PATHOLOGICAL CHANGES IN A CASE OF PERTHES’ DISEASE

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Although the number of affected femoral heads from human cases of coxa plana that have become available for direct study has been surprisingly small, the findings have been generally consistent with the view that the fundamental pathological process is one of infarction, necrosis and subsequent revascularisation of the epiphysis (Zemansky 1928; Gall and Bennett 1942; Mizuno, Hirayama, Kotani and Simazu 1966; Mattner 1968). Nevertheless, it is still not possible fully to account for the clinical features of coxa plana on the basis of a single vascular catastrophe.

The outstanding difficulty is that of accounting for the slowness of the repair process, which may last for several years. In cases of known infarction of the capital epiphysis after trauma, recovery is often complete within a few months (Haliburton, Brockeshire and Barber 1961), and this is also the case after experimental infarction of the femoral head in animals (Kemp 1965, Salter 1966, Freeman and England 1969). The fact that there exists a form of coxa plana in dogs in which recovery is also slow (Lee and Fry 1969, Lee 1970) suggests that this cannot be accounted for simply by the small size of the femoral head.

Because of this tardiness it seems likely that there is some factor which interferes secondarily with the repair process. Trueta (1968) suggested that mechanical collapse of the head might interfere with revascularisation and so retard recovery, but an alternative suggestion put forward more recently by Sanchis, Zahir and Freeman (1973), based on experimental evidence, is that the disease may represent the end-result of more than one episode of major infarction.

The relevance of such observations to human coxa plana can be determined only by a study of material from the disease itself. There follows therefore a description of the findings in the femoral head of a boy aged nine years who had been treated for Perthes’ disease for two years before his accidental death from drowning. Special attention was paid to any evidence which might suggest that there had been interference with the process of revascularisation.

CASE REPORT

A boy aged seven was brought to a local hospital with a history of pain in the left leg and a limp for three weeks. There was no history of injury. The previous medical history was unremarkable except that he was an epileptic receiving phenobarbitone therapy. Examination revealed some wasting of the quadriceps and considerable restriction of abduction and lateral rotation of the left hip. Radiographs of the hips showed an increase in the joint space together with some increased density and flattening of the bony nucleus of the femoral head (Fig. 1). A diagnosis of Perthes’ disease was made.

The boy was admitted to hospital and treated with bed rest and traction for a few weeks, during which the symptoms settled. He was discharged wearing a weight-relieving caliper; he continued to wear this for nearly two years and was still doing so at the time of his accidental death from drowning. A radiograph taken a few weeks previously is shown in Figure 1.

At necropsy the affected femoral head was removed and divided in the coronal plane into two unequal parts. The larger of these was fixed in 10 per cent formal saline and became available for study by us in this form. We have been unable to trace the remainder of the specimen. The available specimen was subsequently decalcified in formic acid and sodium citrate and embedded in low viscosity nitrocellulose. Sections 15 microns thick were cut and stained with haematoxylin and eosin, haematoxylin and van Gieson, Schmorl’s picrothionin, Lendrum’s M.S.B. and Masson’s trichrome.
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FINDINGS

Macroscopic appearance—The articular cartilage of the head appeared to be healthy and had a shiny surface. The head itself was deformed by a large central indentation (Fig. 2). The surface of the bisected head showed that the thickness of the articular cartilage was very irregular, being twice as great in some places compared with others (Fig. 3). The bony nucleus itself was flattened and irregular, and consisted of two well defined areas. The basal portion was red, suggesting that it contained blood vessels, whereas the more superficial parts were

Fig. 1
Radiographs of the left hip taken at the time of initial presentation at the age of seven, and just before death two years later.

Fig. 2
Figure 2—A photograph of the specimen. The deformity of the head is clearly visible.

Fig. 3
Figure 3—A photograph of a cross-section through the specimen. The flattened nucleus consists of a dark vascular basal zone and a pale avascular apical area.
white, indicating that they were substantially avascular. The appearances of the trochanteric epiphysis and of the metaphysial region were unremarkable. The growth plate was irregular and appeared to be breached at one central point. A fine grain radiograph of the specimen showed the two distinct areas of the nucleus (Fig. 4).

**Microscopic appearance**—The general features of the sectioned head are shown in Figure 5, the details being as follows.

**Bony nucleus**—This consisted of two distinct areas separated by a zone of mature fibrous tissue. The basal portion consisted of living bone which was the site of intense osteoblastic activity (Fig. 6). The trabeculae were much thicker than any seen in the metaphysis or in the epiphysis of the greater trochanter, due to appositional bone formation (Fig. 8). The osteocytes in the original trabeculae were alive, except in a few areas, and the plump nuclei of the osteocytes in the newly laid bone could readily be distinguished from the more attenuated osteocytes of the original trabeculae. The area was extremely vascular, being infiltrated by granulation tissue containing large leashes of blood vessels. Both the lateral epiphysial and the inferior metaphysial vessels contributed to this area, together with vessels which were penetrating the central area of the growth plate. No evidence of old thrombosis was seen in any of these vessels.

The appearances of the superficial zone of the nucleus contrasted sharply with those of the basal zone. Here, instead of hypervascularity and osteoblastic activity, were total avascularity and bone death (Fig. 7). The trabeculae contained only empty lacunae to mark the home of former osteocytes, and they were themselves broken and disordered. In some instances the trabeculae lay so close together as to suggest that they had suffered the effects of mechanical compression. Measurement of trabecular thickness indicated that, just as in the basal zone, this was greater than that in the metaphysis or the trochanteric epiphysis (Fig. 8). In several areas the appearances suggested that this increase was due to previous appositional bone formation. This impression was reinforced by the appearance of sections stained by the picrothionin technique. This is a method by which recesses in the bone are
FIG. 5
A histological section of the specimen. (Haematoxylin and eosin, × 2·4.)

FIG. 6
Figure 6—Trabeculae in the basal portion of the capital nucleus showing extensive osteoblastic activity. (Haematoxylin and eosin, × 124.)

FIG. 7
Figure 7—Necrotic bone in the superficial portion of the capital nucleus. (Haematoxylin and eosin, × 124.)
outlined by the accumulation of precipitated deposits and will demonstrate the details of osteocyte lacunae whether the cells be dead or alive. It was found that whereas the osteocytes in the centre of the trabeculae were of the usual mature form, in the more superficial areas of the thickened trabeculae the cell outlines were much more rounded and numerous, suggesting that this bone had been laid down at a later time (Fig. 9). These appearances were therefore identical to those found in the basal part of the bony nucleus, except that the cells were dead. A picrothionin section of this basal area is shown in Figure 10 for comparison.

One of the most important features of the necrotic apical part of the nucleus was the presence of quantities of amorphous necrotic collagenous debris containing remnants of blood vessels (Fig. 11). Occasional fragments of cartilage containing mature chondrocytes were also seen well away from the joint cartilage itself.

Between these two areas of the nucleus was a zone of fibrous granulation tissue (Fig. 12). This had the appearance of an advancing front thrusting into the dead bone, with spearheads
consisting of strong vascular leashes. A striking feature of this invasion was the relative absence of osteoblastic activity. Instead of new bone being laid down on the original trabecular framework the latter was being slowly absorbed by osteoclasts, so that only a few fragments of dead bone remained in this area. Where the vascular front impinged on the joint cartilage endochondral ossification was renewed.

Articular cartilage—The irregular thickness of this tissue was confirmed. For the most part it appeared to be healthy, with preservation of metachromatic staining and the presence of healthy chondrocytes. It was thickest over the avascular bone and in these areas some empty chondrocyte lacunae were observed in the basal layer (Fig. 13). The hypertrophied cells normally seen in this region in preparation for ossification were completely absent, but in the
more peripheral parts of the specimen where revascularisation was established endochondral ossification had recommenced.

**Growth plate**—This was irregular in thickness and in its centre was a deficiency through which vascular granulation tissue connected the epiphysis and the metaphysis. Elsewhere the plate was intact but the process of ossification appeared to be somewhat disrupted. The chondrocyte columns were often irregular, with clone formation in some areas (Fig. 14).

**Metaphysis**—The appearances in this region were normal apart from the medial portion. Here were found small trabecular fragments and bony debris scattered among normal trabeculae. No reaction surrounded these fragments and the appearance was difficult to interpret (Fig. 15).

A striking feature of the area beneath the growth plate was the large number of plasma cells in the intertrabecular spaces. Approximately 40 per cent of the cells found in this area were of this type (Fig. 16), compared with only 2 per cent in similar spaces in both the trochanteric and the capital femoral epiphyses.

**DISCUSSION**

The findings in this specimen of human Perthes' disease support the conclusions from similar studies by others that the essential pathological process is a healing infarct of the capital femoral epiphysis. Although the radiographic diagnosis had been made as long as two years previously, the healing process was far from complete and a substantial area at the apex of the nucleus was still not revascularised. It has already been pointed out that such delay has no parallel in any experimental study of a single episode of infarction, and we believe that the explanation is to be found in a detailed study of the bony nucleus itself.

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**FIG. 13**
Figure 13—Articular cartilage facing the necrotic portion of the capital epiphysis. The empty lacunae of dead chondrocytes are seen in the basal zone. (Haematoxylin and eosin, ×124.)

**FIG. 14**
Figure 14—Delayed and irregular ossification in the growth plate. (Haematoxylin and eosin, ×124.)
When the circulation is withdrawn from an area of cancellous bone its vital functions eventually cease; no pathological processes can then take place in this tissue except those of autolytic dissolution and mechanical deformation. The former rapidly affects the cellular elements, which soon disappear; but the trabecular architecture is unaffected because of its rigid mineral structure. Mechanical failure of this framework may eventually take place but in these circumstances there will be no attempt at repair. When the dead apical area of the nucleus is examined with this in mind, it becomes evident that there are changes present which cannot be explained either on the basis of autolysis or of mechanical damage. The trabeculae, although fragmented, are yet abnormally thickened, and the shape of the osteocyte lacunae suggest that this is the result of appositional bone formation just as it was in the revascularised basal portion of the nucleus. Such thickening must necessarily have occurred before infarction took place. Between the dead fragmented trabeculae are areas of autolysed amorphous material suggesting dead granulation tissue. This is not a normal feature of epiphysial bone and its arrival therefore must also have preceded the infarct.

Further evidence of pre-existing abnormality is provided by the appearance of the joint cartilage overlying the dead nucleus. In experimental animals immature joint cartilage has been shown to derive its nutrition from both the synovial fluid and the subchondral circulation (McKibbin and Holdsworth 1966). Zahir and Freeman (1972) pointed out that in puppies the withdrawal of the subchondral circulation led to a cessation of endochondral ossification while proliferation continued and produced an increase in cartilage thickness. This had the effect of increasing the distance across which the synovial fluid had to diffuse to reach the basal layers of the cartilage, to the ultimate prejudice of its nutrition. It now seems clear that this applies also to the human, for the cartilage overlying the dead bone was not only thickened but also showed necrosis of the basal chondrocytes (Fig. 13). However, in the present
context the most significant feature was the total absence from the bone/cartilage interface of the mature chondrocytes which normally immediately precede ossification. These are the characteristic feature of this layer and often accumulate in the absence of a subchondral circulation, only to be removed when it is restored (McKibbin and Holdsworth 1966). There was no trace of this zone in the present specimen apart from a few ectopic fragments, suggesting that it had been removed by an abnormal process which must have operated when the circulation was intact.

It appears therefore that we are dealing not with a single process of infarction and repair but with the infarction of a head which was already abnormal, and it remains to consider the nature of that earlier pathology. All the findings point to the conclusion that the head had been the site of a previous infarct, following which almost complete revascularisation had taken place. This would have resulted in appositional bone formation and trabecular thickening throughout the bony nucleus and the appearance of granulation tissue in the interstices, just as is now apparent in the basal zone of the specimen. The removal of mature dead chondrocytes from the basal zone of the cartilage would also be expected. Following a second infarct all activity would cease, the thickened trabeculae would remain and autolysis would convert the granulation tissue to an amorphous mass. Revascularisation would then begin once more. In those areas in which the circulation was restored for a second time the effects of the first infarct would be difficult to separate from the second, but in still unrevascularised areas all the changes could be ascribed to the first episode. These are in fact the changes which have been found in this specimen, and they provide strong support for the suggestion by Sanchis et al. (1973) that Perthes' disease is the result not of one but of more than one episode of major infarction. Once this is accepted the prolonged clinical course of the disease is readily understood.

This conclusion carries the important corollary that when an early case of Perthes' disease is diagnosed the active phase of the disease may not yet be over, and it may prove possible eventually to prevent further episodes of infarction once the mechanism is understood. An ability to abort the primary disease process would appear to offer more hope of minimising deformity than the mechanical supportive methods which are the only means at our disposal at the moment. Unfortunately the nature of the primary process could not be deduced from the material available to us. Many causes of infarction have been suggested in the past, but clearly, if one is seeking a recurrent cause, this alters the balance of probabilities of these various proposals. Thus it is difficult to see how trauma could provoke repeated episodes of this sort, and suspicion must fall on causes which could well be recurrent, such as synovitis.

These considerations cannot be taken any further at this point, and it is important to recall that apart from the evidence of repeated infarction the specimen revealed a number of other abnormalities which are not readily explained. The finding of fragmented trabeculae and debris in the medial portion of the metaphysis is difficult to account for, as is the heavy accumulation of plasma cells in the region below the growth plate. Particularly puzzling is the fact that while the basal part of the nucleus responded to revascularisation with increased osteoblastic activity, the advancing front of revascularisation was almost exclusively concerned with bone absorption. These changes are the subject of continuing study in the hope of further elucidating the underlying cause of this mysterious disease.

**SUMMARY**

1. The findings in a femoral head obtained at necropsy on a boy aged nine suffering from Perthes' disease are described.
2. The findings revealed that there had been avascular necrosis of the epiphysis followed by revascularisation and healing, and there was evidence to suggest a second episode of infarction.
3. The findings provide strong support for the suggestion that Perthes' disease is the result not of one but of more than one episode of major infarction.
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REFERENCES


