A REVIEW OF THE MORPHOLOGY OF PERTHES' DISEASE

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There are differences of opinion about the pathogenesis of Perthes' disease. All are agreed that it is due to ischaemia, but the cause of this and the size and number of infarctions are in dispute. Through the generosity of the contributors six whole femoral heads and core biopsies of five other cases have been studied radiographically and histologically. The findings ranged from an ischaemic arrest of ossification in the capital articular cartilage without infarction to multiple complete infarctions of the epiphyseal bone. The ensuing reparative process contributes to the pathology, which is of a range to warrant grading or grouping.

Although Perthes (1913) considered this disease as an osteochondritis it was Phemister (1921) who reported bone necrosis with intact overlying articular cartilage. He later (1930) described the repair of avascular bone by creeping replacement or substitution. Zemansky (1928) and Jonsäter (1953) reviewed the histological findings during the course of the disease and confirmed the intact articular cartilage, the early bone necrosis and the subsequent repair mechanism in which cartilage was sometimes produced. Ponseti (1956) was the only author to comment in detail on the histological changes observed in the metaphysis. Very little has been written about this aspect in the past and his lead in this respect has not been followed. This is largely on account of the fact that these lesions have not figured prominently in the concept of pathogenesis. Mizuno et al. (1966) concluded from large segment biopsies that in the early stages “there was a more or less extensive avascular necrosis in the capital nucleus without any tissue reaction”. In the intermediate and later stages there was an extensive repair “with profuse formation of fibrous tissue and abundant revascularisation” and “cartilaginous bone formation”.

The case reported by Dolman and Bell (1973) of the early phases of the disease confirmed the presence of an infarct in the epiphysis in which radiological sclerosis was in part due to thickening of bony trabeculae and in part to calcification of the necrotic marrow. The theory was advanced from the experimental findings of Freeman and England (1969) and Sanchis, Zahir and Freeman (1973) that the morphological findings seen in most human cases of Perthes’ disease were the result of two or more episodes of infarction of the epiphysis. These views have been supported by McKibbin and Rališ (1974) and Inoue et al. (1976). The former concluded from their histological study of a femoral head in the established phase of the disease that the changes observed in sequential radiographs had resulted from repair of an epiphysal infarct. However, only one of the two cases reported by Jensen and Lauritzen (1976) supported this view. Finally a study of the radiographic features by

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Catterall (1971) suggested that the prognosis was proportional to the degree of epiphysial involvement. Although the whole head is available in experimental disease, it is mainly core biopsy material that is available in the study of human cases. It was felt that further light might be shed on this problem through assembling as much human material as possible. The present paper is the outcome of the generous co-operation of the authors of published cases.

**MATERIAL AND METHODS**

We were able to study histological sections prepared from six affected femoral heads obtained at necropsy, from the unaffected femoral heads in two of these cases, from five core biopsies and from five normal controls. The latter were obtained from children dying from causes unlikely to affect the hip. The details of these cases are listed in Table 1. It should be noted that the posterior part of the femoral head of the case reported previously

**Table 1. Source and details of all sections examined**

<table>
<thead>
<tr>
<th>Case</th>
<th>Source</th>
<th>Catterall group</th>
<th>Stage</th>
<th>Material</th>
</tr>
</thead>
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<tr>
<td>Whole femoral heads</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Jensen and Lauritzen 1976: Case 2</td>
<td></td>
<td>Healing</td>
<td>Whole femoral head</td>
</tr>
<tr>
<td>2</td>
<td>McKibbin and Rali 1974</td>
<td></td>
<td>Active</td>
<td>Anterior half of femoral head</td>
</tr>
<tr>
<td>3</td>
<td>Catterall et al. 1982: Case 1</td>
<td></td>
<td>Healing</td>
<td>Whole femoral head</td>
</tr>
<tr>
<td>4</td>
<td>Dolman and Bell 1973</td>
<td></td>
<td>Active</td>
<td>Anterior half Posterior half</td>
</tr>
<tr>
<td>5</td>
<td>Catterall et al. 1982: Case 2</td>
<td></td>
<td>Healing</td>
<td>Whole head</td>
</tr>
<tr>
<td>6</td>
<td>Jensen and Lauritzen 1976: Case 1</td>
<td></td>
<td>Healing</td>
<td>Whole head</td>
</tr>
<tr>
<td>Core biopsies</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>Kemp (unpublished)</td>
<td></td>
<td>Active</td>
<td>Femoral head and neck</td>
</tr>
<tr>
<td>8</td>
<td>Kemp (unpublished)</td>
<td></td>
<td>Active</td>
<td>Femoral head and neck</td>
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<tr>
<td>9</td>
<td>Ponseti 1956</td>
<td></td>
<td>Active</td>
<td>Femoral head and neck</td>
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<tr>
<td>10</td>
<td>Ponseti 1956</td>
<td></td>
<td>Active</td>
<td>Femoral head and neck</td>
</tr>
<tr>
<td>11</td>
<td>Ponseti (unpublished)</td>
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<td>Active</td>
<td>Femoral head and neck</td>
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<tr>
<td>Opposite unaffected hips</td>
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<td>12</td>
<td>Jensen and Lauritzen 1976: Case 2</td>
<td></td>
<td></td>
<td>Whole femoral head</td>
</tr>
<tr>
<td>13</td>
<td>Catterall et al. 1982: Case 2</td>
<td></td>
<td></td>
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<tr>
<td>Normal controls</td>
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<tr>
<td>14</td>
<td>Ogden (unpublished)</td>
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<td>Whole femoral head</td>
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<td>Lloyd-Roberts (unpublished)</td>
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<td>18</td>
<td>Catterall (unpublished)</td>
<td></td>
<td></td>
<td>Whole femoral head</td>
</tr>
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**Figure 1**—The articular cartilage from the unaffected hip (Case 13), showing the thickening of the articular cartilage and areas of calcification. (x 11.)

**Figure 2**—Normal control for comparison. Figure 3—The deep zone of the articular cartilage (Case 5) seen being remodelled from its deep surface by fibrocartilaginous material. (Haematoxylin and eosin, x 45.)

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by Dolman and Bell was unpublished and is presented for the first time in this report.

In each instance the paraffin blocks of decalcified tissues were available to us. Sections of these were stained with haematoxylin and eosin, azure blue and alcian blue (Scott).

**HISTOLOGICAL FINDINGS**

**Articular cartilage**

**Unaffected hips.** The articular cartilage of these hips was thicker than that of normal controls and showed irregular staining and small areas of sporadic calcification (Figs 1 and 2). The endochondral ossification on its deep surface was not so active as that of the normal controls.

**Affected hips.** The articular cartilage was again thicker than that of normal controls. Where it immediately overlay necrotic bone there were areas of necrosis in its deep part and normal endochondral ossification was absent. In some sites the deep surface of the cartilage was undergoing resorption and replacement by fibrocartilage (Fig. 3).

**Epiphysial growth plate**

This was abnormal in every case. In the unaffected hips it was thinner than normal with irregular cell columns and primary spongiosa (Figs 4 and 5). In the affected femoral heads the interference with ossification was greater, with columns of cartilage stretching unossified into the metaphysial region. These changes were mainly confined to the anterior part of the femoral head.

**Bony epiphysis**

**Group 1** (Case 1). The sequential radiographs did not show a sequestrum (Figs 6 to 8), but demonstrated a defect in the anterosuperior aspect of the epiphysis with irregular new bone at its edges. The remainder of the femoral head continued to grow circumferentially. Histologically (Fig. 9) the majority of the trabeculae were thickened by bony apposition, successive layers being demarcated by cement lines. However, they did not show evidence of bone necrosis. The defect observed radiologically in the anterosuperior part of the epiphysis contained fibrocartilage continuous with the overlaying articular cartilage. This material was cellular with a greater quantity of collagen than the overlaying layers. The bone deep to this had persisting cores of cartilage. There was no active ossification in this region. Penetrating this material on its lateral aspect and through the narrow spaces of the bone on its deep surface was vascular granulation tissue. That on the lateral side showed signs of endochondral ossification, albeit rather inefficient.

**Groups 2 and 3** (Cases 2, 3, 4 and 5). These will be considered together as they are morphologically similar. Radiologically there was a loss of height of the epiphysis with normally textured bone on its medial and lateral

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**Figures**

- **Fig. 4** — Growth plate from Case 12 showing distortion of the columns, some of which have lost their cellular component. These areas have not undergone normal ossification leading to an excess of calcified cartilage in the primary spongiosa. Figure 5 — Normal control. (Haematoxylin and eosin, ×50.)
- **Figures 6 to 8** — Case 1. Serial radiographs. Initially the epiphysis appears dense. In the later radiographs the medial and lateral aspect of the epiphysis have continued to grow while the central superior aspect has not done so, resulting in the defect seen in Figure 8.
appearances with and without deformity of the femoral head. Two types of repair were seen within the epiphysis. In the zone of infarction where the trabeculae were intact, vascular connective tissue was present in much of the marrow space and new bone was laid on the framework of dead trabeculae. Active resorption by osteoclasts was also observed. Where the trabeculae were fragmented the marrow was necrotic, the residual trabeculae being thickened and necrotic. There were zones where only fibrous tissue and fibrocartilage were present, all the bone having been resorbed. On the edges of the loose necrotic trabeculae osteoclastic resorption of bone was occurring with the formation of a chondroid tissue in the fibrous tissue adjacent to it. In many respects this cartilaginous tissue was similar to that seen in immature fracture callus (Dunham 1978).

**Group 4** (Cases 6, 7, 8 and 10). Serial radiographs in Case 6 (Figs 12 to 14) showed that the bony epiphysis in the early films was progressively resorbed until at necropsy very little of it remained. Surrounding this area and along aspects, which on sequential radiographs appeared to have been part of the original epiphysis. In Case 3 the medial and lateral aspects of the femoral head had enlarged but not the central area, producing relative flattening as healing occurred.

Histologically (Case 4, Fig. 10) in the early phases three types of change were observed in the various parts of the femoral head. In the **superior part of the epiphysis** (Area C) the trabeculae were necrotic and many were fragmented; the subchondral bone plate and the trabeculae were thickened with many cement lines; and the marrow was necrotic and, on fine-detail radiographs, dense. In the area **above the growth plate** (Area D) the trabeculae were thickened with central necrosis and viable appositional new bone formation on their surface; the marrow was replaced by granulation tissue; and lying between this and the necrotic area was a vascular tissue with osteoclasts resorbing the necrotic bone at points of contact. In the **medial and lateral segments** (Area B) the trabecular bone showed some remodelling but no evidence of necrosis, the marrow had a normal appearance. The relationship of these areas within the femoral head is shown in Figure 11.

In the later phases of the disease a greater proportion of the tissue was reparative. This was best observed in Cases 3 and 5 which showed the contrast between the
Case 6. Serial radiographs. Figure 12—Typical radiological features of Group 4 disease with a large dense central nucleus and flattened bone on the medial and lateral side. Figure 13—Progressive resorption of the central segment and an increase in the height and size of the bone on the medial and lateral aspects. Figure 14—The disease is in the established healing phase with almost complete resorption of the sclerotic bone and considerable reformation of the femoral head on the medial and lateral aspects.

Fig. 15
Case 6. Figure 15—Central sagittal section showing considerable thickening of the articular cartilage which is perforated by a vessel supplying the epiphysis. The central dense area of the radiographs has been completely replaced by a fibrocartilaginous material. The trabecular bone on the medial and lateral aspects shows extensive avascular necrosis. Even the bone formed by endochondral ossification on the deep surface of the articular cartilage shows evidence of avascular necrosis. (Haematoxylin and eosin, × 2.5.) Figure 16—High power view of Area G showing grossly thickened trabeculae with extensive avascular necrosis. There are many cement lines suggesting recurrent episodes of remodelling. The marrow is viable and there is appositional new bone formation on the surface of the avascular trabeculae. (Haematoxylin and eosin, × 50.)

the growth plate there were islands of sclerotic bone which progressively increased in size with time.

Histological section of the central area (Figs 15 and 16), the site of the original nucleus, showed fibrocartilaginous material. Although in one area calcification was present, there was no ossification in it: there were cystic spaces. Surrounding this cartilaginous tissue were grossly thickened trabeculae, the majority of which were necrotic with many cement lines demarcating successive episodes of ischaemia and remodelling. In the periphery, however, there were bony trabeculae showing one episode of infarction only. Patent blood vessels traversed the full thickness of the articular cartilage and it was possible that intermittent compression of these vessels may have been the cause of the repeated infarction.

Metaphysial changes
Four types of change were noted in the metaphysis. Adipose tissue. During the active phase of the disease, the marrow in the central region of the metaphysis contained adipose tissue only. This area approximated to the shape of the metaphysis at the onset of the disease. The
metaphysial trabeculae appeared for the most part to be normal, although undecalcified sections in one case demonstrated an increase in the osteoid in this region. Osteolytic lesion. In Cases 7, 8, 9 and 11 the radiographs showed a circumscribed osteolytic lesion with a well-defined sclerotic margin. Histologically these lesions were fibrocartilage whose histological appearances were very similar to those observed in the epiphysis but surrounded by reactive new bone. Where this lesion was in contact with the growth plate (Case 5) the normal architecture of the growth plate was lost. Disorganised ossification. In Cases 2 and 9 radiographs showed a wide growth plate and histologically ossification was disorganised with columns of unossified cartilage streaming down into the metaphysis. No necrosis was observed. However, in Case 6 there was one area of avascular necrosis with remodelling on the medial side of the metaphysis. A thrombosed vessel was present in the adjacent periosteal tissues. Extension of the growth plate occurred down the side of the femoral neck in cases where there was deformity of the femoral head.

DISCUSSION

When compared with normal controls the articular cartilage and the growth plate of the unaffected hip show abnormalities which suggest a pre-existing condition which might render these children susceptible to Perthes' disease. This is in keeping with the ideas advanced by Wynne-Davies and Gormley (1978) and by Burwell et al. (1978). The only reservation on this point is whether or not the illness from which these children died could have accounted for the abnormality. This seems unlikely, in that the children died from different causes and we do not consider that systemic diseases from which they suffered were likely materially to influence the pathogenesis of the process.

Correlation of the extent of epiphysial infarction with the degree of radiological involvement is, we believe, supported by the histological appearances. The organisation in Group 1 we interpret to be a result of persistent growth of the articular cartilage which has failed to ossify in its anterior and superior part, but has done so elsewhere by normal appositional growth. The composition of the unossified accumulating cartilage is altered by deposition of collagen and reduction in ground substance. We consider that the completely viable but incompletely remodelled bone on its deep surface is the original bone at this site when the disorder started. This implies that if the onset was due to interruption of the blood supply then this interruption was insufficient to cause infarction and did not affect the growth of the articular cartilage. It did, however, delay the normal process of ossification in this area. The defect is, in effect, the result of differential rates of growth in various parts of the femoral head.

The observations in Groups 2 and 3 we interpret as indicative of two episodes of infarction. Following the first, which does not involve the whole epiphysis, there has been a period of revascularisation and an attempt at repair in which the necrotic trabeculae have been weakened by resorption leading to their collapse and fragmentation. The mechanical deformation so produced has, we believe, caused a second and more local interruption of the blood supply with further local infarction; after this second episode cartilage is formed where the trabeculae are necrotic and fractured in the reparative tissues. Loss of height, which is progressive during the course of the disease, is due in part to collapse of the bony structure and also to progressive resorption of the fragmented necrotic bone from its deep surface. The cartilage in this area explains the radiolucency observed during the active phase of the disease, producing the radiological features of fragmentation. The overlying cartilage remains viable and proliferates. Where the blood supply is adequate enchondral ossification occurs. These changes will result in differential rates of growth within the femoral head, normal growth occurring in the medial and posterior regions and abnormal growth in the anterolateral area. With re-establishment of the blood supply to the anterolateral segment, areas of ossification occur in the articular cartilage. These small islands of bone correspond to the calcification lateral to the epiphysis reported by Catterall (1971, 1981) in his discussion on the "head at risk".

In Group 4 the observations suggest that the whole epiphysis is involved in the ischaemic process and that there may have been repeated episodes of infarction. There are widespread attempts at repair, both by remodelling of thickened trabeculae and by ossification of thickened cartilage. It is not possible to determine from the present study how much of the cartilage is formed reactively and how much is accumulated through the failure of ossification of the thickened articular cartilage.

It seems to have been an assumption of previous reports that the whole epiphysis was infarcted at the onset of the disease. This study of the radiographs and histological sections establishes that the extent of the infarction is variable and consistent with the degree of radiological involvement: absent in Group 1, limited in Groups 2 and 3 and extensive in Group 4. As the radiological grouping corresponds with the extent of epiphysial infarction it may be concluded that the prognosis for a case of Perthes' disease is proportional to the degree of infarction present within the epiphysis. There is no reason to question the hypothesis that Perthes' disease is due to ischaemia. There are grounds for suggesting that this ischaemia may not have been as severe as to cause infarction of the whole epiphysis in every case and in some may only arrest the process of ossification. It is conceivable, but seems unlikely, that in the Group 1 case infarction had occurred but had been completely repaired by the time of necropsy.
Corroboration for the concept of ischaemia producing incomplete infarction of the epiphysis is found from the work of Henard (Henard and Calandrucio 1970; Henard 1971), who produced a range of changes in the femoral head of dogs by periods of ischaemia of six, eight and 10 hours' duration. The changes at eight hours are of particular interest as they reproduce changes very similar to those seen in human Groups 2 and 3 cases. Similar changes have also been observed by Kemp (1973) and Singleton and Jones (1979).

The metaphyseal lesions are for the most part accumulations of unossified cartilage derived from the growth plate. Why this failure of ossification should occur when the blood supply to the metaphysis is normal, or cause such a disruption in the architecture of the growth plate is not clear. The consequence of its presence, however, is differential rates of growth within the femoral neck which in itself will lead to deformity of the femoral head. Whatever the mechanisms and degree of ischaemia, a reaction to this damage is elicited. The reparative process itself leads to alteration in histological appearance through resorption of bone leading to collapse, through "creeping substitution" giving rise to sclerosis, and through chondrification by metaplasia of reactive fibrous tissue formed by resorption of loose necrotic bone giving rise to radiolucencies.

The variable picture which is observed radiologically and histologically is the outcome of a balance of ischaemic episodes of variable severity and the success of the initial and subsequent episodes of repair.

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