THE PATHOGENESIS OF PERTHES' DISEASE


It has been shown that in the puppy, two infarcts separated by an interval of four weeks produce a disorder of long duration which results in flattening and broadening of the femoral head and which reproduces the radiological changes seen in Perthes' disease in man. The histological appearances produced by two infarcts are characteristic.

In this study the histological appearance of fifty-seven femoral head biopsy specimens in Perthes' disease in man have been studied. In 51 per cent of hips histopathological changes characteristic of double infarction were present, and there were grounds for postulating that double infarction might eventually occur in all cases. The findings support the concept that the deformation of the femoral head and the chronicity of Perthes' disease in man may be due at least as much or even more to repeated episodes of infarction and the ensuing abnormalities of growth as to mechanical factors related to weight-bearing.

Perthes' disease is of serious clinical significance because it is of long duration, and therefore interferes materially with a child's life; and because it results in deformation of the femoral head, and hence may be a precursor of osteoarthritis in the adult hip. The generally accepted explanation for chronicity and deformity in this disease is that the infarcted capital epiphysis is slow to revascularise after a single episode of infarction, and that the anaemic ossific nucleus undergoes fracture and collapse. In this paper we shall present evidence in support of a view contrary to the above—namely, that chronicity is due to repeated infarction and that deformity is mainly due to the disturbance of growth produced by two or more episodes of infarction.

The argument to be presented draws upon three collections of material: 1) immature canine femoral heads infarcted surgically on a single occasion; 2) immature canine femoral heads infarcted on two occasions separated by four weeks; and 3) fifty-seven femoral head biopsy specimens obtained from patients suffering from Perthes' disease.

EXPERIMENTAL INFARCTION OF THE FEMORAL HEAD IN THE PUPPY

Methods

The method of infarcting the femoral head in puppies and the experimental design in the single and double infarct experiments have been reported elsewhere by one of the present authors and co-workers (Freeman and England 1969; Zahir and Freeman 1972; Sanchis, Zahir and Freeman 1973).

Findings

Pathology—Four weeks after the first infarction the ossific nucleus had become partly revascularised. In the revascularised areas it was composed of living woven bone deposited upon a scaffold of dead primary and lamellar bone, and the marrow spaces were occupied by living vascular granulation tissue (Fig. 1). When the head was again infarcted at-four weeks, these living tissues died. In those parts of the original ossific nucleus which had been revascularised before the second infarct, the histological appearances of the femoral head were therefore characteristic and diagnostic of two infarcts: the bone comprised dead woven bone superimposed on dead lamellar bone, and the marrow space was occupied by dead granulation tissue (Fig. 2). The appearance of the dead granulation tissue depends upon its maturity, which in turn depends upon the length of time the area under examination has been revascularised (Fig. 3). When the ossific nucleus again became revascularised, these features diagnostic of two infarcts ultimately disappeared as the bone was again remodelled.

After the second infarct, the area of the original ossific nucleus that was not revascularised at the time of the second infarct (that is, the zenith) naturally remained avascular for a further substantial period. In most cases this non-revascularised dead region at the zenith underwent collapse and fragmentation, and thus came to be occupied by structureless debris containing fragments of dead primary bone. At its deeper limit, this necrotic debris was in contact with a zone of confluent heavily collagenised fibrous tissue containing occasional fragments of dead lamellar bone without evidence of appositional new bone formation (Fig. 4). Although the presence...
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Collapse of the dead bone at the zenith of the head caused a true reduction in the height of the head, while dead bone (producing a broad, flat head); the transradiant thickened cartilage, necrotic debris and fibrous tissue at the zenith; the radiological "fragmentation" of the head produced by the failure of some areas of new bone to coalesce by endochondral ossification with the rest of the

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THE HISTOPATHOLOGY OF THE PROXIMAL FEMORAL EPIPHYSIS IN PERTHES' DISEASE IN MAN

We now describe the histopathological and radiological changes in fifty-seven femoral heads from fifty-six children.

Material and methods
There were available to all the participants in this collaborative study the case records, radiographs and femoral head biopsies of fifty-six children (fifty-seven diseased hips) with Perthes' disease referred to the orthopaedic department of Osaka University Medical School Hospital between 1963 and 1969. Forty-five of the children were boys and eleven were girls—a ratio of four males to one female. The age at the time of femoral head biopsy ranged from three years and ten months to fourteen years and two months, the modal age being six years. Between one and four weeks before femoral head biopsy, blood-flow studies were performed on forty-five of the fifty-seven diseased hips by the technique of Matumoto and Mizuno (1966). In this technique, blood flow is assessed by examining radiologically the rate of clearance of 40 per cent Urografin with added heparin which is injected into the femoral head under general anaesthesia. Previous studies had shown that such injections are not harmful to the bone or marrow tissues of the femoral head (Hamada 1968).

Femoral head biopsy—Cylindrical biopsy specimens were taken from the femoral head under general anaesthesia with a special needle after opening the joint capsule during the pedicled capsular flap operation of Mizuno (Mizuno et al. 1964; Mizuno 1970). The needle entered the femoral head inferiorly, anteriorly and laterally and was directed upwards, backwards and medially. Its position was checked radiographically (Fig. 8). Each cylinder of bone measured up to 1·5 centimetres in length and 0·4 centimetre in diameter. The specimens were fixed in 10 per cent formal-saline, decalcified and embedded in wax. Sections 5 μm thick were cut and stained with haematoxylin and eosin. Radiographs were taken before, during and after every operation.

**FIG. 4**
Photomicrograph of section of puppy femoral head twelve weeks after second infarction, showing abundant heavily collagenised fibrous tissue containing fragments of dead bone. (Haematoxylin and eosin, × 120.)

**FIG. 5**
Photomicrograph of section of puppy femoral head eight weeks after second infarction, showing flattening of the femoral head, thickened cartilage of zenith region, cleft underlying zenith, central portion of nucleus occupied by debris and fibrous tissue, irregular contour of epiphysis, and cartilage in metaphysis. New ossification fronts are present in the peripheral portions of the ossific nucleus. (Toluidine blue, × 2.)

**FIG. 6**
Figure 6—Radiograph of the human femoral head in Perthes' disease. Figure 7—Radiograph of the puppy’s femoral head after two infarcts.
Definitions
Pathological grading—To understand the pathological grading which we have used, certain features of the normal proximal femoral epiphysis must be recalled. The normal epiphysis contains two types of bone. The primary bone (primary spongiosa) is the first type of bone to form during the process of endochondral ossification and is composed of irregular trabecular structures having a central core of hyaline cartilage surrounded by bone; different matrix fibre structures when viewed microscopically between crossed polars and by the difference between their osteocyte lacunae.

The femoral head was allocated to one of three pathological grades (1, 2, 3) on the basis of the most advanced pathological changes present. Grades 2 and 3 were subdivided into three further groups according to the maturity of the repair tissue to give seven pathological grades. The features which characterised each of these grades were as follows:

Grade 1—One infarct: no evidence of repair—Entirely dead primary or lamellar bone and dead bone marrow without repair tissue (Fig. 9).
Grade 2A—One infarct: early repair—Entirely dead primary or lamellar bone with ingrowth of young vascular granulation tissue into marrow spaces with or without early appositional living woven bone repair (Fig. 10).
Grade 2B—One infarct: intermediate repair—Entirely dead primary or lamellar bone with appositional living woven bone repair bone, and with marrow spaces occupied by living maturing vascular granulation tissue (Fig. 11).
Grade 2C—One infarct: advanced repair—Abundant living heavily-collagenised fibrous tissue with or without living woven repair bone (Fig. 12).
Grade 3A—Two infarcts: after early repair—Partial or complete death of appositional repair bone or the young vascular granulation tissue (Fig. 13) of early repair (Grade 2A).
Grade 3B—Two infarcts: after intermediate repair—Partial or complete death of appositional repair bone or the

<table>
<thead>
<tr>
<th>Pathological grade</th>
<th>Number of hips in grade</th>
<th>Percentage of all hips</th>
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<tbody>
<tr>
<td>1</td>
<td>One infarct</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>One infarct with early repair</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>One infarct with intermediate repair</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>One infarct with advanced repair</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Two infarcts after early repair</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Two infarcts after intermediate repair</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Two infarcts after advanced repair</td>
<td>7</td>
</tr>
</tbody>
</table>

these structures are therefore easily recognisable microscopically. During remodelling, the trabecula of primary bone and their cartilage cores are rapidly replaced by trabecula of lamellar bone having a parallel collagen fibre structure and relatively sparse ellipsoid osteocyte lacunae. Woven bone, which forms during repair, is not seen in the normal femoral epiphysis: it has a disorderly collagen fibre structure and numerous randomly scattered rounded osteocyte lacunae. Normal lamellar bone and woven repair bone can easily be distinguished by their maturing vascular granulation tissue (Fig. 14) of intermediate repair (Grade 2B).
Grade 3C—Two infarcts: after advanced repair—Partial or complete death of the mature fibrous tissue (Fig. 15) of advanced repair (Grade 2C). Or living mature fibrous tissue with death of thick appositional woven repair bone (Fig. 16).

When the biopsy specimen was heterogeneous, the specimen as a whole was allocated to the most advanced grade present histologically; thus Grade 3 took preced-
ence over Grades 2 and 1 and Grade 2 over Grade 1, regardless of which subdivision of Grades 3 or 2 was present. Within one grade, subdivision C took precedence over B, and B over A.

Radiological staging at the time of biopsy—The radiological appearances of the femoral heads were staged in two ways: first, in accordance with a modification of the traditional method of Jonsäter (1953); and secondly, using the method described by Catterall (1971). "Traditionally" the femoral head changes in Perthes' disease were divided into four stages, but we have combined Jonsäter's "reparative" and "definitive" stages to give a late stage as follows.

Stage 1—Initial stage—Some flattening of the ossific nucleus, homogeneous increase in density (Fig. 17).

Stage 2—Intermediate stage (=fragmentation)—Irregular density or fragmentation with collapse (Fig. 18).

Stage 3—Late stage (=reparative plus definitive)—Reunion of a previously fragmented nucleus (Fig. 19).

RESULTS

Pathological findings—in the fifty-seven specimens studied the amount of ossific nucleus included varied greatly, but in every one there was sufficient for pathological grading. In two further specimens there was insufficient material and these cases have been excluded from the present study.

In every specimen all the bone of which the ossific nucleus was originally composed was infarcted—that is, every hip biopsied showed histological evidence of at least one infarct throughout its extent.
The number and percentage of hips in each grade is set out in Table I, from which it can be seen that definite pathological evidence of double infarction (Grade 3 changes) was found in 51 per cent of hips.

**Relationship between pathology and duration of symptoms**—

The pathological grade has been correlated with the duration of the symptoms from their onset to the time directly related to the duration of symptoms, an observation that helps to validate our interpretation of the histological material.

Of the twenty-three hips with symptoms present for three months or less, eleven (48 per cent) had pathological evidence of two infarcts. Of the fifteen hips presenting at four to six months after the onset of symptoms, ten

![Figure 13](image-url) ![Figure 14](image-url)

Figure 13—Photomicrograph of representative field in pathological grade 3A (two infarcts after early repair) showing dead lamellar bone with a thin layer of dead woven repair bone on some surfaces; also dead loose granulation tissue in the marrow spaces. Two months after the onset of symptoms. (×120.) Figure 14—Photomicrograph of representative field in pathological grade 3B (two infarcts after intermediate repair) showing dead lamellar and dead appositional woven repair bone. The marrow spaces are occupied by dead moderately mature granulation tissue. Five months after the onset of symptoms. (×120.)

![Figure 15](image-url) ![Figure 16](image-url)

Figure 15—Photomicrograph of representative field in pathological grade 3C (two infarcts after advanced repair) showing abundant mature fibrous tissue with marked degenerative changes in the blood vessels and surrounding fibrous connective tissue. Twelve months after the onset of symptoms. (×120.) Figure 16—Photomicrograph of another specimen in pathological grade 3C showing dead lamellar bone with a thick surface layer of dead woven bone. Fourteen months after the onset of symptoms. (×120.)

of operation in fifty-five hips, and the results are shown in Figure 20. (Two hips were omitted from this figure because the duration of symptoms was uncertain.) Since the capsular flap operation was used in the early stage of the disease, most patients had had symptoms for only a few months before operation. It can be seen from Figure 20 that in cases showing evidence of either one or two infarcts, the maturity of the repair tissue was (67 per cent) had evidence of two infarcts. Of the seventeen hips presenting after six months seven (41 per cent) had evidence of two infarcts.

Surprisingly, two cases were in Grade 3C despite having had symptoms for three months or less, and radiologically the femoral head in both cases was fragmented (that is, with the "traditional" method of classification they displayed intermediate radiographic changes).
Relationship between the pathological grades and radiological stages of the disease—The radiological stage as judged by the "traditional" method has been correlated with the pathological grade in each case (Table II). Of twenty-nine hips whose radiographs showed the initial stage at the time of operation, seven (24 per cent) were allocated to Pathological Grade 1; twelve (41 per cent) to Pathological Grade 2; and ten (35 per cent) to Pathological Grade 3.

There were three hips whose radiographs showed the late stage at the time of operation and all exhibited advanced repair histologically; one without definite evidence of a second infarct (Grade 2C) and two with such evidence (Grade 3C).

We attempted to correlate the pathological grade of each femoral head with the radiological appearances classified according to the method of Catterall (1971), but we found no definite relationship between the two:

Of twenty-five hips whose radiographs showed the intermediate stage at the time of operation seventeen (68 per cent) had definite pathological evidence of two infarcts (that is, were in Grade 3) and six (24 per cent) showed advanced repair after one infarct (that is, they were in Grade 2C). Thus in this series two-thirds of the hips whose radiographs showed the intermediate stage changes of collapse and fragmentation had been infarcted twice and most of the remainder showed advanced repair, as evidenced by the presence of abundant, heavily collagenised fibrous tissue with little or no new bone formation and little or no dead bone awaiting repair.

Evidence of two infarcts was seen in 28 per cent of hips in Group 1, in 55 per cent in Group 2, in 57 per cent of Group 3, and in 46 per cent of Group 4. In all the specimens with half-head disease, the whole of the primary bone in every specimen had undergone complete necrosis during the first episode of infarction.

Relationship between pathology, age and sex—There was no correlation between the age at the onset of symptoms and the pathological grade.

The sex distribution was the same in all three grades, suggesting that the chance of progression to a second infarct is the same in the two sexes.
DISCUSSION

In the present study based upon the pathological and radiological examination of fifty-seven hips with Perthes' disease in fifty-six Japanese children, we found definite pathological evidence of more than one infarct in 51 per cent of the hips. The histological changes characteristic of two infarcts seen in this material—the presence of dead repair tissue—were identical to those seen in the dog femoral head after two experimentally-induced infarcts. and may therefore miss histologically diagnostic areas. Thus the incidence of double infarction given in the paper should probably be viewed as the minimum.

In further support of the view that the true incidence of double infarction is higher than 51 per cent, it may be noted that in the dog, Grade 2C changes were seen only in the doubly infarcted femoral head, for after a single infarct revascularisation occurred too rapidly to permit these changes to develop. If Grade 2C changes in the human material are viewed as indirect evidence of more

<table>
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<tr>
<th>Radiological stage</th>
<th>Number in each pathological grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Some flattening and homogeneous increase in density</td>
<td>7</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Irregular density or fragmentation with collapse</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Late</td>
<td>Reunion</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
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We believe that any biopsy technique is likely to underestimate the true incidence of double infarction, because 1) histological evidence of two infarctions can be present only in limited areas of the ossific nucleus (that is, those which have been revascularised after a first infarct and then infarcted for a second time); and 2) the material available for examination constitutes only a small part of the epiphysis (at most 200 cubic millimetres) than one infarction, the incidence of a double infarct in this material rises to 67 per cent (16 per cent for Grade 2C plus 51 per cent for Grade 3).

We found that a second infarct may occur very early after the onset of symptoms, and it is interesting that 34 per cent of heads classified radiologically as being in the initial stage of the disease displayed histological evidence of double infarction. This may explain the difficulty of making a prognosis in the initial stage of Perthes' disease in man, for at this stage there is no way of telling clinically which heads have already had a second infarct and hence have (presumably) a worse prognosis than the remainder.

As the disease progresses radiologically the incidence of double infarction rises, so that in the intermediate stage the incidence is 68 per cent for Grade 3 changes and 92 per cent for Grade 3 plus Grade 2C. The corresponding figures for the late stage were 67 per cent and 100 per cent respectively. Thus once the disease has progressed to fragmentation, two infarcts are perhaps almost universal and, not surprisingly, the prognosis is correspondingly more likely to be poor.

Our material has revealed no cause for either the first or the second infarct, but the following deductions as to the location of the vascular catastrophe may be drawn.

First, our findings suggest that the whole of the femoral head had died during the first episode of infarction in all cases. This is in agreement with the findings of Jonsäter (1953) and of Nagasaka (1930). If the first
episode of infarction involves the whole of the femoral head, the femoral head is presumably deprived of all its major blood supply by some extrinsic event during the initial episode.

Secondly, in contrast to our conclusion that the whole head is involved in the first infarct, our observations show that histological evidence of two infarcts is patchily distributed. Evidence supporting the patchy distribution of a repeated process of infarction during revascularisation after an initial major infarct in the human femoral head in Perthes' disease has been collated by McKibbin (1975).

Conclusion
In conclusion we believe that our histological observations in man prove that more than one infarct occurs in at least half, and perhaps eventually in all, cases of Perthes' disease. Since in the dog Perthes' disease can be reproduced by two infarcts but not by one, we regard this observation as being crucial to an understanding of the cause of chronicity and femoral head deformation in Perthes' disease in man. We wish to emphasise our belief that deformation may be due as much to a disturbance of growth produced by two infarcts as to weight-bearing: a single infarct in the dog does not produce deformation even though the animal is fully weight-bearing.

We now suggest that treatment aimed at weight-relief may be of only partial relevance in this disease. In future, clinical attention should be directed towards detecting and preventing repeated episodes of infarction (perhaps by bone scanning (Danigelis et al. 1975)) rather than simply towards the prevention of weight-bearing.

We are grateful to Professor K. Ono, Dr Y. Matumoto, Dr H. Takarada and Dr K. Hiroshima for providing clinical records, radiographs and biopsy specimens. We are also grateful for financial support from the Medical Research Council, the Arthritis and Rheumatism Council, and the Department of Orthopaedic Surgery of Osaka University Medical School.

REFERENCES