treatment of Calvé Perthes disease by intertrochanteric osteotomy was combined with the taking of arthrographs and inspection of the femoral head. Furthermore, biopsy material was obtained in the form of a wedge of articular cartilage, including part of the ossification centre, from the anterior part of the femoral head.

Fourteen hip joints were examined at different stages and three normal joints (obtained at autopsy) were used for comparison.

Arthrography and gross inspection showed that even late in the fragmentation stage there was only little or no contour disturbance of the femoral head. The joint fluid was not increased, and, apart from slight hyperaemia, there were no changes of the joint capsule or synovial membrane.

The histological examinations showed that there was only one case in the early stage with bone necrosis. Slight proliferation of the cartilage basally could be seen already in the early stages. In the intermediate stages, marked regeneration processes were in progress. There was pronounced cartilage proliferation basally and osteoblastic apposition of the bone trabeculae, which were thickened and had islands of cartilage indicating endochondral ossification. However, some of the islands were presumed to have occurred on cutting and to have originated from the proliferating cartilage. The superficial layer of the cartilage was normal but thicker than usual. In the late stages, there were large islands of cartilage in the bone trabeculae. These were presumed to be the explanation of the fragmentation seen on the radiograph. The thickened bone trabeculae were presumably the reason for the sclerosis observed.

There was no instance of collapse or crushing of the bone trabeculae. It is concluded, therefore, that treatment should be aimed at creating good contact between the femoral head and the acetabular wall to induce a spherical shape during the re-ossification rather than a treatment which aims at a relief of weight-bearing.

## REFERENCES

- Ferguson, A. B. & Howorth, M. B. (1934) Coxa plana and related conditions at the hip. *J. Bone Jt Surg.* **16**, 781-803.
- Haythorn, S. R. (1949) Pathological changes found in material removed at operation in Legg-Calvé-Perthes disease. *J. Bone Jt Surg.* **31-A**, 599-611.
- Hulth, A., Norberg, I. & Olsson, S.-E. (1962) Coxa plana in the dog. *J. Bone Jt Surg.* **44-A**, 918-930.
- Jonsäter, S. (1953) Coxa plana. *Acta orthop. scand.* Suppl. 12.
- Mattner, H. R. (1968) Zur Histopathologie der Pertheschen Erkrankung. *Beitr. Orthop. Traum.* **15**, 62-64.
- Mizuno, S., Hirayama, M., Kotani, P. T. & Simazu, A. (1966) Pathological histology of the Legg-Calvé-Perthes disease with special reference to its experimental production. *Med. J. Osaka Univ.* **17**, 177-209.
- Perthes, G. (1913) Ueber Osteochondritis deformans juvenilis. *Arch. klin. Chir.* **101**, 779-807.
- Pemister, D. B. (1921) Operation for epiphysitis of the head of the femur (Perthes disease). *Arch. Surg.* **2**, 221-230.
- Ponseti, I. V. (1956) Legg-Perthes disease. *J. Bone Jt Surg.* **38-A**, 739-750.
- Riedel, G. (1922) Beitrag zur pathologischen Anatomie der Osteochondritis deformans coxae juvenilis. *Zbl. Chir.* **39**, 1447-1450.
- Trueta, J. (1957) The normal vascular anatomy of the human femoral head during growth. *J. Bone Jt Surg.* **39-B**, 358-394.

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