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# Vascular aspects of degenerative joint disorders
## A synthesis

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# Acknowledgements

This book is about vascular disturbances in degenerative disorders of mesenchymal tissues with emphasis on arthrosis and related joint disorders. The central theme is the effects of intermittently and chronically increased resistance to venous drainage and the signs and symptoms related to local venous hypertension and distension.

My interest in these aspects of circulatory pathology was awakened in the 1960s during studies of the venous pump of the calf in healthy subjects and in patients with chronic venous insufficiency of the lower limb; the cause of pain in this group of vascular disorders; the pathogenesis of the venous leg ulcer and the skeletal and articular changes in the ankle.

During thirty years of research I have, of course, had the help of many colleagues. I want to stress that the line of investigation presented here was initiated in close cooperation with Håkan Linderholm, Professor of Clinical Physiology at the University of Umeå, Sweden. I remember those hectic years with pleasure and gratitude and also the great contributions of Rudolf Lemperg, then Professor of Orthopedics in Umeå. The research that began in Sweden was continued in Copenhagen, where Inge Reimann and Steen Bach Christensen were my closest co-workers during the early years. Their importance to our work is apparent both in the text and in the list of references. Hakon Kofoed's pioneer work on mass spectrometry was another important factor in our effort to understand what was happening during the progress of joint degeneration.

An important member of our team was and is Karen Elisabeth Sønderlev, HTL, our chief laboratory technician, whose ability and sense of priorities have been invaluable and whose slightly dictatorial disposition has helped to keep an increasingly crowded laboratory in order.

In 1980 Niels Hejgaard and I planned the investigations on patients with patellar pain syndromes, but his untimely death postponed the analysis of our findings. His scientific curiosity and enthusiasm are greatly missed.

During the years in Copenhagen, I have enjoyed close cooperation with the Royal Veterinary and Agricultural University and have had considerable help from the Department of Physiology, University of Odense. I thank both institutions.

An orthopedic surgeon venturing into the field of vascular physiology and pathophysiology is often keenly aware of being in an almost impenetrable jungle. I am therefore very grateful to Per Sejrsen, Professor of Physiology at the University of Copenhagen, for his professional advice.

The interest in normal and pathological bone circulation, once sporadic, has grown steadily and has recently led to the establishment of ARCO, the international association for bone circulation research (current President, Professor Jaques Arlet of Toulouse). The lively discussions in this forum have been important for the research presented here.

Professor Murray Brookes of Guy's Hospital, London, and Medical Research Director John Paul Jones, Jr., Kelseyville, California, have permitted me to use Figures 64, 65 and 87, respectively, for which I thank two old friends.

I thank both the VELUX Foundation of 1981 and Susanna and Erik Olesen's Fund for liberal financial help in the extension and equipment of our laboratories and education of laboratory personnel.

My friend and secretary Elsebeth Theil Gylling has prepared the manuscript. I thank her for her remarkable patience.

The language has been edited by Andrew Cameron-Mills and Jean Arnoldi.

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# Introduction

Degeneration seems to be the end stage of a number of joint affections and in most degenerative disorders all structures of the joint are affected—synovium and synovial fluid, subchondral bone and cartilage, the fibrous capsule and the muscles involved in movement and stabilisation.

What are the processes and how do they begin? The literature on etiology and pathogenesis of, for example, primary arthrosis is extensive and several theories have been proposed, but we cannot say honestly that we are much wiser, either about the cause of pain, or about the processes that ultimately lead to tissue degeneration and impaired joint function.

As orthopedic surgeons we may be justifiably proud of the considerable advances made during recent decades in the surgical treatment of more severe cases. Alloplastic operations have also given us a unique opportunity to study not only the joint in its entirety, but also the pathological changes characteristic for each separate structure.

The work presented here is centered on the results of vascular changes in most of the joint structures, and an attempt has been made to compare and correlate these changes with pain, tissue changes and impaired joint function. While results obtained under controlled experimental conditions represent a truth, valid under the given circumstances, any attempt at interpretation is inevitably influenced by the preferences and ideas of the interpreter. This is also true here and I make no excuse. Collecting bricks without trying to build is a dull business. However, as any interpretation of facts is certain to evoke discussion, it usually serves the interest of scientific progress.

A note on nomenclature: In Scandinavia and on the Continent it has become the custom to use the term arthrosis instead of osteoarthritis. To my mind arthrosis has become too closely linked to the conception of a passive, purely mechanical, age-dependent wear-and-tear process. My experience from clinical work, the laboratory and the operating theatre has convinced me that inflammatory processes play a more or less important role during the development of all these disorders. I consider the term osteoarthritis to be the more accurate (and less soporific). However, arthrosis seems to gain popularity also in American and British orthopedics, and I shall abide by the house style of *Acta Orthopaedica Scandinavica*.

# Early experimental arthrosis

## Changes in synovium, synovial fluid, cartilage and bone

McDevitt et al. (1977) induced experimental arthrosis in the knees of adult dogs by sectioning the anterior cruciate ligament, the contralateral knee serving as control. The dogs were kept postoperatively mobile until killed at 1 to 48 weeks after operation.

Vascular proliferation in the synovial membrane was seen at 1 week. Generally, vascularity intensified over the first 12 weeks and then subsided. Increased thickness of the synovial membrane with yellowish discoloration, villous folds and adhesions were also noted after 2 or more weeks.

*Microscopic changes.* Increased cellularity of the superficial layers of the synovial membrane was due to proliferation of lining cells and by infiltration of mononuclear cells. The earliest changes were detected at 1 week, and by 4 weeks the synovial layer was many times thicker than normal. Slightly increased vascularity of the synovial membrane was also noted at 1 or 2 weeks, becoming gradually more pronounced. After 2 to 8 weeks it was moderate to marked and persisted for 24 weeks and then subsided. Fibrosis of the subintimal layers of the synovial membrane was noted from 3 to 4 weeks and was especially pronounced in dogs killed after 12 to 24 weeks.

### *Perfusion changes in the synovial membrane*

To evaluate the time relationship between the synovial reaction and the development of arthrosis, Christensen et al. (1982) used rabbits in which one knee was made unstable using the method of Hulth et al. (1970). This involves cutting the cruciate ligaments, excising the medial collateral ligament, and extirpating the medial meniscus.

The relationship was evaluated by calculating the ratio between the washout rates of 133-xenon injected intra-articularly into both knees. Radio-xenon is an inert, lipophilic gas which readily crosses cell membranes and is rapidly exhaled after one circulation through the lungs (Lassen 1964).

In normal joints, Phelps et al. (1972) found a bi-exponential washout curve after intra-articular injection of 133-xenon. Analysis of its location in joint tissue during the fast and slow phases of the washout curve revealed that the initial rapid phase was explicable by washout to the blood vessels across the synovial membrane, whereas the subsequent slower phase was from articular fat. Christensen et al. (1982) in a 1-year follow-up of 6 rabbits found bi-exponential washout curves, and the initial washout proved faster on the arthrotic side throughout the period (Figure 1). The ratio between the initial washout rate constants in the

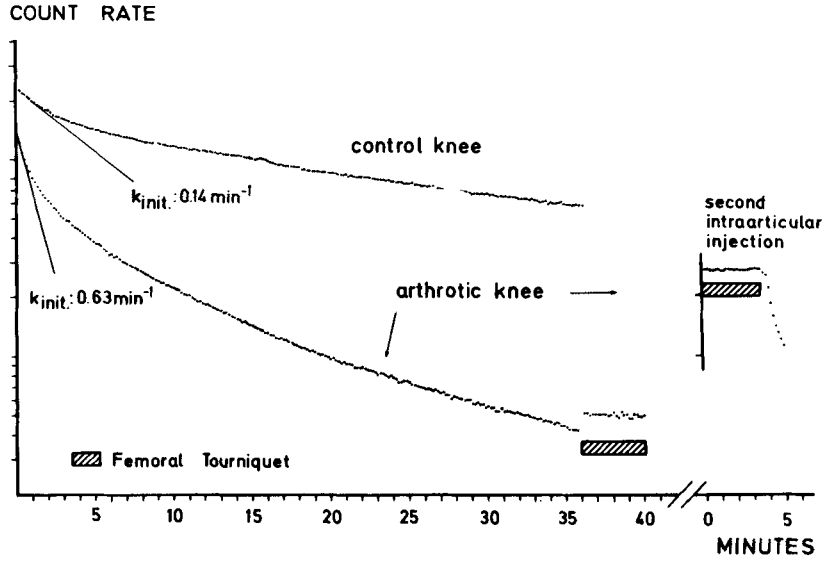



Figure 1. 133-Xe washout curves from the knee joints of rabbits 23 weeks postoperatively. The biexponential curve and the constant count rate after circulatory arrest is seen both in the later slow phase and the initial phase of the washout curve.

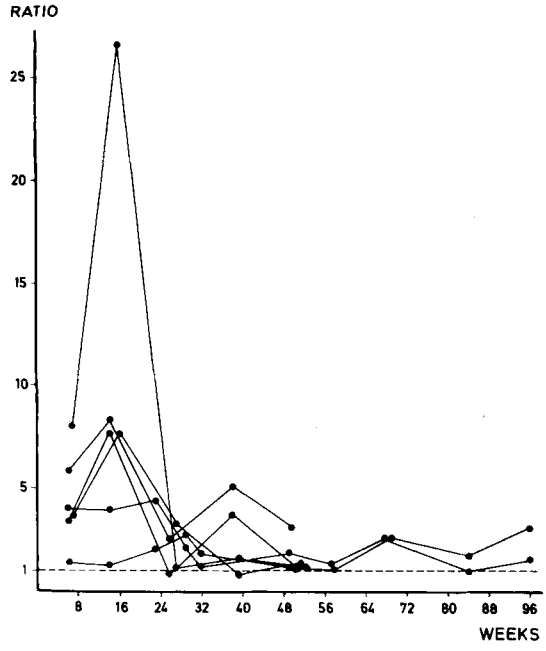



Figure 2. Ratio between the washout rates of the arthrotic and the control knee of 6 rabbits at different periods, postoperatively. Ratios above 1 indicate increased clearance from the arthrotic knee. The highest ratios are seen within the first half year.

arthrotic and the control knee was particulary high during the first 16 weeks. At that time it was higher than ratios at 6 months and later ($p < 0.001$, Mann-Whitney (Figure 2).

Scintigraphy of the knee region of rabbits given $^{99m}$TC-microspheres intracardially showed a marked increase in the flow to the knee region on the arthrotic side, thus supporting the xenon measurements.

The study thus showed a considerable increase in the synovial blood flow during the early stages of arthrosis. The flow increase partly reflects a major surgical trauma, but the continued effects are more likely due to traumatic synovitis caused by instability of the knee. In other words, the model incorporates a synovial reaction of several months' duration in the early stages of arthrosis. This applies to all models, even the non-traumatic of Langenskiöld et al. (1979), in which rabbit knees are immobilized. Joint effusion and histologically evident traumatic synovitis are also characteristic features in these knees (Finsterbusch and Friedman 1973).

### *Early synovial fluid changes in arthrosis in rabbits*

Kofoed (1986) used the method of Hulth et al (1970) to produce unilateral arthrosis in the right knees of 6 rabbits. Three weeks after the operation, when synovitis was well established in the unstable knees, he performed in vivo measurements of $PO_2$, $PCO_2$ and pH in the synovial fluid and the subchondral bone of the lower femur and the upper end of the tibia.

The partial pressures of gases were measured with a mass spectrometer (SX 200, VG Micromass Gas Analysis, Winsford, UK) via a blood-gas catheter (Lundsgaard et al. 1980). The application of the method in subchondral bone was described in detail by Kofoed et al. (1983). pH was measured by a monocrystalline antimony pH electrode (Edwall 1976). Calibration techniques and correction of the oxygen sensitivity of the antimony electrode are described by Kofoed and Lindenberg (1984) and calculation of pH, using mass spectrometry, by Markdahl-Bjarme and Edwall (1981).

### *Experimental design*

Special bone cannulas (inner diameter 1.4 mm, outer 2.0 mm) were introduced percutaneously through the lateral femoral and tibial condyles using image intensification. The tips of the cannulas were placed in the medial condyles on both sides. Similar cannulas were inserted through the patellar tendon with the tips between the femoral condyles in both knee joints. Measurements continued until a steady signal was recorded for at least 5 min. Arterial blood samples were withdrawn when signals were stable.

The animals were anesthetized via a marginal ear vein using pentobarbitone. Orotracheal intubation was used and the animals were kept on spontaneuos respiration. The right carotid artery was catheterized with an open-ended catheter connected to a 3-way stop-cock used partly for recording mean arterial blood pressure and partly for extraction of arterial blood samples to be analysed in a conventional acidbase blood-gas analyser.

### *Results*

Notable hypoxia, hypercapnia and acidity were demonstrated in synovial fluid and subchondral bone marrow in the joints with synovitis (Table 1). Kofoed concludes that this is probably due to regional venous congestion. His findings and conclusions agree well with the findings of Grønlund et al. (1984) who observed that acute simulated effusion into a joint resulted in decreased regional blood flow and hypoxia (cf. Arnoldi et al. 1979).

### *Early bone changes*

Christensen (1983), in his experiments on rabbits, observed marginal osteophyte formation as early as 1 week postoperatively. Further, he found that uptake by osteophytes was responsible for the high early (4–12

Table 1. $PO_2$, $PCO_2$ and pH values in synovial fluid from rabbits with unilateral, experimentally produced knee-joint synovitis

| Animal | Normal joint | | | | Synovitis | | | |
|---|---|---|---|---|---|---|---|---|
| | RA | $PO_2$ | $PCO_2$ | pH | RA | $PO_2$ | $PCO_2$ | pH |
| 1 | 0.78 | 70 | 33 | 7.53 | 0.76 | 17 | 55 | 7.32 |
| 2 | 0.81 | 20 | 45 | 7.47 | 0.73 | 17 | 52 | 7.36 |
| 3 | 0.56 | 46 | 56 | 7.36 | 0.59 | 22 | 77 | 6.92 |
| 4 | 1.17 | 20 | 31 | 7.45 | 0.75 | 12 | 55 | 7.26 |
| 5 | 0.66 | 45 | 58 | 7.47 | 0.60 | 15 | 80 | 7.03 |
| 6 | 0.77 | 36 | 45 | 7.32 | 0.74 | 23 | 53 | 7.03 |
| Mean | 0.79 | 39 | 45 | 7.43 | 0.70 | 18 | 62 | 7.15 |
| SD | 0.21 | 19 | 11 | 0.07 | 0.08 | 4 | 23 | 0.17 |
| *Arterial values during the experiments* | | | | | | | | |
| Mean | | 100 | 32 | 7.41 | | 101 | 31 | 7.39 |
| SE | | 25 | 5 | 0.02 | | 20 | 4 | 0.04 |

Paired t-test: $PO_2 < 0.05$, $PCO_2 < 0.001$, and pH < 0.001.

weeks after operation) uptake of $^{99m}$Tc-phosphate in the affected joint. In later stages (18–24 months) many osteophytes were inactive.

Increased subchondral uptake in the weight-bearing part of the knee joint was not seen until arthrosis was advanced. Thus, according to Christensen, osteophyte formation is an early phenomenon, coinciding with the early phase of intense vascularity and synovitis. In McDevitt et al.'s (1977) studies on dogs the earliest macroscopic osteophytes were observed 2 weeks after operation and their size increased during the whole period of the experiment.

Microscopically, fluorochrome uptake due to new bone deposition in the marginal zone was recorded 3 days after operation. At 48 weeks, the osteophytes consisted of mature bone trabeculae that appeared confluent with those of the epiphysis.

Thus, both McDevitt et al. and Christensen, using different models and methods, demonstrated osteophyte formation as the first visible bone changes appearing during the early period of hypervascularity and synovitic joint effusion, in unstable knees developing arthrosis.

### *Early reaction of articular cartilage*

In 42 rabbits, 6 in each group, in which one knee was destabilized by the method of Hulth et al. (1970), *patellar* cartilage of affected and control knees was examined by Reimann et al. (1982) 1–26 weeks as well as 18–24 months, postoperatively.

The sulfated GAG content of the cartilage was evaluated by staining with 0.01 % toluidine blue 0 at pH 3 (Krygier and Kazimierz 1961, Spicer 1962). The thickness of the non-stainable, GAG-depleted superficial zone was measured both visually and by optical densitometry in which the cartilage was scanned from its surface to the tidemark. As early as 1 week postoperatively there was increased surface depletion of GAG. The height of the unstained superficial zone rapidly increased during the subsequent weeks, reaching maximum GAG depletion at 4 weeks (Figure 4). Thereafter, the depleted areas decreased and at 26 weeks, postoperatively, their height was lower than at 4 weeks, indicating regeneration of proteoglycans in the matrix (Figure 5). As this experimental model primarily leads to cartilagineous degeneration in the medial femoro-tibial compartment, loss of GAG in the patellar cartilage may be interpreted as a sign of an initial, generalized action upon all articular cartilage and not a local reaction. Reimann et al. (1982) concluded that it is reasonable to relate the early generalized GAG depletion to the simultaneous severe post-traumatic synovitis demonstrated by the xenon washout (Christensen et al. 1982). In this phase the cartilage is soft and vulnerable, but if the mechanical forces are not too great and the synovial reaction subsides, there is evidence that healing may occur via the filling of the demasked collagen network with proteoglycans. If, however, the arcaded construction of the collagen fibres is destroyed, the possibility for regeneration reaches a point of no return and the development of arthrosis is inevitable. Cartilage degeneration will manifest itself on the most heavily loaded or stressed areas.

This matter will be discussed further in the section on surface and basal cartilage degeneration.

### *Comments*

These investigations of the reaction of various joint tissues—synovium, synovial fluid, bone and cartilage —to experimentally induced joint instability clearly indicate that the reactions are not only rapid but also seem to be universal, i.e. not confined to the area directly exposed to the mechanical changes induced by the operative procedure (surgical trauma, local overloading).

It appears that the first reaction is inflammatory with increased blood flow to the affected joint and that the tissue receiving most of this extra supply is the synovium. Traumatic synovitis produces increased synovial fluid and the first bony reaction appears at the junction of synovium and cartilage as osteophytes. The transitory, but universal, cartilage reaction could be due to compositional changes in the synovial fluid caused by stasis in the synovial veins and capillaries, as a consequence of the increase in intra-articular pressure.

As observed by Reimann et al. (1982) traumatic syn-

Figures 4 and 5. Sections of articular cartilage prepared at various postoperative intervals.

Histological sections for visual measurements of surface depletion of GAGs from unstable joints (Toluidine blue, pH3, original magnification x25).

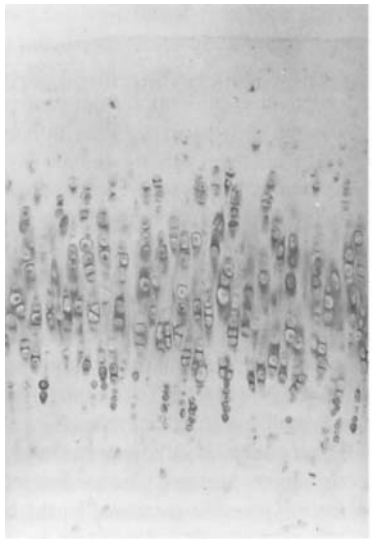


Figure 4A. 4 weeks postoperatively.

Histologic sections from contralateral control joints (Toluidine blue, pH3, magnification x25; Reimann et al. 1982).

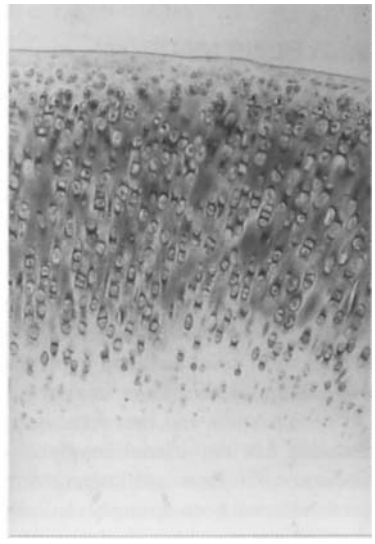


Figure 4B. 4 weeks postoperatively.

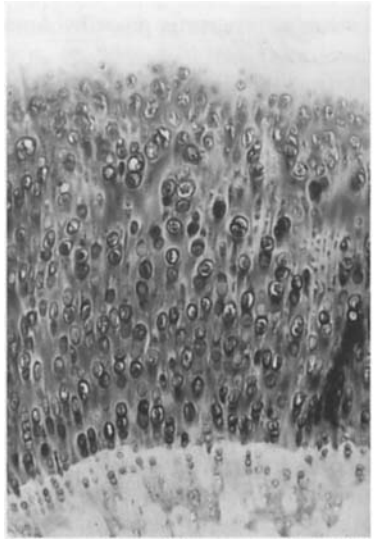


Figure 5A. 6 months postoperatively.

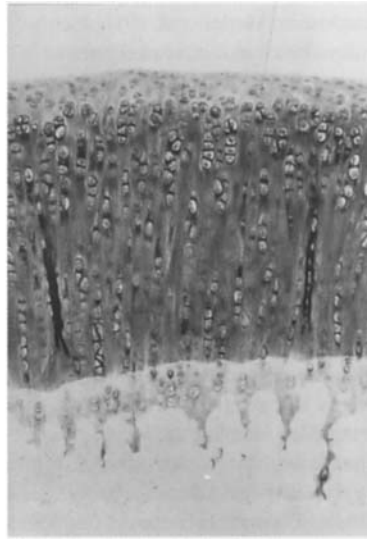


Figure 5B. 6 months postoperatively.

ovitis, which is a very common disorder in man, often disappears within a short period and most of the tissue changes are reversible, at least to some extent. In the rabbits and dogs used in the studies mentioned here, the trauma was so severe that it always leads to secondary arthrosis.

Danielsson's (1964) observation of frequent osteophytes in hips with no other clinical or radiographic signs of arthrosis, may indicate that these osteophytes are the only residue of previous transitory joint disorder.

# Arthrosis of human hip and knee

## BONE AND BONE MARROW

### Investigations of juxtachondral bone marrow by intraosseous pressure and flow measurements, intraosseous phlebography and $^{99m}$Tc-phosphate scintigraphy

Until the 1950s it was a widely held opinion that the degenerative changes observed in sub- and juxtachondral bone in osteoarthrotic joints were the results of partial or total failure of the arterial supply (Pridie 1952). In 1953 Harrison et al. found hyperplasia of the femoral head intraosseous arteries in arthrosis, as well as signs of venous stasis and interstitial lymphedema. They concluded that the arterial supply to the bone marrow seemed to be increased instead of reduced, a conclusion that has not been seriously challenged since. Later investigations provided evidence of disturbed venous outflow from the femoral head and neck in coxarthrosis, from the distal part of the femur in patients with gonarthrosis (Meriel et al. 1955, Hulth 1959, Helal 1962, Philips 1966) and increased intramedullary pressure in juxtachondral bone marrow (Arlet et al. 1968).

These early observations have been confirmed by many others and, at present, there seems to be a consensus that vascular changes in joint-bearing bone marrow are characteristic features of manifest arthrosis. However, opinions differ widely as to the importance and place of circulatory joint changes in the pathogenesis of the disorders. This and subsequent chapters examine research into abnormal changes in the drainage of venous blood from joint-bearing bone, the mechanisms that are responsible as far as they are known, and the signs and symptoms caused by venous distension and impeded capillary flow.

Until quite recently our knowledge of pressure and flow in juxtachondral bone marrow derived from examinations of immobile and unloaded joints, and discussions and conclusions have been based on these data, exclusively. The effects of joint movement and simulated loading on intraosseous pressure and flow have now been examined (Arnoldi 1990, 1991); and recent investigations of the femoral head in non-traumatic osteonecrosis are reported in the chapter on this disorder. At present, however, it seems advantageous to deal with the unloaded and loaded joints separately.

### Own investigations on the supine patient at rest

#### *Methods*

*Intraosseous and intravenous pressure measurements.* Measurements were performed with the patient in a horizontal or nearly horizontal position. In most series a polyethylene catheter was introduced into the internal saphenous vein at the ankle and the end placed at the same distance from the heart and from the heart level as the points of measurement in the bones. The midaxillary plane at the level of the fourth costal insertion at the sternum was chosen to indicate heart level, and this was the reference level for all pressures measured. The extraosseous venous pressure was used as a control or reference for the pressure measured in the bone marrow; intraosseous pressure is dependent on, and varies with, the pressure in the veins draining the bone (Arnoldi and Linderholm 1966). A description of the pressure recording system is given by Arnoldi et al. (1972).

*Statistical methods.* Conventional statistical methods were employed. P values were obtained from the tables of Fisher and Yates (1957). The arithmetical mean and median of the groups were compared and agreement between them was taken to indicate an approximately normal distribution.

*Intraosseous phlebography.* Intraosseous phlebography was used to determine: 1) changes from normal in the direction of venous blood flow from juxtachondral bone marrow; 2) morphological changes of the intra- and extraosseous drainage system; 3) change in the speed of drainage from bone marrow (serial phlebography). This information required the investigation of unilateral joint disorders.

*Procedure.* Local anesthesia of the skin and periosteum was used in our first intraosseous phlebography experiments. Later, as no difference in the results could be detected, general anesthesia was preferred. However, the first series provided useful subjective information particularly about the character and localisation of pain during injection of contrast medium (raising intramedullary pressure). Placement of cannulae varied according to the joints examined and the purpose of the investigation. In most cases intraosseous phlebography was preceded by measurements of bone-marrow pressure.

Specially constructed conical needles (AB Stille-Werner, Stockholm), 15 or 17 cm long, with an external diameter of 4.55 mm at the tip and a lumen measuring 2.60 mm were used for the larger joints (knee and hip). Shorter needles were found more practical for the ankle joint, the patella, vertebrae and smaller bones.

The position of the tip of the cannula was controlled by image intensification. If, after placing the cannula, gentle suction with a syringe showed a flow of blood through the cannula, it was regarded as a sign that the tip was in the bone marrow. Breakdown of cancellous trabeculae with lacerations of adjacent blood vessels produces a pool of blood surrounding the tip of the cannula. The wider the cannula, the larger the pool, and, thus, the greater the likelihood of representative and reproducible pressure recordings.

Various types of contrast material have been used during the years and the amount of contrast injected has varied according to the size of the bone: 8 mL has been the standard injection in the hip and knee, 2 or 1 mL in the small joints and the patella.

Film – focal distance and exposures have been adapted in accordance with the joints examined.

*Serial phlebography* was performed in some studies, the first exposure being taken during the injection of contrast material, with subsequent exposures at 30 sec and 1, 3, 6, 12, 20 and 30 min. Occasionally, a final exposure was made after 50–60 min. In analysing these phlebographic series the emptying time was taken as the number of minutes between the injection of contrast and the first contrast-free exposure.

*$^{99m}$Tc-polyphosphate scintigraphy.* Most of the scintigraphic examinations of the hip and knee described were made during the period 1972–1979. The technique used was: 12 mCi of $^{99m}$Tc-polyphosphate administered 2 hours before the patient was examined with a 5-inch, dual probe, wholebody rectilinear scanner (Elscint). The collimators used had an almost depth-independent response over the range of 7–12 cm, and joint regions were examined in positions symmetrical to the collimators. Scintigrams were assessed visually, from photorecordings, and from corresponding video display processing. The positive result from these series was an increased osseous tracer uptake in the joint region, based on visual assessment of the scintigram.

In cases with unilaterally positive scintigraphic findings, visual observation was supplemented by numerical assessment. Rectangular regions of interest were established on the VDU framing the whole joint region of each of a pair of knees or hips. Anatomically, the size of these regions corresponded to frames of 9 x 11 cm around a knee joint and 6 x 6 cm around a hip joint. The count ratio between the affected and normal sides was calculated from the number of counts in each joint region of the pair. Assuming that counts in each region of interest are Poisson distributed, the standard deviation (*SD*) of the ratio (*R*) is

$$SD = R\sqrt{\frac{1}{x} + \frac{1}{y}}$$

where $x$ and $y$ are the number of counts on either side.

## Results

*Intraosseous and venous pressures.* Two series of patients with painful primary arthrosis of the hip joint were examined (Arnoldi et al. 1972). The first series consisted of 15 patients with unilateral arthrosis, in whom the intraosseous pressure of the femoral neck was measured on both sides at the same time as the pressure in the femoral vein. Bilateral intraosseous phlebography was performed immediately after these pressure measurements.

The second series measured the intraosseous pressure of the femoral head and neck on one side only in 15 patients undergoing operation for severe painful arthrosis; venous pressures were not determined.

The first series examined differences between normal and affected hips, while in the second series measurements were taken to determine possible pressure differences between the femoral head and neck.

## Results, first series

*Femoral vein.* In the first 5 patients examined the femoral venous pressure was measured on both sides. These results showed, however, that the pressures from the normal and the affected sides were equal (mean difference = 0.2 mmHg). Therefore in the other 10 cases the pressure in the femoral vein was measured on one side only, in the unaffected limb in 6, on the arthrotic side in 4 patients. The pressures ranged between 6.5 and 16 mmHg, with a mean pressure of 12 mmHg (Table 2a).

*Intraosseous pressure of the femoral neck.* The pressure tracings were always pulsatile, and the pulse pressure was higher on the arthrotic side than in the normal limb (Table 2a). The intraosseous pressure was always higher than the femoral venous pressure. In the normal hips the difference between intramedullary and venous pressures ranged between 2.3 and 17 mmHg, with a mean difference of 6.8 mmHg (Table 2b). The intraosseous pressure of the arthrotic hip was higher than in the healthy hip (Figure 6). There was relatively wide variation in the differences (12–59 mmHg), with a mean difference of 30 mmHg.

## Results, second series

Pulsatile pressure tracings were always obtained from

Table 2a. Pulse amplitude, intraosseous pressure of the femoral neck, and femoral vein pressure in mmHg (mean, range and *SD*) in 15 patients with unilateral arthrosis of the hip joint

| Site of measurement | Unaffected hip | | | Arthrotic hip | | | Difference | *P*-value |
|---|---|---|---|---|---|---|---|---|
| Intramedullary pulse pressure amplitude | 4 | 2–11 | *3* | 7 | 2–18 | *5* | 2.8 | < 0.01 |
| Neck pressure | 19 | 14–25 | *3.6* | 48 | 28–75 | *16* | 30 | < 0.001 |
| Femoral vein pressure | 12 | 6–16 | *2.5* | 12 | 6–16 | *2.5* | | |

Table 2b. Intramedullary pressures in mmHg (mean, range and *SD*) of the femoral head and neck, measured simultaneously in patients with coxarthrosis

| Measurement | | Femoral head | | | Femoral neck | | | Difference | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| Intramedullary pulse pressure | 15 | 6 | 1–29 | *7* | 4 | 1–17 | *4* | 1.4 | |
| Intramedullary pressure | 15 | 54 | 31–89 | *16* | 43 | 23–67 | *14* | 11 | < 0.001 |

both points of measurement. The average pulse pressure in the femoral head was somewhat greater than in the neck (Table 2b), but the difference was not significant. The intraosseous pressure of the femoral neck was of the same order as that observed in the arthrotic joints of the first series. The intraosseous pressure in the femoral head was always higher than that in the neck.

### *Intraosseous phlebography*

Bilateral serial intraosseous phlebography was performed on 13 of the 15 patients of the first series (Arnoldi et al. 1972).

*The healthy hip.* The veins draining the femoral head and neck usually follow the same path as the arteries. Blood leaves the bone marrow through superior and inferior retinacular vessels draining to the medial circumflex and gluteal veins, while the distal part of the femoral neck drains into the lateral circumflex veins that usually empty into the deep femoral vein, but connections to the obturator veins are not uncommon. No veins leaving the femoral head via the femoral head ligament were observed in this series.

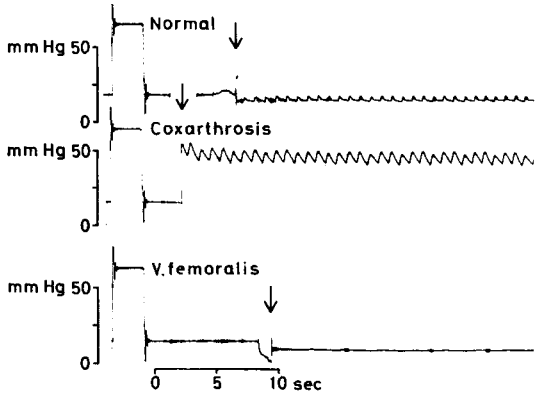



Figure 6. Pressure recordings from the femoral neck and femoral vein from patient with unilateral coxarthrosis.

In normal hips the injected contrast material leaves the intramedullary space within 3 to 6 min. The extraosseous veins are thus well filled, and such details as valves are clearly seen (Figure 7). Filling of intramedullary vessels was observed only in a small, circumscribed area around the tip of the cannula. The intraosseous channels of this area formed a fine-meshed network of minute vessels. In all cases the contrast medium had disappeared from the intramedullary and extraosseous veins within 6 min, except for occasional retention of contrast in the valvular sinuses of the extraosseous veins.

*The arthrotic hip.* Generally, the phlebographs of arthrotic hips were characterized by partial or complete absence of extraosseous veins that normally drain the femoral head and neck. Foveolar veins were never observed. The retinacular vessels had often disappeared completely and the medial circumflex veins were narrowed or missing in most of cases. The filling of remaining extraosseous veins was generally poor.

The area of small intraosseous vessels around the tip of the cannula was enlarged. The vessels of this area were generally wider and more irregular than the corresponding vessels on the unaffected side. In all cases tortuous intraosseous vessels filled with contrast medium were seen extending from the region of the injection site distally towards or into the diaphysis. In many cases, drainage from the femoral head and neck occurred solely through these descending intramedullary vessels to slender perforating veins emerging from the proximal half of the femoral shaft to join branches

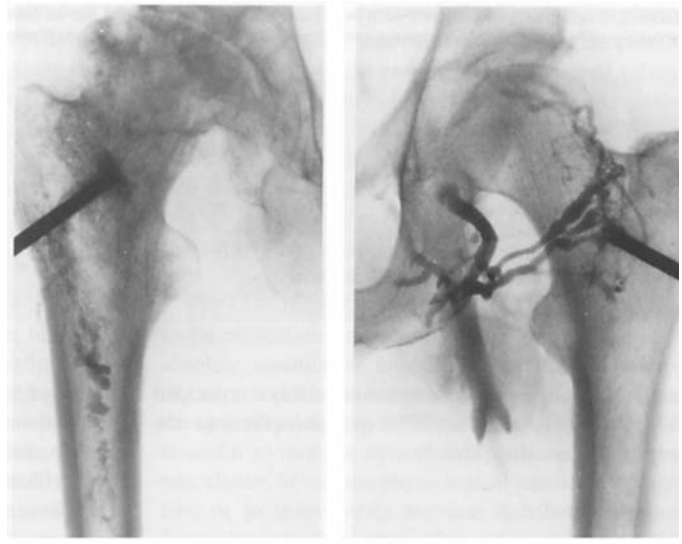


Figure 7. Intraosseous phlebographs from normal left hip and from right hip with severe arthrosis, exposed 30 sec after injection of contrast material. In the normal hip the contrast-mixed blood leaves the intraosseous space without noticeable filling of intraosseous vessels. Drainage takes place through superior retinacular veins to gluteal veins and via two medial circumflex veins to femoral and obturator veins, as well as through inferior retinacular veins emptying into the trunk of the medial circumflex vein. The extraosseous veins are well filled and the arrangement of valves visible. In the right hip the contrast material is collected in large, tortuous intraosseous vessels, extending from the injection site distally into the diaphysis. No extraosseous veins visible.

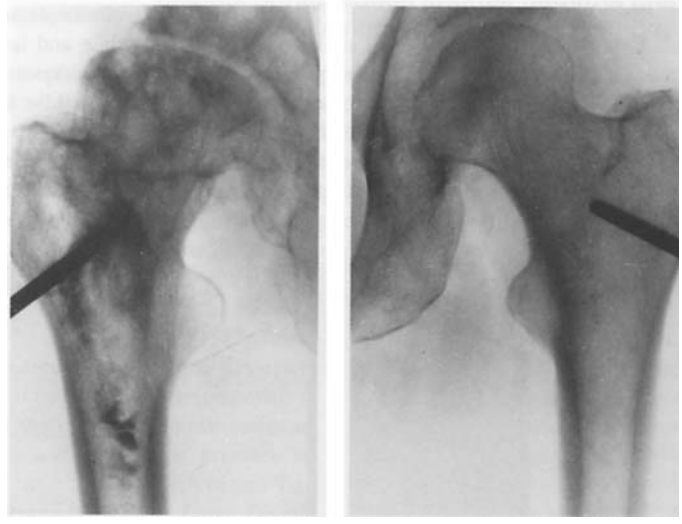


Figure 8. Intraosseous phlebographs from the same patient as 7, exposed 30 min after the injection. In the left hip there is no sign of contrast material in extra- or intraosseous veins (complete evacuation was noted 3 min after the injection). In the arthrotic hip large quantities of contrast remain in the intraosseous space. No filling of extraosseous veins.

of the deep femoral vein or superficial veins on the lateral aspect.

As a rule, the extraosseous veins were empty of contrast material within a few minutes of injection. However, the drainage of contrast material from the intramedullary vessels was delayed in comparison with the healthy side. The intraosseous veins generally remained filled with contrast medium for the duration of observation (Figure 8).

### $^{99m}$Tc-polyphosphate scintigraphy

Ten patients with arthrosis of the hip or knee and suffering from severe rest pain, were assessed using intraosseous pressures, phlebography, and $^{99m}$Tc-polyphosphate scintigraphy (Arnoldi et al. 1980, Table 3). Severe painful arthrosis in the hip or knee was always accompanied by intramedullary venous stasis (Figure 9). In the knee joint the signs of venous retention were more often found in the femur than in the tibia.

The pressure measurements showed the same differences as previously, between normal and affected joints and these differences were of the same order as in the earlier series. Again, high intramedullary pressure was more often found in the distal femur than in the proximal tibia. Finally, the investigation showed that high intraosseous pressure and abnormal distribution

Table 3. Findings in 10 patients with rest pain and arthrosis of the hip or knee, examined by means of bilateral intraosseous phlebography, intraosseous pressure measurements and $^{99m}$Tc-polyphosphate scintigraphy

| Group / Joint | n | Age mean (range) | Men | Hip / knee | Abnormal phlebogram affected | Abnormal phlebogram normal | Intraosseous pressure affected | Intraosseous pressure normal | Increased scintigraphy affected | Increased scintigraphy normal |
|---|---|---|---|---|---|---|---|---|---|---|
| A | 6 | 54 (30–68) | 4 | 2 / 4 | 6 | 0 | 44 (33–80)[c] | 15 (3–24)[c] | 6 | 0 |
| B | 4 | 53 (34–61) | 2 | 0 / 4 | 8 | ... | 41 (42–50) | ... | 8 | ... |

A. Patients with unilateral pain and arthrosis
B. Patients with bilateral pain and arthrosis.
[c] One set of measurements was excluded due to technical faults. Thus, the pressure measurements were from only 5 patients.

and retention of contrast material always coincided with a high uptake of $^{99m}$Tc-polyphosphate in the region (Figure. 10; Table 3).

## Intraosseous pressure and flow in normal and arthrotic femoral heads during loading and passive joint movements

It has long been known that in patients with intermittent supra-articular venous resistance to drainage from bone marrow (chronic venous insufficiency of the lower limb), the pressure in the marrow of the ankle skeleton undergoes extreme variations during such activity as walking (Arnoldi and Linderholm 1971) and that continuing abnormally high ambulatory pressure rises may lead to skeletal and occasionally joint changes in this region (Arnoldi et al. 1972).

However, until recently our knowledge of intraosseous pressure in joint-bearing bone marrow in degenerative joint disorders stemmed exclusively from measurements on patients and animals with the joint immobile and unloaded during the measurements, and the techniques employed by the various investigators have varied but little.

Pressure variations during joint movements were first reported by Arnoldi et al. (1980) and by Bünger et al. (1982) in horses and puppies, respectively. Pressure

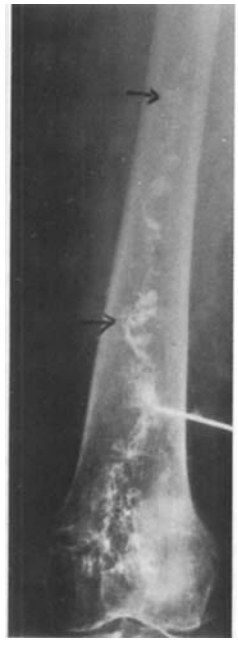


Figure 9. Intraosseous phlebograph from a patient with severe rest pain and arthrosis of the knee, exposed 30 min after injection of contrast material.

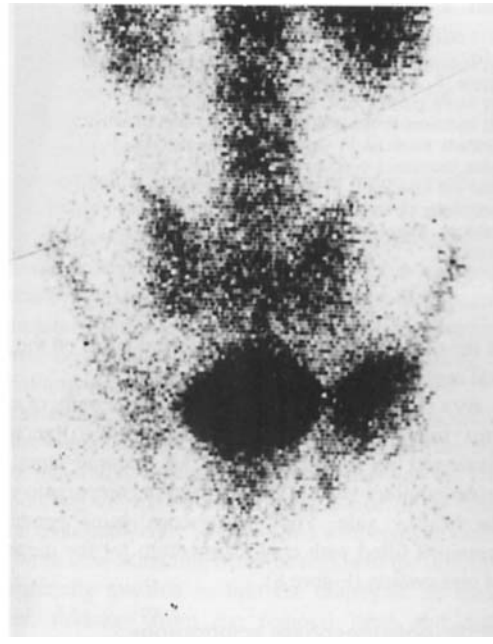


Figure 10. $^{99m}$Tc-polyphosphate scintigraph from patient with arthrosis of the left hip.

measurements during joint loading were published by Hejgaard and Arnoldi (1984) and Arnoldi (1991), who examined pressures in the patella and the femoral and tibial condyles in pain-free knees and knees with patellar pain syndromes. A preliminary report on the effect of loading and movement on the pressure in the femoral head in arthrotic hip joints was given by Arnoldi (1990).

### *Own investigations*

We (Arnoldi, unpublished data) found it of interest to evaluate both pressure and blood flow in the bone marrow of the femoral head of normal and arthrotic hip joints under conditions that simulate weight-bearing and joint movements.

*Material.* Six patients, 4 women and 2 men; median age 69 (58–79) years, were examined bilaterally. Eight hips had moderate to severe arthrosis and significantly increased uptake of $^{99m}$Tc-polyphosphate. Their symptoms were severe enough to warrant alloplasty. Four hips were without symptoms, were radiographically normal and had neutral isotope uptake.

*Methods. Pressure measurements.* The patients were examined on the operating table, prior to alloplasty, lying supine under general anesthesia. The cannula for pressure measurement was placed with the tip in the centre of the femoral head under guidance of an image intensifier. The general procedure for measurements followed that described above. The catheter in the extraosseous vein, when used, was placed with the tip at the junction of the internal saphenous and superficial femoral veins.

*Pressure recording.* The cannulae for pressure measurements were connected to Bentley transducers (American Edwards Laboratories, Santa Ana, CA. U.S.A.) that in their turn were connected to a 4 Press 8041 measuring system (Simonsen & Weel, Copenhagen, Denmark) with a 6-channel printer (BBC SE 460, Austria). The pressure (and flow) tracings were controlled visually during the measurements on a Quadriscope (Simonsen & Weel).

*Laser Doppler flowmetry.* The laser Doppler flowmetry (LDF) is based on the Doppler shift of a monochromatic beam of light from a 2-mV He-Ne laser source that is reflected from moving blood cells in the tissue. This shift of wavelength is converted into an electronic signal and is presented digitally in millivolts (mV). LDF can provide a continuous, real-time monitoring of changes in local perfusion and an estimate of the relative blood flow in different regions of a tissue, e.g. the bone marrow of the femoral head.

The laser Doppler flowmeter produces an output signal that is linear over the entire measured range and is proportional to the microvascular blood cell perfusion of the target tissue. The perfusion value is the product of the number of cells moving in the measured volume and the mean velocity of these cells, but is independent of the direction of the movement of the blood cells. The measured area is about 1.5–2 mm$^2$ and the maximum penetration depth in trabecular bone is about 3.5 mm, and 2.9 mm in cortical bone (Nötzli et al. 1989). The reproducibility error of the perfusion recorded with this method is approximately 7 percent (Tenland 1982).

The LDF output signal is strictly relative in nature, and a calibration standard to convert the signal into an absolute quantitative index of blood flow in various organs and different individuals is not possible due to the spatial variation in the vascular bed. However, LDF is useful to monitor dynamic responses of the microvasculature to various physiological stimuli at a single site, or to demonstrate regional distribution of perfusion in a specific organ (Swiontkowski et al. 1986, Smits et al. 1986, Obeid et al. 1990).

In animals, LDF has proven useful in measuring perfusion in cancellous bone following regulation of the systemic blood pressure (Hellem et al. 1983). More recently, the blood perfusion of the femoral head was monitored by LDF following selective occlusion of the blood supply to the femoral head (Bassett et al. 1991) and after introduction of intracapsular hyperpressure (Vegter and Klopper 1991). The LDF signal was obtained either through the cartilage of the femoral head (Bassett et al. 1991) or though a drill hole in the bone (Vegter and Klopper 1991). However, Swiontkowski et al. (1987) found a close correlation between measurements through the articular cartilage and those obtained intraosseously through a drill hole. Animal studies have shown undisturbed blood flow after bone cannulation for pressure measurements (Bouteiller et al. 1984, Wilkes and Visscher 1975).

*Laser Doppler flowmetry in own investigations.* A cannula, identical to the one used for pressure measurement, was inserted parallel to the pressure cannula. The tips of the two cannulae were always placed at the same level in the femoral head with a distance measuring 1–1.5 cm. After removal of the trocar, the cannula was flushed with heparine-saline and a 15 cm long LDF probe, ensheathed in metal and with a diameter of 2.2 mm was inserted into the cannula. The tip of this probe reached just beyond the tip of the cannula and was placed lightly against the bone marrow tissue. The probe was connected to the laser Doppler flowmeter (Periflux PF 3, Perimed, Stockholm, Sweden) and the output signal, measured in mV, was recorded on the same strip chart as the pressure tracing. The time constant selector could be set to 0.02 sec to observe wheth-

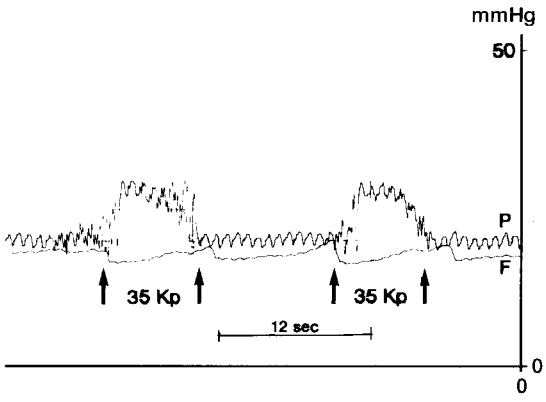



Figure 11. Pressure and flow chart from centre of normal femoral head in neutral position, before, during and after two periods of joint loading. P = pressure; F = flow.

er the flow was pulsatile or not, or to 0.2 sec for average and more comparable readings. All tracings in the figures should be read from right to left.

*Manoeuvres during examination.* The first measurements were performed with the hip joint in the neutral position. After measurements at rest, an assistant put pressure on the straight leg with the patient's foot pressed to the flat surface of a weight-recording device on the chest of the assistant. A series of brief periods of pressure was then applied to the patient's foot and the force used was recorded. Total immobility was attempted between each period of loading. With the patient's limb still straight, 2–3 brief periods of external and internal rotation of the femur were performed. The force used during these movements was not measured numerically. They were all done quickly and forcefully.

The next set of manoueuvres, comprising external and internal rotation of the femur and flexion beyond 70°, was performed with the hip at 70° flexion and the knee 90°.

## Results

***Pressure and flow at rest.*** In normal hips the pressure in the centre of the femoral head was low, median 18 (15–22) mmHg; the corresponding flow 180 (150–200) mV. In arthrosis the median pressure was 44 (32–56) mmHg, and the flow 130 (80–160) mV.

***During loading.*** *Normal hips.* In normal hips the pressure in the femoral head rose steeply to a moderately high pulsatile plateau and the pressure rise was dependent upon the load applied. The flow showed very moderate changes with a small increase during the initial phase, followed by a slight decrease during continued loading, and ending with a moderate increase when the load was released. After repeated periods of loading, the flow showed a slightly higher velocity than in the pre-exercise period (Figure 11).

*Arthrotic hips.* Two different patterns were observed: Type 1 (Figure 12) resembled the pressure curves from normal femoral heads, while Type 2 showed an initial, brief rise of pressure immediately followed by a fall below the pressure level at rest (Figure 13). Cessation of loading brought the bone marrow pressure back to resting level. It was characteristic that the pulse amplitudes increased slightly during loading in Type 1, while they decreased during the pressure fall in Type 2.

A comparison between pressure tracings and radiographic findings showed that the two Type 1 curves came from joints with femoral heads showing moderate radiographic changes, while the Type 2-pattern joints showed more severe changes, especially deformity and lateral displacement of the femoral head.

*Flow.* Flow charts during loading were only obtained from femoral heads with Type 2 pressure patterns (Figure 13). Essentially, they showed the same flow variations as observed in normal femoral heads, but the difference between high and low flow rates was accentuated.

***During joint movement.*** *Normal femoral head in neutral position.* The pressure and flow charts from the femoral head of normal hips were fairly uniform (Figure 14). The pressure in the centre of the head was hardly affected by the manoeuvre, while the flow velocity increased steeply during the movement to maximal rotation, but showed a decrease of velocity as inward rotation was sustained.

*Normal femoral head at 70° flexion.* Figure 15 shows essentially the same characteristic minimal pressure reaction. A considerable increase of flow was observed as long as inward rotation in flexion was maintained.

*Arthrotic femoral head in neutral position.* In these femoral heads internal rotation produced pressure and flow charts similar to those observed in Type 2 charts on loading.

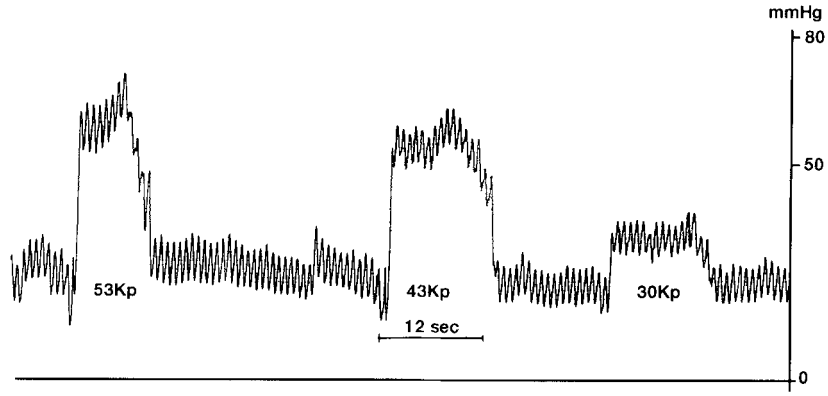



Figure 12. Pressure tracing from arthrotic femoral head in the neutral position, before, during and after three periods of joint loading (Type 1 pattern).

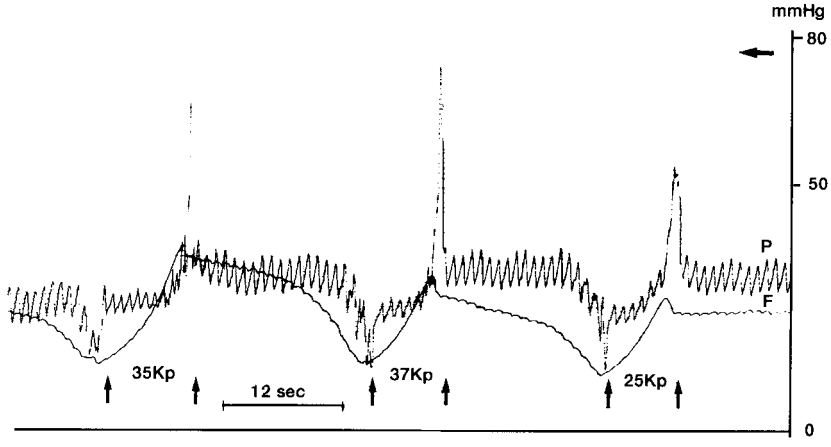



Figure 13. Pressure and flow chart from severely deformed and displaced arthrotic femoral head, before, during and after three periods of joint loading (Type 2 pattern).

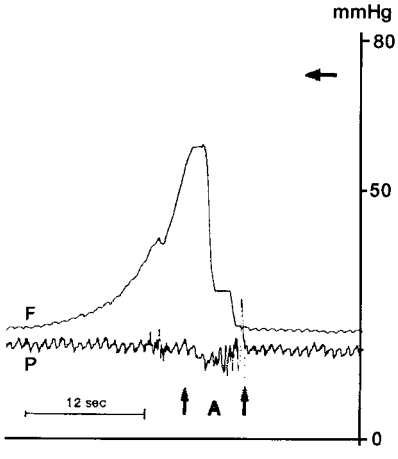



Figure 14. Pressure and flow chart from normal femoral head, before, during and after one forceful internal rotation of the femur with the joint in neutral position (A).

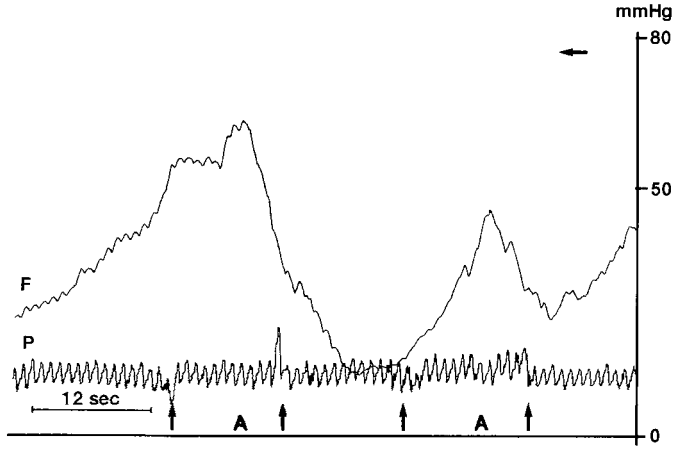



Figure 15. Pressure and flow chart from normal femoral head, before, during and after forceful internal rotations with the hip joint in 70° flexion (A).

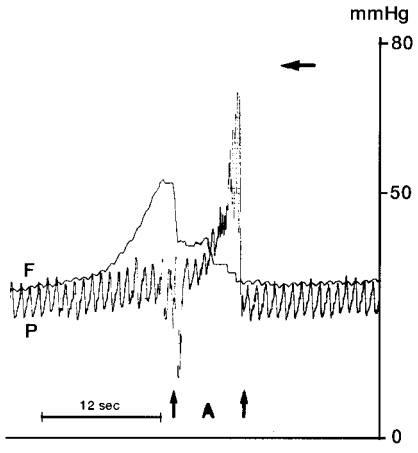



Figure 16. Pressure and flow chart from arthrotic femoral head, before, during and after a period of forceful internal rotation of the femur (A).

*Arthrotic femoral head at 70° flexion.* The initial abrupt rise in pressure at the beginning of the manoeuvre was followed by a relatively quick return to resting level. A gradual increase of flow velocity during the period of rotation was followed by a steep increase as the hip was brought back to a neutral position in flexion (Figure 16, compare with Figure 15 showing pressure and flow in the contralateral normal femoral head during the same manoeuvre).

### Comments

The results from this, albeit limited, material show clearly that arthrosis of the hip affects both pressure and flow in the femoral head during loading and joint movements. When considering the changes observed during the loading experiments, it should be remembered that the compression forces applied to the hip joint were very modest compared to the forces at play during, for example, standing and walking. The rotation manoeuvres, however, were performed forcefully and quickly and can be assumed to correspond more closely to real life conditions.

The overall results indicate a free flow from the normal bone marrow of the femoral head and, consequently, modest pressure variations. The opposite seems to be the case in arthrosis.

## $^{99m}$Tc-phosphate scintigraphy

Clinical experience shows that in painful arthrotic joints the uptake of bone-seeking agents is increased, even at a very early stage. The uptake is also increased in knee and hip joints suffering from intraosseous engorgement-pain syndromes, possibly a pre-arthrotic state (see the section on this syndrome and radiographically normal arthrosis), and in the early stages of non-traumatic femoral head necrosis (Ficat 1985). However, the physiological basis for the binding of the tracer to skeletal tissue and the cause of increased uptake are still subjects of discussion.

Recently, Christensen (1985) reviewed the literature on these subjects and published the results of his investigations which form the basis of the brief analysis presented here. For a full discussion the reader is refered to his thesis.

***Factors involved in skeletal uptake.*** *Blood flow.* Perfusion through bone is essential for the uptake of bone-seeking isotopes. In the absence of perfusion, as in infarction and sequestration of bone, this area will appear in the scintigram as a cold spot (Bohr and Heerfordt 1977). Inversely, we may conclude that increased uptake means the area is supplied with arterial blood. In all examinations on immobile and unloaded joints with arthrosis and intraosseous engorgement-pain syndromes the pressure tracings from juxtachondral bone marrow showing increased tracer uptake have been pulsatile.

*Location of $^{99m}$Tc-phosphate in skeletal tissue.* Christensen and Krogsgaard (1981) used rat epiphyses in which there is a good morphological distinction between the various bone forming stages of enchondral ossification: provisional calcification, ossification and resorption.

*Autoradiography.* $^{99m}$TC-MDP (methylene diphosphonate) was administered intravenously to 4–5-week-old rats 3 hours before they were killed. The knee region was freeze-embedded and cut on a hard-tissue cryostat by Ullberg's technique (1954). Contact autoradiography of the sections was performed in the cryostat using nuclear plates coated with a G5 emulsion, post-fixed in 4 percent Baker's formol calcium (4 percent formaldehyde), and stained. Microautoradiography was on fixed sections (formol calcium) by the dip method (Kopriwa and LeBlond 1962): dipping the tapes suspended from metal frames.

*Vital staining.* To compare the radionuclide uptake with the remodelling processes in skeletal tissue, rats were labelled *in vivo* with oxytetracyclin, administered with a short labelling interval (3 hours), after administration of $^{99m}$TC-MDP. This will label both formative and resorptive bone surfaces (Harris et al. 1962, Olerud and Lorenzi 1970). The sections were either photographed under incident fluorescence microscopy prior to the autoradiographic procedure or coated with 0.5 celloidin which somewhat diminishes the fading of the fluorescence conditioned by the autoradiographic procedure.

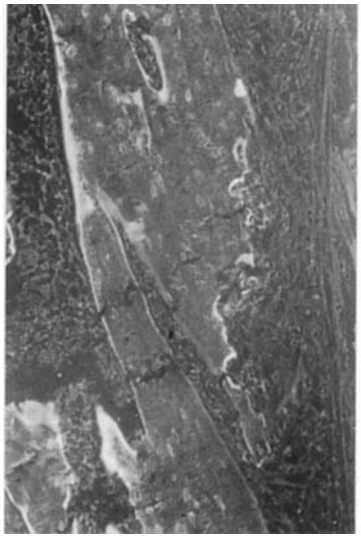


Figure 17. Tetracycline fluorescense micrograph. Bone trabeculum with periosteal area and osteoclastic resorption to the right, and marrow with new bone formation to the left.

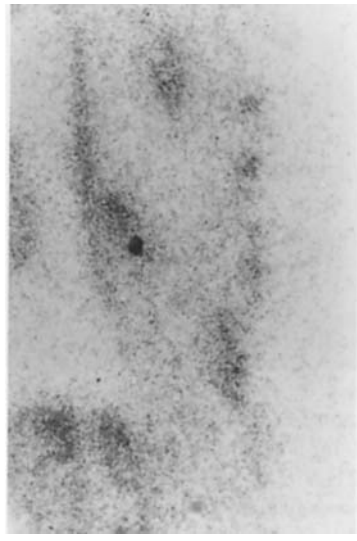


Figure 18. Uptake of $^{99m}$Tc-MDP in osteoclastic (resorption area) and osteoblastic (bone formation) area. Radionuclide accumulation coincides with tetracycline fluorescense with short labelling period (cf. Figure 17).

Figure 19. Fibrocartilage at the articular surface with enchondral ossification. Alkaline phosphate activity (Burstone, x10).

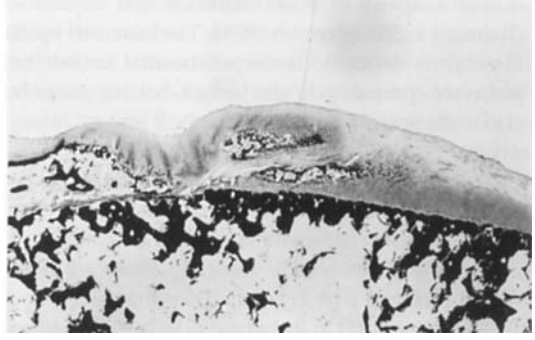


Figure 20. Same area as in Figure 19 (reversed). Von Kossa's stain for calcium phosphate (x10).

The short-interval tetracyclin labelling showed fluorescence of both formative areas, in particular the provisional calcifications, as well as of the resorptive surfaces in Howship's lacunae. There was good agreement between fluorescences of the tetracyclin and the autoradiographic uptake of $^{99m}$TC-MDP within the same section (Figures 17, 18).

*Location in advanced arthrosis.* In bone scintigraphy, even when using a gamma camera with a high resolution collimator, it is difficult to locate the bone-seeking isotopes accurately in the arthrotic joint and its surroundings. Therefore, we found it of pathogenetic interest to elucidate the distribution by means of macroautoradiography (Christensen and Arnoldi 1980). Patients with arthrosis of the hip were injected intravenously, 2 hours before arthroplasty, with 10 mCi of $^{99m}$TC-polyphosphate. The arthrotic femoral head was freeze-embedded and freeze-cut into halves on a hard tissue cryostat. The cut surface of the remaining part of the head formed the background for the macroautoradiography. The sections cut last were used for comparison after staining with Burstone's method for alkaline phosphate activity and with von Kossa's stain for calcium phosphate (Pearse 1968; Figures 19, 20). The macroautoradiography was also compared with radiographs of the remaining half of the femoral head.

The uptake was markedly increased in the weight-bearing area, in cyst walls beneath the denuded joint

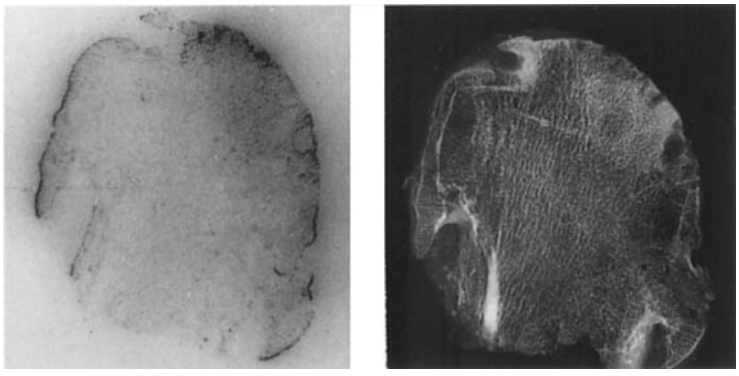


Figure 21. Autoradiogram from arthrotic femoral head given $^{99m}$Tc-polyphosphate preoperatively (left). The radionuclide is predominantly accumulated at the cyst wall of the weight-bearing area and at the osteochondral junction in the osteophytes. Corresponding radiograph of a thin slice of femoral head (right).

surface, at the osteochondral junction of the osteophytes, and in fibrocartilaginous areas of some cysts (Figure 21).

The autoradiographic distribution was supported by scintimetric counting of activity in the various areas of the section (Figure 22). Thus, the increased uptake by the arthrotic femoral head was not evenly distributed and the distribution of radionuclide uptake was analogous with that of alkaline and acid phosphatase activity, marker enzymes of bone formation and breakdown (Reimann and Christensen 1979). The increased uptake in arthrosis thus reflects the subchondral remodelling processes, primarily in the weight-bearing area, but also in the growth of osteophytes.

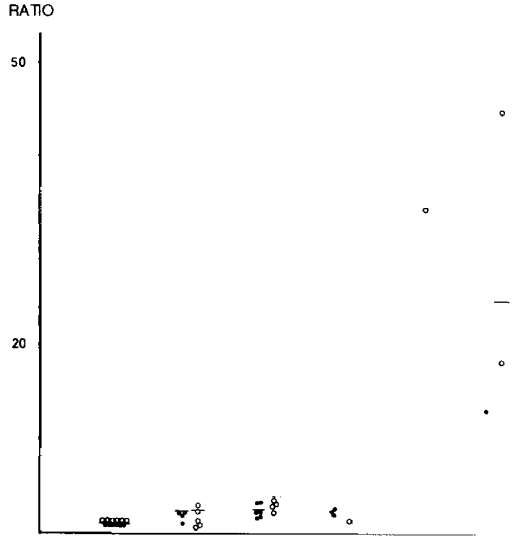



Figure 22. Target-to-background ratio in different areas in 12 arthrotic femoral heads, using the uptake of radionuclide in the fibrous capsule as background. WB = weight-bearing area. ● $^{99m}$Tc-polyphosphate and ○ $^{99m}$Tc-methylendihosphate

## THE SYNOVIAL MEMBRANE

Seen with the naked eye the internal surface of normal synovial membrane is smooth, moist, glistening and pink. Villi are few and small. Microscopic examination reveals an inner layer of synovial lining cells (synoviocytes), covering a mostly loose fibrous stroma containing nerves, blood vessels and lymphatics (Figure 23). The vessels in the stroma are not a prominent feature.

### *Vascular changes in synovial membrane in advanced arthrosis and rheumatoid arthritits*

In the literature on arthrosis the changes in the synovial membrane are usually compared with those taking place in rheumatoid arthritis. As our own early investigations followed the same pattern, the tradition is kept here.

*Previous investigations.* Light microscopy of the synovium in arthrosis has revealed either no characteristic abnormality or only mild non-specific inflammatory changes (Waine 1958, Cooper 1964), sometimes

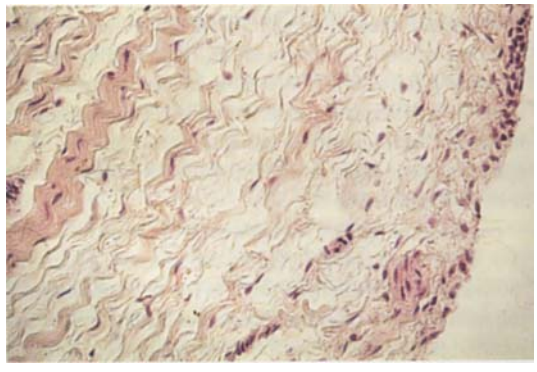


Figure 23. Normal synovium removed from knee of an elderly patient (H&E, x250).

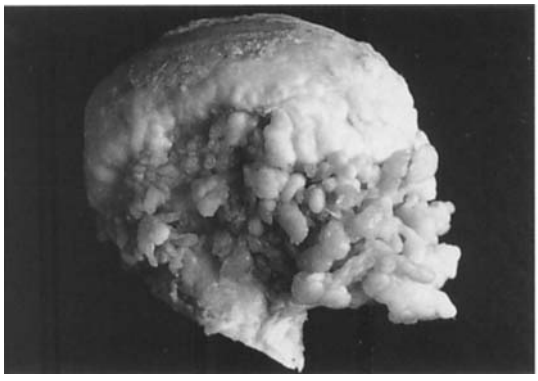


Figure 24. Femoral head from 71-year-old woman with coxarthrosis. *Proliferative synovitis.*

Figure 25. Femoral head from a 71-year-old man with coxarthrosis. *Fibrous synovitis.*

accompanied by hyperplasia of the lining cells (Wilkinson and Jones 1963).

Roy (1967) showed electron-microscopically that most aspects of the synovium's cellular and stromal ultrastructure were normal. He noted proliferation of the lining cells and, at the ultrastructural level, the appearance of a large number of lysosomes and cytolysosomes was quite striking. These quantitative changes are non-specific and may occur as a result of cell injury by a variety of agents.

Roy (1967) further observed abnormal retention of fluid in the synovial lining cells resulting either from intracellular damage or from changes of membrane permeability. He and many others believe these synovial changes are non-characteristic, i.e. not attributable to any specific pathological agency, but are probably secondary to other arthrotic abnormalities, in particular synovial reaction to cartilage detritus (Lloyd-Roberts 1953, Hamerman 1966).

Apart from the early changes in cartilage in experimental arthritis discussed above, findings of such changes in the synovial fluid in arthrosis as decreased oxygen content (Lund-Olesen 1970), changes in the protein pattern (Nettelbladt and Sundblad 1959, Kushner and Somerville 1971, Pruzanski et al. 1973, Veys 1974, Willumsen and Friis 1975) and reduction of boundary lubrication (Reimann 1976), indicate that changes in the synovium may, in fact be extremely important to the fate of articular cartilage and subchondral bone, and merit serious re-examination.

### Own investigations

*Material and methods.* During hip replacement surgery, synovial membrane biopsies were taken from 44 hips (Arnoldi et al. 1980), 24 with arthrosis, 12 with rheumatoid arthritis, and 8 with fresh fractures of the femoral neck. All biopsies were from the lower medial area of the joint at the attachment of the fibrous capsule. Histological sections for light microscopy were prepared from all of them. Several strips for electron microscopy were removed from 3 of the arthrosis specimens and one from the controls.

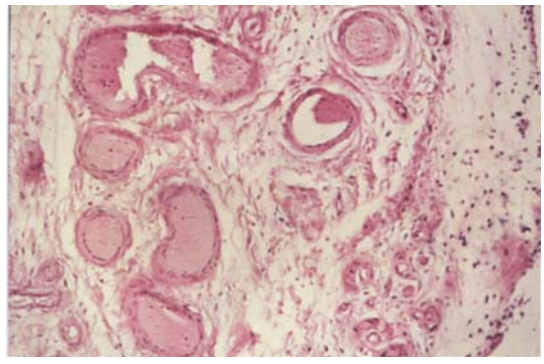
***Results.*** Gross inspection of synovial membrane from the arthrosis group showed various degrees of hyperemia, edema, fibrosis and hypertrophy of the villi. Contrary to the findings in the rheumatoid arthritis group, surface fibrin deposits were never present. In the arthrosis patients synovial changes fell into two relatively distinctive groups: one predominantly proliferative and one predominantly fibrous synovitis. Proliferative synovitis is characterized by bulky volume, the edematous tissue often resembling bunches of small juicy grapes (Figure 24). In these cases the synovial fluid is always increased. In fibrous synovitis, the joint is usually dry. Most of the grapelike protuberances have disappeared and been replaced by patches of stringy bands of fibrous tissue (Figure 25).

For patients with proliferative and fibrous synovitis the average duration of symptoms was 4 years and 8 years, respectively.

### Microvascular changes in the synovium

*Previous investigations.* It has been suggested that the vascular changes in the synovium are caused by a vasculitis localized to venules and capillaries; however, electron microscopic examinations in rheumatoid arthritis (Brånemark et al. 1987) and arthrosis (Dryll et al. 1977, Goldie 1970) have shown that the capillary structure is normal, but that the transcapillary migration of circulating blood cells is greatly increased. This is in agreement with the electron microscopic findings in our study (Arnoldi et al. 1980).

| | | | |
|---|---|---|---|
| Number of biopsies | 10 | 21 | 14 |
| Surface fibrin | 0 | 0 | 8 |
| Rows of synoviocytes | | | |
| 1 | 5 | 3 | 0 |
| 2–3 | 4 | 15 | 6 |
| > 3 | 1 | 2 | 8 |
| Vascularisation of synovial membrane | | | |
| poor | 7 | 4 | 0 |
| moderate | 2 | 5 | 2 |
| rich | 1 | 12 | 12 |
| edematous | 2 | 14 | 10 |
| fibrous | 0 | 6 | 4 |
| neutral | 8 | 1 | 0 |
| Vessels | | | |
| stasis | 1 | 19 | 14 |
| unstructured aggl. of erythrocytes | 0 | 14 | 10 |
| fibrin thrombi | 0 | 11 | 11 |
| Free erythrocytes in stroma | 0 | 11 | 12 |
| Interstitial bleeding | 0 | 1 | 3 |
| | | 4 | 0 |
| scattered | 1 | 5 | 2 |
| masses | 0 | 12 | 12 |
| Calcium deposits | | | |
| *none* | 0 | 16 | 2 |
| scattered | 1 | 5 | 11 |
| masses | 0 | 0 | 1 |



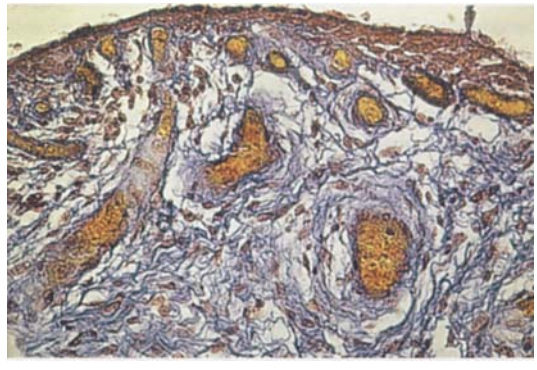


Figure 27. Light microscopy of histological section of the synovial membrane from a 63-year-old man with rheumatoid arthritis of the hip, showing dilation of venules packed with erythrocytes, and interstitial edema (MSB, x25).

Microvascular disturbance is an essential factor in most mesenchymal diseases and it is generally agreed that vascular changes in rheumatoid synovium are part of an inflammatory process. Goldie (1970) found that, although less intense in arthrotic synovium, the pattern of vascular changes in both types of synovium is the same and, in his opinion, the changes in arthrosis are also caused by an inflammatory process.

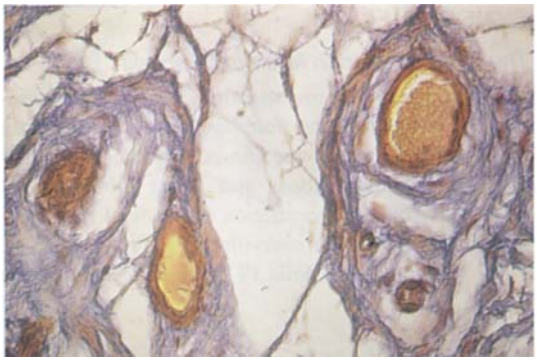
### *Own investigations*

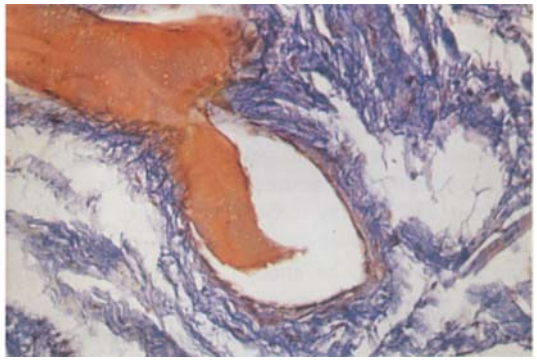
Our previous investigations (Arnoldi et al. 1980) led us to agree with Goldie (1970) that the microvascular changes in these two types of synovial affection seem to be of the same pattern. In the meantime, other staining methods have permitted a more detailed histological investigation of the changes found both in the vessels and in the surrounding stroma (Arnoldi and Sønderlev 1990, unpublished data).

*Material.* Synovial biopsies from 10 normal joints, 21 arthrotic and 14 rheumatoid were examined by light microscopy. Both hip and knee joints were included (Table 4).

*Methods.* The following staining methods were used in all cases: 1) hematoxylin/eosin; 2) Martius scarlet blue (MSB) was used to visualize erythrocytes in the interstitial tissues, intravascular erythrocyte stasis, erythrocyte agglutination and fibrin thrombi of various ages. By this method erythrocytes are stained a bright yellow, as are recently formed fibrin thrombi. Later on these thrombi are stained scarlet, and old thrombi a deep blue. MSB is also an excellent stain for collagen (blue); 3) Perl's Prussian blue demonstrated hemosiderin deposits; and 4) von Kossa's method visualized calcium deposits in the synovium.

*Results.* The overall results of the investigation are summarized in Table 4. In this context only the findings directly connected to changes in vessels and their contents in arthrotic and rheumatoid arthritic synovium are





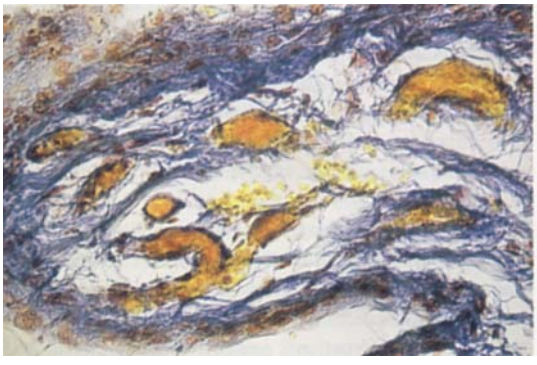


Figure 30. Arthrotic synovium from hip joint. Dilated vessels showing intravascular agglutinations of erythrocytes. Edematous stroma with extravascular red blood corpuscles (MSB, x400).

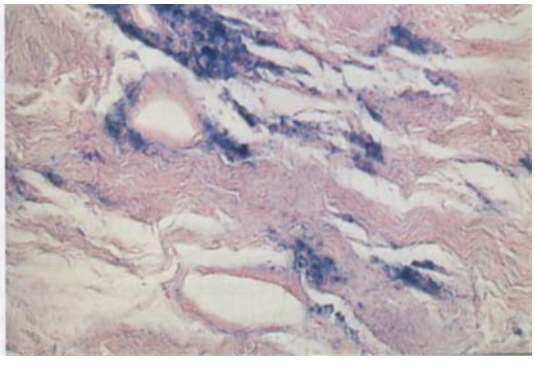


Figure 31. Hemosiderin deposits in arthrotic subsynovial tissue in close juxtaposition to solid bands of collagen. Fibrous synovitis (Perl's Prussian blue, x25).

*Number and calibre of vessels.* Compared with normal (Figure 23), the arthrotic (Figure 26) and rheumatoid (Figure 27) synovium were characterized by a rich network of, mostly, dilated vessels.

*Intravascular erythrocytes.* More than 80 percent of smaller veins were tightly packed with erythrocytes, still distinguishable as separate blood corpuscles (Figure 28). In very many vessels gradual changes could be observed, often inside the same vessel, the aggregations of erythrocytes becoming structureless agglutinations (Figure 28) and transition from this stage into fibrin thrombi was a common sight (Figures 29, 30). These changes were common to both disorders.

*Vessel wall permeability.* Permeability to formed blood elements was increased, as judged by the number of single, free erythrocytes in extravascular stroma (Figure 30). The number seemed greater in rheumatoid than in the arthrotic synovium.

*Interstitial hemosiderin deposits.* Hemosiderin crystals lying free in interstitial tissue or engulfed by macrophages were common in both disorders. In arthrosis the free crystals were commoner in the late fibrous stages of synovitis than in the early proliferative stage, and the juxtaposition to massive strands of collagen was notable in arthrosis as well as in rheumatoid arthritis (Figure 31).

*Calcium deposits.* These were noted in 5 of 6 arthrotic specimens with fibrous synovitis, and in 12 of 14 with rheumatoid arthritis, with proliferative as well as fibrous synovitis.

*Comment.* Thus, our investigations showed that dilation, stasis and thrombotic occlusion of synovial vessels, especially smaller veins and venules, are prominent features in both arthrosis and rheumatoid arthritis. We are in no doubt that the vascular changes in rheumatoid synovium are initiated by an inflammatory process; however, the same changes were observed in

arthrotic synovium where the histological signs of inflammation were slight or modest.

In fact, the vascular changes observed indicate chronic venous stasis. In the hip and, to a lesser degree, the knee with their tough and rigid fibrous capsules, an increase in synovial fluid and the bulk of the synovium is accompanied by a rise in intra-articular pressure (Eyring and Murray 1964). A pressure rise of 10 mmHg, which leaves the arterial inflow to the synovium intact, would be enough to compress the thin-walled intra-articular veins and create a blockage to venous drainage, and chronic stasis is probably one of the factors mainly responsible for the remarkable tendency to chronic blockage (thrombosis) of synovial and subsynovial veins.

The effect on mesenchymal tissue of long-standing intermittent high pressure on the venous side of the capillary is well known from patients with chronic venous insuffiency of the lower limb. These abnormal pressures are evoked by a purely mechanical dysfunction of the venous pump of the calf (Arnoldi and Linderholm 1968). The ambulatory pressure during systole (calf muscle contraction) remains at a high level during walking, instead of falling as it does normally. Increased resistance to flow and capillary dilation result in subcutaneous edema. The high protein content of the interstitial fluid and the presence of strong irritants, such as hemosiderin, give rise to a secondary inflammatory reaction, that gradually transforms the pliant edematous subcutis into fibrous scar tissue, known as induration, often with scattered soft tissue calcifications (Arnoldi et al. 1972).

Our gross inspection and histological findings, combined with the changes in the amount of intra-articular fluid indicate that chronic venous stasis and hypertension lead to a similar development in arthrotic synovium, with proliferative synovitis as an early stage of a process that gradually leads to fibrous transformation of the synovial membrane.

The similarity of vascular changes in arthrotic and rheumatoid synovium and the clinical appearance of the joints in the late stages of rheumatoid joint disease, indicate that the same mechanism is influential in rheumatoid joints.

## SYNOVIAL FLUID

### *The synovial fluid in late coxarthrosis*

The main purpose of investigating changes in the composition of the synovial fluid has been to differentiate between inflammatory and non-inflammatory joint diseases. In arthrosis Ropes and Bauer (1953) found increased protein concentration in synovial fluid, and others (Kushner and Somerville 1971, Pruzanski et al. 1973, Willumsen and Friis 1975) an abnormal protein pattern.

### *Own investigations*

*Permeability of synovial membrane to plasma proteins in arthrosis of the human hip joint. Relation to molecular size and histological changes.* The histological and vascular changes in arthrotic synovium indicate a state of severe venous and capillary stasis with increased vessel wall permeability. Reimann et al. (1980) attempted to analyse changes in the permeability of the synovial membrane to plasma proteins of varying molecular size and to correlate these changes to the histological features in the synovial membrane of patients with coxarthrosis.

*Material and methods.* By means of bilateral arthropuncture, synovial fluid from the hip joints of 46 patients with unilateral arthrosis was obtained during total hip replacement. Blood samples were taken simultaneously. The 46 patients comprised 31 women and 15 men, mean age 67 (40–81) years. The criteria of unilateral disease were: a radiographically normal contralateral hip joint without clinical symptoms, and no accentuation of the normal uptake pattern on osteoscintigraphy with $^{99m}$Tc-polyphosphate (Heerfordt et al. 1976).

From 34 of the 46 arthrotic hips it was possible to obtain fluid samples ranging from a few drops to a maximum of 10 mL. However, as blood was present in 5 of the samples, only 29 were suitable for analysis. One to 2 drops of synovial fluid were obtained from 26 of the 46 normal hips, but 3 samples were omitted because of blood. Extraction of synovial fluid from both hips was only possible in 8 patients.

Quantitative estimation of 4 non-immunoglobin proteins was performed. The proteins studied were orosomucoid, MW 44,000; transferrin, MW 74,000; ceruloplasmin, MW 160,000 and α-2-macroglobulin, MW 820,000. The simultaneously aspirated synovial fluids and sera were analysed by electro-immunoassay according to Laurell (1966) in antibody containing 1 percent agarose gel (Latex) in barbital buffer pH 8.6; the antibodies used were monospecific from Dako (Copenhagen). A standard pooled serum was calibrated against Behringwerke standard human serum. Samples

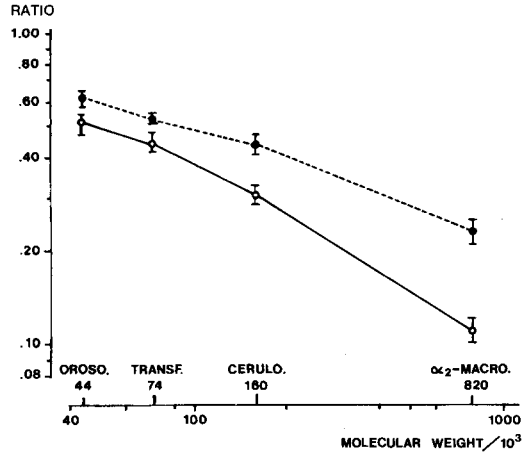



Figure 32. Log/log plot of SF/S ratio and molecular weight from hip joints with arthrosis (black circles) and from normal hip joints (open circles). Ratios determined for the 4 non-immunoglobulin proteins represent the mean ± SD of 29 and 23 samples, respectively.

Table 5. Synovial fluid/serum ratios (*SD*) of four proteins

| Proteins[a] | OM | TF | CP | MG |
|---|---|---|---|---|
| Arthrosis (29) | 0.61 *0.14* | 0.53 *0.11* | 0.44 *0.14* | 0.23 *0.10* |
| Normal (23) | 0.51 *0.16* | 0.45 *0.12* | 0.30 *0.09* | 0.11 *0.04* |
| *P*-value[b] | < 0.05 | < 0.05 | < 0.01 | < 0.01 |

[a]OM orosomucoid, TF transferrin, CP ceruloplasmin, and MG α-2 macroglobulin.
[b]Mann–Whitney's rank-sum test.

Table 6. Synovial fluid/serum ratios (*SD*) of four proteins in intra-individual comparisons.

| Proteins[a] | OM | TF | CP | MG |
|---|---|---|---|---|
| Arthrosis (8) | 0.57 *0.17* | 0.55 *0.08* | 0.44 *0.04* | 0.23 *0.06* |
| Normal (8) | 0.54 *0.09* | 0.49 *0.14* | 0.30 *0.09* | 0.13 *0.05* |
| *P*-value[b] | NS | NS | < 0.01 | 0.01 |

[a]OM orosomucoid, TF transferrin, CP ceruloplasmin, and MG α-2 macroglobulin.
[b]Mann–Whitney's rank-sum test.

were kept at –20 °C until analysis. Synovial fluid was diluted in 0.8 percent saline solution containing 500 units of hyaluronidase/mL approximately 30 min before analysis. Synovial fluid and serum from the same patient were analysed within the same run and performed as double determination. Analytical variations between each run were 5 percent.

The proteins studied were chosen because they have different molecular weights and because all are synthesized in the liver. Local synthesis or destruction has never been demonstrated (Kushner and Somerville 1971).

Biopsies of synovial membrane from arthrotic hips and from hips with femoral neck fractures (controls) were obtained and prepared as described previously (Arnoldi et al. 1980).

*Results.* The ratios of synovial fluid concentration to serum concentration (SF/S) from the arthrosis group were higher than those from normal joints (Table 5). Average ratios for the 4 proteins related to molecular weight are illustrated in Figure 32 (total material). Log SF/S against log MW indicated an almost straight curve, steeper for the normal than for the arthrosis group, indicating increasing difference with increasing molecular weight. In the 8 patients from whom synovial fluid was obtained in both hips the difference between diseased and normal joints was significant for α–2 macroglobulin and ceruloplasmin (Table 6).

*Histological examination.* Light microscopic examination of the 29 arthrotic synovial membranes showed all to have slight to moderate inflammatory changes compared with normal. The degree of inflammation was estimated according to Salvati et al. (1977) by grading hypertrophy of lining cells and villi, signs of chronic focal or diffuse inflammation with lymphocytes and plasma cells, or acute inflammation with polymorphonuclear leucocytes. As the degree of inflammation was only slight to moderate (grade 1–2) it was not possible to correlate any minor variations with the protein pattern. As described previously, Arnoldi et al. (1980) distinguished between two types of synovial changes in the arthrotic hip joint: a proliferative and a fibrous synovitis. The proliferative type appears to be an earlier state and is characterized by obvious dilation and frequently, blockage of venules and capillaries and marked edema of the interstitial tissue with free erythrocytes and deposits of hemosiderin. Proliferative synovitis was always accompanied by increased fluid in the joint. Fibrous synovitis showed the same features, except that the interstitial edema was more or less masked by fibrous scar tissue, and the joint usually contained very little fluid.

Proliferative synovitis showed higher SF/S ratios than the fibrous type. The difference was significant for α-2-macroglobulin and ceruloplasmin (Table 7). Only characteristic cases were included with all transitional types excluded.

A comparison between Tables 6 and 7 gives the impression that the permeability of the 4 proteins did not differ significantly in fibrous synovitis and normal synovium.

*Comments.* In this study we have correlated ratios to

Table 7. Correlation between histological type and synovial fluid/serum ratios (*SD*)

| Proteins[a] | OM | TF | CP | MG |
|---|---|---|---|---|
| Proliferative | 0.60 *0.16* | 0.53 *0.12* | 0.47 *0.16* | 0.27 *0.12* |
| n | 12 | 10 | 11 | 13 |
| Fibrous | 0.57 *0.10* | 0.47 *0.10* | 0.37 *0.10* | 0.16 *0.07* |
| n | 8 | 7 | 8 | 8 |
| *P*-value[b] | NS | NS | < 0.05 | < 0.01 |

[a]OM orosomucoid, TF transferrin, CP ceruloplasmin, and MG α-2 macroglobulin.
[b]Mann–Whitney's rank-sum test.

molecular weight. However, Burnett et al. (1976) estimated that Stokes' radius, a function of molecular weight, volume and shape, is a more appropriate expression of protein size than molecular weight alone. Thus, the fact that fibrinogen, which has a lower molecular weight than α-2-macroglobulin, is rarely seen in synovial fluid from arthrotic, as opposed to rheumatoid arthritic joints, may be because fibrinogen, being thread-shaped, has a very large Stokes' radius, considerably larger than that of α-2-macroglobulin. Stokes' radius for the 4 proteins investigated by Reimann et al. (1980) has been determined (Felgenhauer 1974, Burnett et al. 1976, Renkin 1977) and correlates roughly with their molecular weights.

Kushner and Somerville (1971) using the criteria of average total protein concentration and average serum C-reactive protein, compared their relationship quantitatively to inflammation, and found that increased synovial inflammation corresponded to higher SF/S ratios, the larger the molecule the greater the increase. On comparing different joint diseases it was found that arthrotic patients had least evidence of synovitis. The findings (Table 7) that proliferative synovitis had the highest ratios and that the largest molecules showed the greatest increase indicate that increased permeability of the synovial membrane to plasma proteins is due to transcapillary migration. The very slight inflammatory signs in the synovium suggest that mechanical factors (stasis due to increased resistance to venous drainage) are predominantly responsible for the increased capillary permeability in arthrosis. Thus, with compression or blockage of the veins draining the synovium, increasing the intraarticular pressure, this mechanism will substantially affect all forms of exudative synovitis at an early stage. (See also the section on pain and the effects of neuropeptides, pp 72–74).

## CARTILAGE AND BONE MARROW HISTOLOGY IN ARTHROSIS AND RHEUMATOID ARTHRITIS

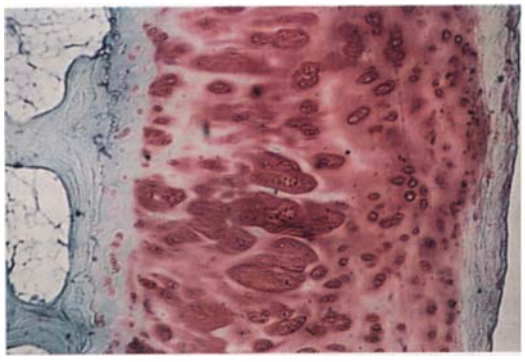
The general histology in joint disease is well covered in textbooks. Only the vascular changes and changes probably or possibly caused by vascular derangement will therefore be discussed here.

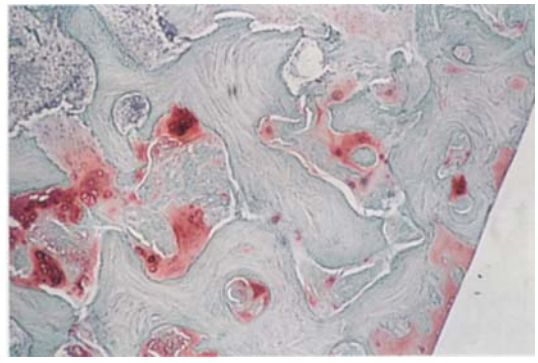
*Material and methods.* 7 femoral heads from arthrotic hips, 5 from women and 3 from men, median age 71 (58–78) years, and 5 from hips with late stages of rheumatoid arthritis, 3 from women and 2 from men, median age 62 (55–72) years, were examined by light microscopy. All femoral heads were removed during hip alloplasty. The decalcified specimens were stained by hematoxylin/eosin, MSB, Safranin-0 and Perl's Prussian blue.

***Results—cartilage.*** *Arthrosis.* Findings varied from very moderate fibrillation of the surface (Figure 33) to complete denudation of the osteochondral end-plate (Figure 34), often in the same slide. Cloning of chondrocytes was seen in all stages (Figure 33), also in the extensions of cartilage into the denudated end-plate. In most sections the tidemark was single, but duplication was observed in some specimens, and in two of these lacunae with small vessels, partly blocked by fibrin, were observed peripheral to the outer tidemark (Figures 35, 36).

*Rheumatoid arthritis.* A layer of pannus tissue peripheral to cartilage was noted in 3/5 specimens. The surface layer of pannus had the appearance of rheumatoid synovium. The appearance of chondrocytes varied from hyperactivity, over cloning to complete disappearance, sometimes over extended areas. Chondroclastic activity of cells in vascularized invasive tissue from the surface pannus was observed in some cases. Fasciculation of collagen strands was a prominent feature. The tidemark was absent in parts of several specimens. Strands of vascularized invasive tissue, apparently extensions of the vessels in the end-plate, were occasionally observed in the basal cartilage layer. Horizontal and vertical clefts were common. Areas of end-plate denudation were rare in this limited material.

***The osteochondral end-plate.*** *Arthrosis.* Generally, the thickness of the end-plate increased parallel to the gradual destruction of the overlying cartilage. In areas with slight or moderate cartilage changes the end-plate was thin, the bone structure laminar, and cell structures and vessels apparently normal. With increasing cartilage degeneration and destruction the end-plate became thicker, its structure typically woven bone, often with inclusions of Safranin-0 stained cartilage islands. H & E staining showed empty lacunae in some areas, alter-





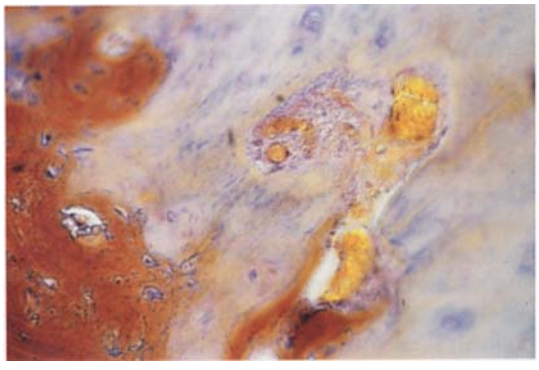


Figure 35. Vascular canals in basal layer of rheumatoid arthritic cartilage from hip joint. Erythrocyte agglutination changing into fibrin thrombi in vessels (MSB, x250).

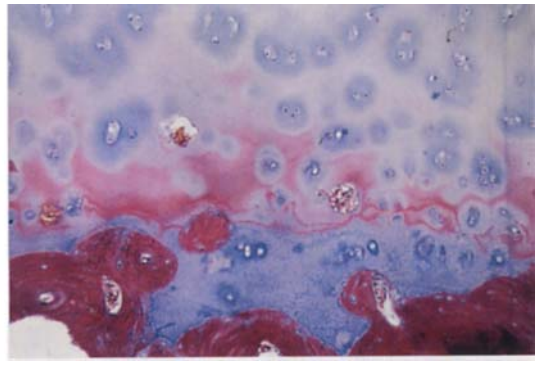
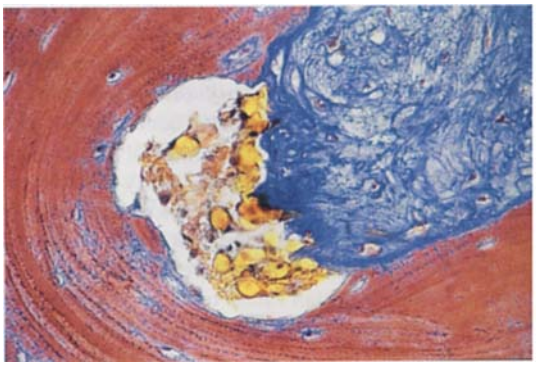
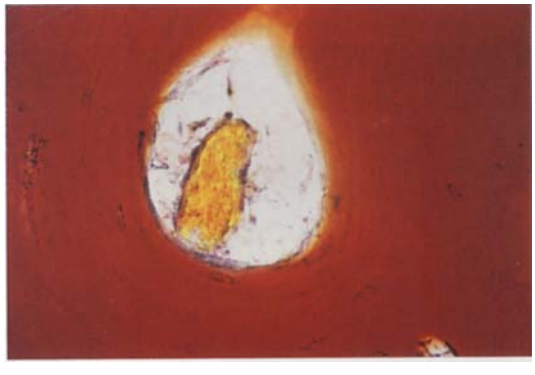


Figure 36. Vascular canals peripheral to duplicated tidemark. Cartilage from arthrotic hip joint (MSB, x100).





nating with areas of apparently normal osteocytes. A common, almost typical finding, was areas of vascularized non-characteristic fibrous tissue invading the end-plate from the bone marrow. Intravascular fibrin thrombi were common in the small vessels of this tissue (Figure 37) and were seen occasionally in the Haversian canals (Figure 38).

*Rheumatoid arthritis.* As in arthrosis the end-plate was generally thin, sometimes missing, in specimens with but moderate signs of cartilage destruction, and in

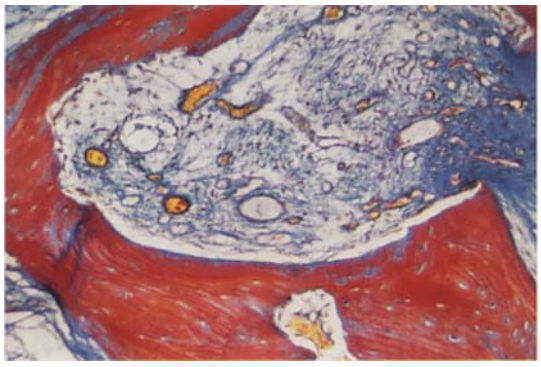


Figure 39. Invasive bone marrow tissue with trabeculae from arthrotic femoral head (MSB, x100).

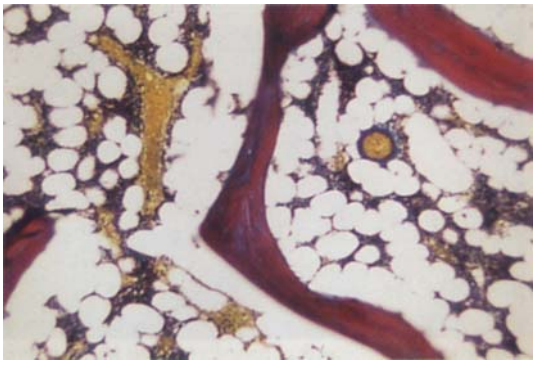


Figure 40. Subchondral, relatively normal bone marrow from arthrotic femoral head. Aggregations and agglutinations in most visible venules and some sinusoids (MSB, x100).

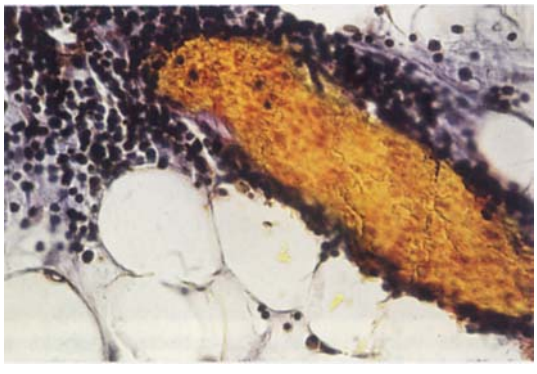


Figure 41. Rheumatoid arthritis, femoral head. Venule in bone marrow blocked by erythrocyte agglutination. Nodule of inflammatory mononuclear celss and fat vacuoles (MSB, x400).

our material, where denudation was rare, it never reached the thickness observed in arthrosis. The bone structure was more often laminar than woven. The vascularity was more pronounced; erythrocyte aggregation, agglutination and fibrin thrombi commoner, both in marrow extensions and in Haversian canals. Invasion from bone marrow of extremely vascularized primitive fibrous tissue was observed in all specimens (Figure 39).

***Bone marrow and trabeculae.*** *Arthrosis.* Generally, the cell contents and structure appeared normal for the age of these patients. Fat vacuoles were abundant. Small vessels (sinusoids and venules) often showed erythrocyte aggregation and agglutination (Figure 40). Free erythrocytes and hemosiderin deposits were frequently observed. Over considerable areas the bone marrow was replaced by fibrous tissue. In the trabeculae the bone structure varied between laminar and woven. The vessels in the Haversian canals were usually open, but areas of erythrocyte agglutination and fibrin thrombi of various ages were not uncommon.

*Rheumatoid arthritis.* Generally, the changes found in rheumatoid bone marrow resembled those found in arthrosis, except for substantial aggregations of mononuclear inflammatory cells, often adjacent to vessels clogged with erythrocyte agglutinations (Figure 41) or thrombi. Replacement of bone marrow cells with vascularized fibrous tissue was observed in all specimens.

*Comments.* In both disorders the typical picture of cartilage degeneration indicated a process progressing from the surface towards the osteochondral junction. In both disorders the cartilage changes were symmetrical, i.e. they involved both opposing joint surfaces. In the femoral head vascular invasion from the surface pannus was common in rheumatoid arthritis, and invasion from the bone marrow vessels was occasionally observed in rheumatoid, as well as arthrotic, cartilage. Apart from the collections of inflammatory cells in rheumatoid bone marrow, the sparse areas of bone marrow cells appeared normal, considering the age of the patients. Normal cells had been replaced by richly vascularized fibrous tissue in large areas of marrow. Blockage of vessels by erythrocyte agglutination and thrombi was highly characteristic of both disorders. Although the vessels in the Haversian canals quite often showed the same picture, such findings were far less numerous than in non-traumatic femoral head necrosis. The overall impression of vascular conditions in the synovial membrane, as well as in the bone marrow of the femoral head was a state of impaired venous drainage, the blocking especially prominent in venules and small veins.

## INTRAOSSOUS ENGORGEMENT-PAIN SYNDROMES AND RADIOGRAPHICALLY SILENT ARTHROSIS

### *Rest pain*

One of the cardinal symptoms of arthrosis is pain in the joint region at rest. It is more frequently experienced in coxarthrosis than in gonarthrosis. It may occur early or late in the course of the disease. It is usually aggravated by previous activity, and prolonged rest may bring relief. In its most severe form it is constant, and present at night as well as during the day.

The pain is described as deep, aching or boring and radiates from the hip towards the knee, from the knee down into the calf and upwards into the lower thigh. Osteotomy or fenestration of juxtaarticular bone is usually accompanied by an immediate fall of intraosseous pressure and relieves rest pain within 24 hours (Arnoldi et al. 1971).

This type of hip or knee pain is quite often met with in those without visible arthrotic radiographic changes, and conversely, instead of sclerosis, joint-bearing bone often displays a (transient) osteopenia. Synovitic effusion can be demonstrated in most of the painful joints. Patients usually belong to the 35–55 year age group. The painful state may last for months, sometimes years, may disappear spontaneously or after conservative or surgical (fenestration) therapy. However, preliminary information indicates that a high percentage of such cases (at present about 30 percent) develop manifest arthrosis in the same joint at a later stage (unpublished data). Rest pain is often accompanied by more or less severe restriction of movement in these joints.

The term intraosseous engorgement-pain syndrome (Lemperg and Arnoldi 1978) defines a syndrome characterized by rest pain in a radiographically non-arthrotic joint with juxtachondral bone marrow engorgement, as observed by intraosseous phlebography, and increased uptake of bone-seeking isotopes. In unilateral cases the intraosseous pressure is most often, but not invariably, higher on the painful than on the unaffected side.

Rest pain in the knee region in the patellar pain syndromes (Hejgaard and Arnoldi 1984) and in the hip region in the first stages of non-traumatic femoral head necrosis (Ficat and Arlet 1980), especially, create diagnostic problems.

### *Own investigations*

***Intraosseous engorgement-pain syndromes.*** Arnoldi et al. (1975) investigated whether or not pain at rest in the knee is associated with increased intraosseous pressure.

Table 8. Age (mean, range), sex and grouping of 53 patients with knee disorders

| Group | Rest pain | n | Men/women | Age |
|---|---|---|---|---|
| A. No arthrosis | – | 16 | 15/1 | 35 (17–70) |
| B. No arthrosis | + | 17 | 7/10 | 36 (21–54) |
| C. Arthrosis | – | 11 | 9/2 | 44 (21–63) |
| D. Arthrosis | + | 9 | 5/4 | 52 (25–73) |

*Patients.* 36 men and 17 women admitted to hospital during the years 1971–1973 for suspected lesions of the semilunar cartilages or loose bodies in the knee were examined. All the patients were operated, prior radiographs of the knees having been taken in the standing position. At arthrotomy the state of the articular cartilage in the medial, lateral and patello-femoral compartments was assessed by eye. The presence of erosion was taken as evidence of arthrosis.

Before operation, the type of pain felt by the patient was fully assessed. Almost all patients had had typical episodes of locking of the knee with acute pain. Some had pain on movement or weight bearing. Others complained of rest pain. The presence or absence of rest pain and arthrosis created four groups (Table 8).

*Methods.* The methods for measuring intraosseous and intravenous pressures have been described previously. In this investigation the points of measurement were in the most distal part of the femur and the most proximal part of the tibia. The pressure in the internal saphenous vein was measured at the level of the knee joint.

***Results.*** *Venous pressure.* The pressure in the saphenous vein was within the expected range and there were no intergroup differences (Table 9).

*Intraosseous pressure* (Tables 9 and 10). Of the 16 patients with no arthrosis and no rest pain (Group A) 14 had normal intraosseous pressure measured in the cancellous bone, 2–12 mmHg above the pressure measured in the adjacent peripheral vein (Arnoldi and Linderholm 1966). Similar normal values were found in 6 of 11 patients with arthrosis, but no rest pain (Group C). In 7 of 9 with arthrosis and rest pain (Group D) low pressures were found in the tibia, but in 6 of them abnormally high intraosseous pressures were recorded in the femur. In contrast, high pressures were found in either or both the tibia and femur in 15 of 17 patients with no arthrosis, but with rest pain (Group B). Of this group 5 had anatomically normal knees with neither meniscus injury nor loose bodies.

In Group D (rest pain and arthrosis) the highest pressure was usually found in the femur, but in Group B (rest pain, no arthrosis) it was equally distributed

Table 9. Mean pressure (*SD*, range) in the saphenous vein and intramedullary pressures in the proximal tibial and distal femoral metaphyses from knee joints with and without pain at rest and arthrosis, respectively

| Group | Rest pain | n | $P_{vein}$ | $P_{tibia}$ | $P_{femur}$ | $P_{\Delta}{}^{a}$ | $P_{max}{}^{b}$ | T[c] | F[c] |
|---|---|---|---|---|---|---|---|---|---|
| A. No arthrosis | – | 16 | 10 *1.3* (3.8–22) | 9.8 *2.1* (1.1–30) | 8.6 *1.8* (0–20) | 1.2 *1.6* | 12 *2.1* (1.1–30) | 10 | 6 |
| B. No arthrosis | + | 17 | 11 *1.7* (1.0–29) | 32 *5.0* (5.1–79) | 28 *4.1* (4.1–59) | 3.5 *5.4* | 40 *4.3* (5.4–79) | 10 | 7 |
| C. Arthrosis | – | 11 | 11 *1.6* (5.9–25) | 13 *3.1* (0.3–38) | 13 *3.0* (0.3–29) | –0.3 *3.7* | 18 3.3 (1.7–38) | 5 | 6 |
| D. Arthrosis | + | 9 | 12 *1.8* (3.1–23) | 13 *4.0* (0–35) | 25 *4.7* (2.9–46) | –12 *7.6* | 30 3.2 (16–46) | 2 | 7 |

[a]Mean pressure difference between tibia and femur.
[b]Mean maximal pressure in tibia or femur
[c]Number of patients with maximal pressure in T tibia and F femur.

Table 10. The mean differences of intraosseous pressures in tibia and femur, and the maximal pressures in tibia or femur between the groups specified in Tables 8 and 9, and *P*-values

| Groups | $P_{\Delta tibia}$ | | $P_{\Delta femur}$ | | $P_{\Delta max}$ | |
|---|---|---|---|---|---|---|
| B–A | 22 | < 0.001 | 20 | < 0.001 | 28 | < 0.001 |
| D–A | 2.7 | NS | 16 | NS | 19 | < 0.001 |
| C–A | 3.3 | NS | 4.8 | NS | 6.3 | NS |
| D–C | 0.6 | NS | –11 | 0.05 | –12 | < 0.02 |
| B–D | 19 | < 0.02 | 3.7 | NS | 9.2 | NS |
| B–C | 19 | < 0.01 | 15 | < 0.02 | 22 | < 0.001 |

between the tibia and femur. In Group D the pressure difference between the tibia and femur was not significant.

Thus, in this series increased intraosseous pressure seemed to be more closely associated with the symptom of rest pain than with radiographic signs of arthrosis.

***Intraosseous phlebography and $^{99m}$Tc-polyphosphate scintigraphy.*** These examinations were performed on a series of patients with rest pain, but without signs of arthrosis of the knee and hip joints (Arnoldi et al. 1980). The techniques were as described previously, including those for serial phlebography where an evacuation time of up to 6 minutes was regarded as normal.

*Intraosseous phlebography.* The intraosseous engorgement-pain syndrome results were similar to those obtained from cases of manifest painful arthrosis (Tables 3, 11). The bone marrow on the painful side always showed intraosseous stasis, often in conjunction with intraosseous hypertension (Figures 42, 43).

*$^{99m}$Tc-polyphosphate scintigraphy.* The scintigrams from the joints with intraosseous engorgement-pain always showed increased tracer uptake (Table 11).

***Radiographically silent coxarthrosis.*** In patients with intraosseous engorgement-pain syndromes of the hip and knee joints, routine radiography is by definition negative, i.e. they show none of the accepted changes of arthrosis: narrowing of the joint space, subchondral cysts or osteosclerosis. On the contrary, the joint-bearing bone is often osteopenic compared with the bone further from the affected joint (Lemperg and Arnoldi 1978). Occasionally, osteophytes may be observed, but if all other parameters are negative, we have not considered this proof of arthrosis (Danielsson 1964; see also the discussion of osteophyte formation in the section on experimental arthrosis).

Thus, while routine radiography of the hips did not suggest the presence of arthrosis, the subjective symptoms of the group dealt with here were largely identical with those felt by patients with manifest painful arthrosis. Thus, pain at rest and on loading was always present and most patients with long-standing subjective

Table 11. Findings in 7 patients with intraosseous engorgement-pain syndrome of the hip or knee, examined by means of bilateral intraosseous phlebography, intraosseous pressure measurements, and Tc-polyphosphate scintigraphy. Compare Table 3

| Group | n Joints | Age mean (range) | Men | Hip / knee | Phlebogram (normal/abnormal) affected | normal | Intraosseous pressure affected | normal | Scintigraphy (normal/increased) affected | normal |
|---|---|---|---|---|---|---|---|---|---|---|
| A | 4 | 49 (33–69) | 3 | 0 / 4 | 0 / 4 | 3 / 1[c] | 44 (33–80) | 15 (3–24) | 0 / 4 | 4 / 0 |
| B | 6 | 47 (25–58) | 2 | 2 / 4 | 1 / 5[d] | ... | 41 (32–47) | ... | 1 / 5 | ... |

A. Patients with unilateral rest pain.
B. Patients with bilateral rest pain.
[c] Clearance time > 6 min, distribution of contrast normal.
[d] Clearance time < 6 min, distribution of contrast normal.

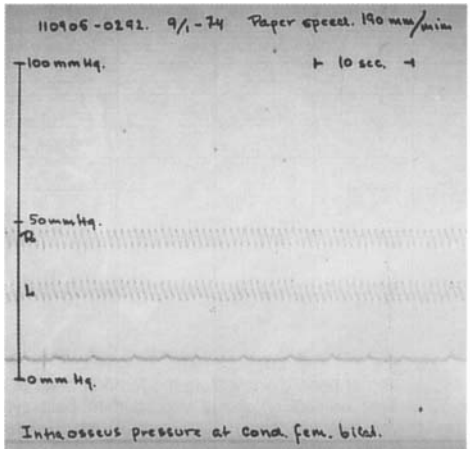



Figure 42. Simultaneous bilateral pressure measurements from the femoral condyles and internal saphenous vein of a patient with intraosseous engorgement-pain syndrome of the right knee.

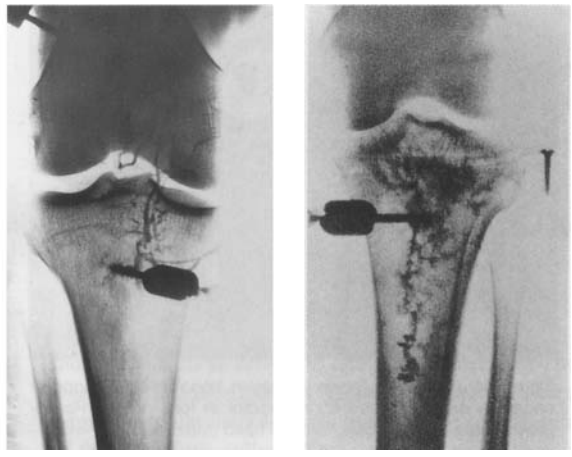


Figure 43. Bilateral intraosseous phlebography from the tibia of a patient with intraosseous engorgement-pain syndrome of the left knee (B). B exposed 30 min after contrast injection.

complaints in the hip also showed more or less severe restriction of joint movement, typically initiated by increasing pain as the joint was moved into extreme internal rotation in flexion, or extreme flexion.

In most cases intraosseous engorgement-pain symptoms either disappear spontaneously or after conservative treatment for synovitis. In rare cases pain and restriction of function may become so severe and intractable that operative treatment is indicated. Fenestration (forage, core-decompression) has been useful in many cases and total alloplasty is only rarely necessary.

However, we have performed this operation in a number of radiographically negative joints with persistent and intractable rest pain and have, thus, had the opportunity to study the changes in the different structures of these joints.

*Patients.* During the years 1975–1989 severe intraosseous engorgement-pain led to total alloplasty of 11 hip joints in 9 patients (Table 12). Scintigraphy was performed on this group but not intraosseous phlebography or pressure measurements.

The median age was 51 (36–72) years. In 10 of 11 hips one or several abnormalities were observed that

**Table 12. Clinical, radiographic and peroperative findings in 11 hips with radiographically silent arthrosis**

| Hip no | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | m | m | f | f | f | f | f | f | f | f | f |
| Age | 72 | 40 | 43 | 69 | 36 | 44 | 44 | 40 | 40 | 61 | 69 |
| Predisposing factors | | | | | | | | | | | |
| Dyplasia | – | – | + | + | + | + | + | + | + | – | – |
| Perthes | – | + | – | – | – | – | – | – | – | – | – |
| Coxa vara | – | + | – | – | + | – | – | – | – | – | – |
| Coxa valga | – | – | + | + | – | + | + | + | + | + | – |
| Abnormal anteversion | – | – | – | – | + | – | – | + | + | – | + |
| Trauma | – | – | + | + | – | – | – | – | – | – | – |
| Symptoms | | | | | | | | | | | |
| Rest pain | + | + | + | + | + | + | + | + | + | + | + |
| Pain on loading | + | + | + | + | + | + | + | + | + | + | + |
| Restricted movement | – | + | – | + | + | + | + | – | – | – | + |
| Pain on movement | + | + | + | + | + | + | + | + | + | + | + |
| Radiography | – | – | (+) | – | – | – | – | – | – | – | – |
| Scintigraphy | + | + | + | + | + | + | + | + | + | + | + |
| Operative findings | | | | | | | | | | | |
| Proliferative synovitis | + | + | + | + | + | + | + | + | + | + | + |
| Arthrosis | + | + | + | + | + | + | + | + | + | + | + |
| Years of symptoms | 2 | 3 | 1 | 8 | 5 | 1 | 2 | 2 | 3 | 3 | 2 |

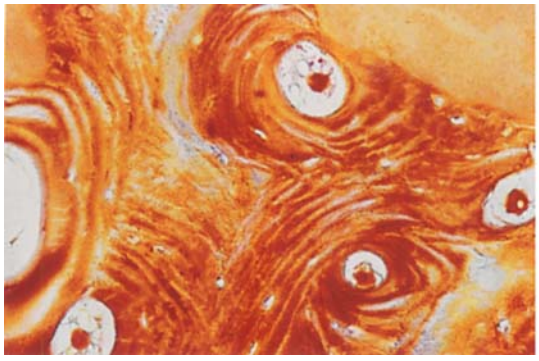


Figure 44. Haversian canals in woven bone in osteochondral end-plate. Medium aged fibrin thrombi in four canals. Radiographically silent arthrosis, femoral head (MSB, x250).

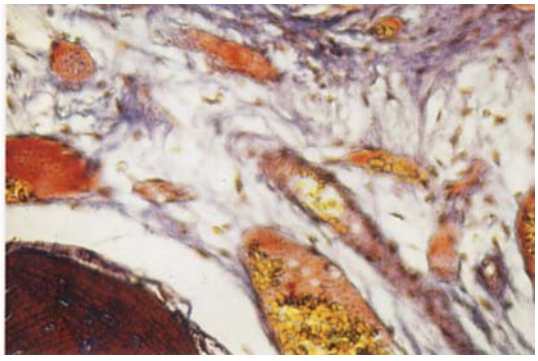


Figure 45. Section of bone marrow from the femoral head of a 61-year-old patient with intraosseous engorgement-pain syndrome (radiographically silent arthrosis). Invasive vascularized and edematous fibrous tissue (MSB, x250).

are usually regarded as disposing to arthrosis. Rest pain and pain on loading were present in all hips. Radiographic signs of arthrosis were absent in all cases, except for one hip that showed an osteophyte at the lateral margin of the acetabulum. $^{99m}$Tc-polyphosphate scintigraphy showed increased uptake in all affected hips, but of varying location, the most common configuration being a ring encircling the femoral head at the border between the cartilage of the femoral head and the femoral neck. Proliferative synovitis was present in all hip joints, and inspection of the femoral head and acetabulum showed localised, symmetrical and usually very modest areas of slight cartilage degeneration, the three main areas being the cartilagenous border of the femoral head, the area around the fovea, and restricted sections of the weight-bearing area of the femoral head and acetabulum.

*Microscopic examination.* Synovium, cartilage, osteochondral end-plate and juxtachondral bone marrow were examined by light microscopy. The following staining methods were used: hematoxylin & eosin for all joint structures. MSB (Martius scarlet blue). The Safranin-0 stain was used to assess abnormalities of glycosaminoglycan distribution and contents in cartilage, and also to detect cartilage in such abnormal locations as the synovium. Perl's method for ferric iron was used to demonstrate deposits of hemosiderin, especially in the synovium. Finally, von Kossa's stain was used to demonstrate calcification of soft tissues.

***Results.*** *Synovium.* In all the hips examined the synovium was edematous and showed increased vascularity of the peripheral layer; 2–4 rows of synoviocytes were generally visible. In 2 of the 11 cases isolated aggregations of mononuclear inflammatory cells were observed near the surface of the synovium. MSB-staining demonstrated numerous dilated veins and venules and a few thick-walled arterioles near the synovial surface. Scattered erythrocytes were observed in the interstitial tissue in 8/11 specimens, and in 10/11 cases intravascular erythrocyte agglutinations and fibrin thrombi were numerous.

Perl's Prussian blue, von Kossa's stain and Safranin-0 staining failed to show deposits of hemosiderin, calcium or synovial inclusions of cartilage particles.

*Cancellous bone and osteochondral bone plate.* All specimens were characterized by osteopenia of the joint-bearing cancellous bone. The bone structure was mostly laminar with living osteocytes in the trabeculae. In 4 of 11 hips circumscribed areas of woven subchondral bone were observed. The osteochondral bone plate was, generally, thin. Vascular penetration into the deep calcified layer of cartilage was observed occasionally, but penetration through the single tidemark did not occur. Fibrin thrombi in some cases clearly intravascular in Haversian canals were not uncommon (Figure 44), especially near the osteochondral junction. They were usually placed in woven bone and surrounded by empty lacunae.

*Bone marrow vessels.* Over large areas the cellular contents of the bone marrow seemed normal, but most of the marrow vessels, including some arterioles, showed erythrocyte aggregations. In veins and venules agglutination and fibrin thrombi of different ages were common. The sinusoids appeared of normal width. Invasion of vascularized fibrous tissue was not as dominant as in manifest arthrosis, but had the same character (Figure 45).

*Cartilage.* All specimens had a single tidemark and large areas of normal cartilage revealed by MSB and Safranin-0 staining. Both these methods showed, however, areas of surface degeneration with lack of matrix staining, fibrillation of cartilage surface, cloning of

Figure 46. Cartilage and osteochondral end-plate from a patient with intraosseous engorgement-pain syndrome of the hip (radiographically silent arthrosis; MSB, x40).

chondrocytes and, sometimes, deep clefts reaching to the basal layers (Figure 46). The areas of degeneration were always circumscribed and denudation of the osteochondral plate was never observed.

***Comments.*** Clinically, patients with joint complaints classed as intraosseous engorgement-pain syndromes form a rather distinctive group. They have all the symptoms and signs of arthrosis, except the radiographic changes. Phlebographically, they show the same intraosseous venous stasis as patients with manifest arthrosis; in unilateral cases the intraosseous pressure is usually higher than in the bone marrow of the pain-free contralateral joint, and the uptake of radionuclides is increased.

The group that was operated on showed the early proliferative form of synovitis, and the vascular changes here and in the bone marrow were largely identical with those described in connection with arthrosis. The lack of hemosiderin and calcium deposits may also indicate an early stage of the disorder.

Thus, the evidence collected indicates that although intraosseous engorgement-pain is usually reversible, it is a potential precursor to arthrosis.

## Summary of findings in experimental, early radiographically silent and late manifest arthrosis

Synovitis seems to be a constant feature of early experimental, as well as early and late human arthrosis. The results of the investigations referred to above indicate a largely vascular disorder with initial active hyperaemia of the synovium, followed by a stage of venous stasis and edema, ending in fibrosis. The first osseous changes (osteophytes) already appear during the phase of active hyperemia. In the stasis phase, increased resistance to venous flow, capillary dilation and synovial edema are responsible for marked changes in synovial fluid composition and the onset of general symmetrical degeneration of the superficial layers of cartilage. This process seems to be reversible, at least up to a point. At this stage, the cartilage is, however, vulnerable, and in places exposed to extreme mechanical stress in the form of loading or shearing forces, degeneration and breakdown continue, ending with denudation of the subchondral bone plate.

As in the synovial membrane, the venules and smaller veins of the bone marrow become to a large degree blocked by intravascular erythrocyte agglutinations and fibrin thrombi, indicating severe drainage problems. It is noteworthy that this vascular derangement is observed in the earliest stages examined. It may well be the reason for the intraosseous stasis demonstrated by phlebography, the elevated intramedullary pressure, and the increased skeletal metabolism of juxtachondral bone indicated by the increased uptake of radionuclides.

# Hemophilic arthropathy

The severity of hemophilia is constant in any given individual, but varies from case to case. It is usual to distinguish between mild, moderate, moderately severe and severe forms based on the functional factor plasma level. In the mild form, the patient has a functional plasma level of 20 to 60 percent of Factor VIII and IX and may bleed excessively only during surgery. In the moderate form, the plasma level is between 5 and 20 percent and bleeding may occur after surgery or trauma.

Patients with moderately severe disease have plasma levels between 1 and 5 percent, while those with severe disease have levels below 1 percent. Spontaneous bleeding episodes occur in patients with plasma levels below 5 percent.

Several clinical classification systems exist, mostly based on a combination of radiographic and clinical manifestations (DePalma 1967, Brower and Wilde 1966). I have used the classification proposed by Arnold and Hilgartner (1977) based largely on radiography, and that attempts to separate joint changes of surgical significance:

*Stage 1.* There are no skeletal abnormalities, but there is soft tissue swelling secondary to hemarthrosis or bleeding in soft tissues surrounding the joint.

*Stage 2.* This usually coincides with the clinical stage of subacute arthropathy. There is osteopenia, particularly in the epiphyses, as well as overgrowth of the epiphysis. The integrity of the joint, however, is maintained, with no narrowing of the cartilage space and no bone cysts.

*Stage 3.* Disorganisation of the joint is evident, but there is no significant narrowing of the cartilage space. Subchondral cysts which occasionally communicate with the joint space are visible, as is squaring of the patella. The synovium may be opacified with hemosiderin deposits.

*Stage 4.* Characterized by narrowing of the joint space and cartilage destruction.

*Stage 5.* The end stage is manifest by fibrous joint contracture, loss of joint space, extensive enlargement of the epiphyses, and substantial disorganisation of joint structures. There is marked restriction of joint movement and bleeding episodes may be less frequent. Pathologically, the synovium has been altered so that little or no recognizable synovial tissue is found when the joint is opened. In addition, the articular cartilage is absent and only eburnate bone ends remain, discoloured with striking green, brown, or black pigment.

These changes begin to develop at about the age of 6 years in a child with severe hemophilia and may become apparent after a few hemarthroses. The development of joint changes expressed in the staging system, may be regarded as a description of the natural history of the untreated patient.

## Pathophysiologic and histologic findings

### *Previous investigations*

"What we know of the pathogenesis of haemophilic arthropathy is pieced together from relatively scanty specimen material and from deductions based on comparative and experimental data of other sorts. The end-stage lesion is fairly well known. Haemophilic joints are deformed through a series of destructive events that ultimately include collapse and subchondral cyst formation. Massive fibrosis and haemosiderosis of synovial and periarticular soft tissues lead to contracture and at times even to ankylosis of the joint.

*Two stages must be distinguished in the development of these changes: an early synovial reaction to intra-articular bleeding and a later cartilaginous degeneration resembling that of arthrosis*" (Sokoloff 1975; italicization by the present author).

Arnold and Hilgartner (1977), admitting that most of the evidence comes from animal experiments, also distinguish between two stages in the development of arthropathy: an early synovial reaction to intra-articular bleeding which resembles the reaction seen in rheumatoid arthritis, and a later stage of cartilage degeneration and joint destruction similar to that seen in both arthrosis and rheumatoid arthritis. They found the early stage characterized by synovial hypertrophy, hemosiderin deposition in phagocytic cells, and some early fibrosis of the subsynovial tissues.

*Hemarthrosis in animals.* The effects of repeated intra-articular injections of whole blood on articular cartilage and synovial tissues have been examined by several authors. Wolf and Mankin (1965) injected 1 mL of homologous blood into the right knee of 28 rabbits. The left knees served as controls and received simultaneous injections of normal saline solution. At 1 day to 8 weeks, 2 of the animals were killed and the synovial membrane and cartilage from the knee joints were resected for study.

The synovial tissues demonstrated the classic changes of inflammation followed by progressive fibrosis, scarring and deposition of iron. In the cartilage there was no significant change in the microscopic appearance of the cells or matrix, nor were there depositions of iron. The metabolic activity of the cartilage was quantitatively assayed using the synthesis rates of ribonucleic acid and protein, and essentially there were no changes noted during the 8-week study. They concluded that repeated hemarthroses over an 8-week period have a profound effect on synovial tissues, but little or no effect on the histological, histochemical, or metabolic activity of cartilage. They speculated that cartilage damage, so common in hemophilia probably requires more than just the presence of blood and that hemarthrosis (or hemarthroses) may not be particularly harmful to the articular surfaces of a joint. Similar findings were reported by Key (1929), Soeur (1949) and Young and Hudacek (1954).

Hoaglund (1967), using 12 mongrel puppies, 8 weeks old, injected their left knees with stored anticoagulated autologous blood six times weekly for 12 to 18 weeks. Contralateral knees were injected with equal volumes of saline solution or with saline solution containing 250,000 units of aqueous penicillin. He found in the knees injected with blood, changes similar to those found in human hemophilic arthritis, such as synovial pigmentation and fibrosis, cartilage fibrillation on the tibia, enlargement of the distal femoral epiphyses, changes in the shape of the patella, and changes in the configuration of the joint surfaces. Articular cartilage was markedly thickened in all joints injected with blood. Hoaglund suggests that previous experimental hemarthroses were not of sufficient intensity and duration to produce cartilage change.

*Observations in hemophilic dogs.* Swanton (1959) examined at autopsy the joints of 34 hemophilic dogs. The age range of those with joint lesions was 11 days to 8 years. She found the same synovial changes seen in human hemophilia. The cartilage was slightly softer than normal, often had a finely granular or slightly velvety surface texture, and had histological evidence of fibrillary degeneration and fraying. In more severe cases, there might be pitting, focal gray or reddish eroded areas, or extensive, coarse roughening of the surface. The articular portions of the bones often had changes of the type seen in arthrosis and, in her opinion, the subchondral cysts did not seem to be the direct result of hemorrhage.

## Own investigations

*Material.* During the years 1972–1978, 13 patients, median age 24 (9–40) years with hemophilia (11 Type A and 2 Type B) were operated in our clinic for hemophilic arthropathy. In all the patients several joints were affected, all had a factor plasma level < 5 percent and all fell into Stage 3–5 of the Arnold and Hilgartner (1977) classification system. 17 operations were performed, 6 knees and 2 hips were treated by synovectomy and alloplasty, the rest with synovectomy alone. There were thus 8 specimens that included synovium, cartilage and subchondral bone, while 9 specimens consisted of synovium alone.

The preoperative radiographs showed various degrees of joint deformation, corresponding to the changes described by Arnold and Hilgartner (1977), ranging from epiphyseal overgrowth, various degrees of cartilage space diminution, subchondral bone cysts and deformities by contractures. In addition, all radiographs showed a marked degree of juxtachondral osteopenia.

*Methods.* Seven of the 8 specimens from joints treated by alloplasty and 6 from synovectomies were examined by light microscopy. The following staining methods were used: hematoxylin/eosin and Martius scarlet blue (MSB) were the basic stains for all tissues. Safranin-0 was used for cartilage, and Perl's Prussian blue and von Kossa's methods for demonstration of hemosiderin and calcium deposits, respectively, in the synovium.

***Results.*** *Synovium.* The general picture was one of inflammation with increased number and size of the synoviocytes. In the stratum just beneath these lining cells, the interstitial tissue was generally edematous, but in the deeper layers coarse bundles of collagen dominated. The whole of the synovium was characterized by a profuse network of rather thick-walled and mostly empty vessels that seemed even more dilated than was the case in arthrotic and rheumatoid synovium (Figure 47).

*Intravascular erythrocytes.* The dilated vessels were generally empty or contained very few red blood corpuscles. The intravascular blocking by aggregations or agglutinations of erythrocytes, characteristic of arthrosis and rheumatoid arthritis, were thus missing, and fibrin thrombi were never observed.

*Vessel wall permeability.* In no cases were erythrocytes observed in the act of penetrating the vessel wall. However, the masses of extravascular erythrocytes, probably caused by bleeding and characteristic of every microscopic section, made it impossible to determine whether any of these had left the vessels through diapedesis. In H&E preparations, bleeding episodes of different age could be distinguished by the brownish colour of the older erythrocyte emissions.

*Hemosiderin deposits.* These were far more massive

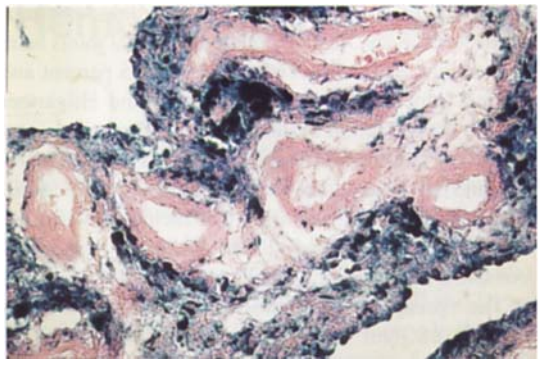


Figure 47. Synovium from hemophilic knee joint, dominated by hemosiderin deposits in interstitial stroma. The unstained thick-walled, empty vessels and the perivascular edematous tissue are typical (Perl's Prussian blue x 250).

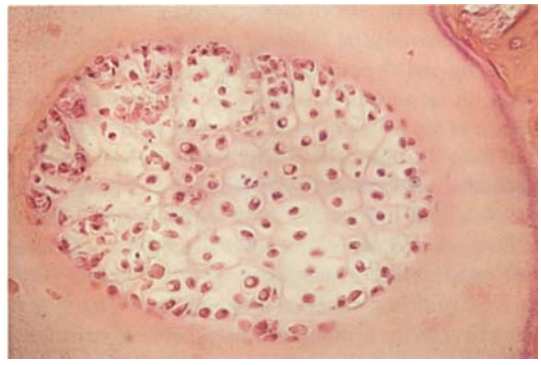


Figure 48. Cloning of chondrocytes in hemophilic knee joint (H&E, x250).

Figure 49. Cartilage and bone marrow from patella of hemophilic knee joint. Only one clone of chondrocytes stained by Safranin-0. Fading clones faintly visible in other areas. The thin end-plate and the extremely osteoporotic patellar bone are typical (Safranin-0, x25).

than seen in arthrosis and rheumatoid arthritis, and in many cases the blue plaques covered all interstitial space, leaving the vessels and their walls as the only unstained areas (Figure 47). Most of the slides showed hemosiderin in large phagocytes, but masses of extracellular collections of hemosiderin crystals were also observed, generally in close juxtaposition to the strands of collagen fibres.

*Calcium deposits.* In 2 of 6 specimens very small calcium deposits were observed in collagen-dominated subsynovial tissue.

*The osteochondral end-plate.* This was always very thin and in many areas it was perforated by channels containing vessels, or it was simply missing. These channels did not perforate the tidemark. The cancellous bone reaching from the plate back into the metaphysis was extremely osteoporotic, but the bone trabeculae contained living osteocytes, and neither osteoblasts nor osteoclasts were present in abnormal quantities.

*The bone marrow.* In large areas the cellular elements were scarce. The vessels were mostly dilated, thin-walled and intravascular aggregations of erythrocytes were common. Fibrin thrombi were not observed. Areas of tightly packed extravascular erythrocytes indicated recent bleedings. The preparations were from decalcified bone, and hemosiderin deposits were not observed.

*Bone marrow cysts.* Some specimens showed large subchondral cysts. In several cases they were connected with the joint cavity through channels transversing the cartilage.

*Cartilage—general appearance.* In many specimens parts of the surface were covered by pannus-like tissue, obviously of synovial origin. Fibrillation of the surface was present in all cases and all parts of the cartilage, whether weight-bearing or not. Clefts running parallel to the surface were common in the outer layer, others, perpendicular to the surface, in the middle and inner layer. The height of cartilage varied from abnormally thick (edematous?) to complete erosion down to the osteochondral end-plate. The tidemark was generally single, but in a few specimens small areas showed duplication. All cartilage changes were symmetrical, i.e. all joint surfaces were involved.

*Chondrocytes.* The appearance of chondrocytes, their arrangement and the extent of their territorial matrix varied considerably, even in the same specimens. Extensive areas of large chondrocyte clones, sometimes containing more than 100 more or less degenerated cells, were seen in all specimens (Figures 48, 49).

Sometimes these clones had a common territorial matrix, stained normally with safranin-0; in other locations the territorial matrix was missing and in still others the clones were surrounded by a distinctive membrane. In these cases shadowy clones or more normally arranged chondrocytes, obviously dead, could be seen gradually fading into the amorphous substance of the matrix (Figure 49). These changes were found throughout the cartilage, from the periphery to the tidemark.

### *Comments*

All visible vessels in the richly vascularized synovial membrane were obviously dilated and the layer of stroma directly beneath the lining cells edematous. This could indicate a state of venous and capillary stasis similar to conditions observed in arthrosis and rheumatoid arthritis. Measurements of intra-articular and intraosseous pressures have not been reported in the literature. Clinical findings indicate, however, an increased intra-articular pressure, especially during the period following hemorrhage (Sokoloff 1975). Arnold and Hilgartner (1977) described the typical joint fluid as dark-red and viscous and with a hematocrit averaging 24 percent. This indicates that the fluid contained a large amount of ordinary synovia in addition to intra-articular blood.

In hemophilic arthropathy, as in arthrosis and rheumatoid arthritis, the changes in cartilage were always symmetrical with changes in both opposing joint surfaces. Further, the cartilage degeneration in these disorders seems to begin at the joint surface and to be caused by changes in the composition of the synovial fluid. Exactly what these changes are in the hemophilic joint and how they work is not known at present. Among the suspected agents are the increased amount of iron in the synovial fluid and the chondrocytes and changes in pH (Sokoloff 1975, Choi et al. 1981), and an increase of proteolytic enzymes in this fluid—collagenases, acid phosphatasis and cathepsin D (Hilgartner et al. 1972). Robinson and Granda (1974) found that prostaglandin levels were elevated to levels surpassing those found in rheumatoid arthritis.

The remarkable peri-articular osteopenia in hemophilic arthropathy may to a large extent be due to disuse and immobilisation. However, inflammatory hyperemia could also be influential, and in this connection it is worth remembering that osteopenia is also characteristic of rheumatoid arthritis in its active state and, to a smaller degree, of the very early stages of arthrosis.

# Non-traumatic femoral head necrosis

## Idiopathic, alcohol- and steroid-induced femoral head necrosis

In non-traumatic femoral head necrosis the anterior-superior portion of the femoral head becomes infarcted and the precise cause or causes of this infarction is unknown. Following death of bone tissue, spontaneous repair does occur, but seems to be arrested, again by unknown factors, and subchondral fracture, impaction, collapse and fragmentation of the sequestered part of the femoral head result in secondary disabling arthrotic changes.

Non-traumatic femoral head necrosis is known to be associated with alcoholism, steroid therapy, dysbaric phenomena, sickle-cell anemia and several rarer diseases. In many cases, however, no such connections can be determined (idiopathic femoral head necrosis). Our own experience is confined to idiopathic, alcohol- and steroid-induced osteonecrosis.

### *Incidence*

In 1961 Mankin and Brower found only 29 patients, including their own 5, reported in the English language literature. However, since then increasingly larger series have been reported both from Europe and the United States, and a clear clinical picture, common to these disorders, has emerged. 80 to 90 percent of the patients are male, mostly between 30 and 60 years old. Bilateral involvement is observed in about 70 percent (Boettcher et al. 1970). Despite the increasing interest in non-traumatic femoral head necrosis, the true incidence is not known.

### *Clinical picture*

The patient complains of pain in the groin and trochanteric region, frequently irradiating to the thigh and knee. From the very beginning the pain is felt even at rest and is accentuated by loading of the hip and by joint movements, especially inward rotation. Limping and restricted movement are other typical signs. The disorder may begin suddenly (Merle d'Aubigne et al. 1965), or insiduously, sometimes related to minor physical exertion (Patterson et al. 1964).

### *Paraclinical examinations*

The patients' radiographs are often negative. A narrow translucent zone, the crescent sign, near the osteochondral junction may be the first sign of developing necrosis. In later stages, radiography shows large defects in the contour of the femoral head or cyst formations in the bone marrow.

Scintimetry or scintigraphy reveals high uptake of radionuclides in the femoral head (Bauer 1971 and others). In the early stages this uptake is evenly distributed in the femoral head, indicating a generally increased bone metabolism. Later, the necrotic part of the head may lose its ability to bind bone-seeking isotopes and appears as an empty area surrounded by bone with high isotope uptake (the cold in hot spot). The increased isotope uptake is especially marked in the border-zone between the necrosis and normal bone marrow (Lausten and Christensen 1989).

Pertrochanteric intraosseous phlebography shows a delay in venous drainage, reminiscent of the drainage disturbances in arthrosis (Serre and Simon 1962, Arlet 1971, Hungerford and Zizic 1978), and intraosseous pressure measurements reveal even higher pressure in the femoral neck than observed in arthrosis (Ficat and Arlet 1980, Hungerford and Lennox 1985, Pedersen et al. 1989, Kiær et al. 1990). In later years CT-scanning and especially Magnetic Resonance Imaging (MRI) have become increasingly useful diagnostic instruments (see Staging of osteonecrosis).

The articular cartilage generally remains unaffected for a long time and the joint space is of normal height until narrowed by secondary arthrosis.

The final diagnosis is made by histological examination, e.g. core biopsy. No specific pathological differences between idiopathic and alcohol- or steroid-induced femoral head necrosis have been recorded (Catto 1976).

### *Interpretations of paraclinical and histological findings*

The most widely accepted interpretation of these findings is that for some unknown reason blood supply to the superior part of the femoral head is interrupted (Patterson et al. 1964, Welfing 1971, Atsumi et al. 1989). The site and character of the vascular blockage is uncertain and many believe that arterioles and capillaries are more prone than larger vessels (Riniker and Huggler 1971, Welfing 1971, Zinn 1971 and others). Invasion of granulation tissue into the necrotic marrow space has been noticed, as has the hyperemic character of the living bone marrow beneath the necrotic zone (Merle d'Aubigne et al. 1965). Under the pressure of

weight-bearing, dead trabeculae break down, and the femoral head gradually flattens; debris is formed beneath the cover of living and usually well-preserved cartilage. With deformation of the femoral head and breakup of cartilage, secondary arthrosis develops with narrowing of the joint space and formation of marginal osteophytes.

This explanation of the progress of femoral head necrosis may seem reasonable, but is by no means universally accepted. Jacqueline and Rutishauser (1971) agree that the primary abnormality is vascular, but suggest that it is caused by venous stasis giving rise to a gradually worsening ischemia followed by resorption of bone and fibrous replacement.

Another variation of the vascular theory is proposed by Zinn (1971) who favors the view that mechanical stress in an area of localized subchondral osteopenia leads to capillary compression, while impaired bone-remodelling causes the accumulation of microcracks with rupture of small intra-trabecular vessels. Diminished resistance of the affected bone to mechanical stress is thus thought to bring about secondary vascular impairment at the capillary level (Frost 1964, Zinn 1971, Lagier 1971).

*Fat embolism.* Kahlstrom et al. (1939) suggested that bone necrosis might result from fat embolism, and this theory has been accepted by Jones. Clinical evidence of fat embolism has been reported in many of the conditions associated with nontraumatic necrosis (Jones et al. 1965), including sickle cell anemia, decompression sickness, pancreatitis, alcoholism and hypercortisonism. From 1971 Jones and his co-workers have demonstrated fat globules which appear to be intravascular in the subchondral Haversian canals of necrotic femoral heads from alcoholics and patients on high steroid dosage. His conception of the role of fat embolism in the pathogenesis of osteonecrosis was summarized in 1985 (Jones 1985). Among those critical of Jones et al.'s histological findings are Catto (1976) and Glimcher and Kenzora (1979).

The pathogenesis of femoral head necrosis will be discussed in greater detail below (General discussion).

### *Staging of nontraumatic femoral head necrosis*

Several staging systems have been proposed (Ficat and Arlet 1980, Steinberg et al. 1984, Jones 1985, Japanese Investigation Committee for Intractable Diseases 1986). These systems were merged into an international classification of osteonecrosis at the IV International Symposium on Bone Circulation (Acquaviva et al. 1989), and is the one followed here.

*Stage 0.* All of the diagnostic examinations are normal and the patient is asymptomatic. The diagnosis is made purely on the basis of histology which demonstrates osteonecrosis. In one sense, Stage 0 is a theoretical stage, but is useful for necropsy studies or for defining silent osteonecrosis which may be diagnosed at the time of intervention on the contralateral hip. Acceptance of this stage is to recognize that osteonecrosis can exist histologically without any associated clinical or paraclinical signs.

*Stage 1.* Radiographs in both AP and lateral projections are normal, but the pathological condition is suspected from other examinations. These include standard $^{99m}$Tc diphosphonate bone scan, angioscintigraphy, CT-scan, MRI and functional exploration of bone (intramedullary pressure, stress test, intraosseous phlebography, oxymetry of bone blood). To define Stage 1 requires that one of the above examinations is positive. However, as several of these examinations are also positive in joints with intraosseous engorgement-pain syndrome and radiographically silent arthrosis (scintigraphy, intraosseous pressure and phlebography), the only confirmation of Stage 1 was thought to be by biopsy. As histologic differentiation between the various degenerative disorders of the hip joint may be difficult, a special place should be reserved for MRI (Hauzeur et al. 1989, Mitchell et al. 1989). A single T1 band is suggestive of osteonecrosis, but is not specific. A double T2 band, although infrequent, is, nonetheless, virtually pathognomonic for osteonecrosis. Diagnosis in such cases does not need histological confirmation. Decreased radionuclide fixation in the centre of an area of increased fixation (cold-in-hot sign) is also virtually pathognomonic. In Stage 1 the patient may or may not be symptomatic.

*Stage 2.* A variety of radiographic abnormalities which are signs of eventual bone death are evident within the femoral head. These may include areas of linear sclerosis, focal head mineralisation, or cysts in the femoral head nor neck. However, the femoral head is perfectly spherical as seen on both the AP and lateral radiographs. There is no subchondral translucency. As Stage 2 covers a wide range of radiographic abnormalities, a subclassification according to the area of radiological involvement, as proposed by Steinberg (1984), is incorporated: A) mild (< 20 percent), B) moderate (20–40 percent), C) severe (> 40 percent).

*Stage 3.* The femoral head has begun to fail mechanically. Evidence of this includes flattening, eccentric joint space increase and subchondral radiolucency (crescent sign). These are the first signs of Stage 3 and have important therapeutic implications. The differentiation between Stage 2 and Stage 3 can best be shown by CT-scan and MRI, which are more sensitive than conventional radiography.

*Stage 4.* Evidence of any or all of the preceding radiographic changes to which is added a decrease of joint space. In such case, there is an arthrosis secondary to the mechanical collapse of the femoral head.

Staging as above, although it does not consider pathogenesis, is based on the assumption of a progressive disorder. The general consensus is that the disease begins in the bone marrow of the femoral head, and that the joint cavity changes (synovium and cartilage) seen in the late stages (3 and especially 4) are secondary manifestations.

## Intraosseous flow and pressure in the femoral head

Several authors have shown intraosseous pressure in the bone marrow of the femoral neck to be elevated in non-traumatic femoral head necrosis (Solomon 1973, Hungerford 1979, Ficat 1985, Kiær et al. 1990, Lausten and Mathiesen 1990). High intraosseous pressure is assumed to slow down the blood flow (Hungerford and Lennox 1985) and the resulting hypoxemia is suggested as the major cause of osteonecrosis (Solomon 1973, Ficat and Arlet 1980, Hungerford 1981, Cruess 1986). However, until recently no method has allowed a direct measurement of blood flow in human bone, and simultaneous measurements of intraosseous pressure and blood flow in the osteonecrotic femoral head are not reported in the literature.

### *Own investigations*

Our investigations (Arnoldi 1990, Lausten and Arnoldi 1992) were performed to examine regional intraosseous pressure and blood flow at various levels in the normal and osteonecrotic femoral heads and to compare the findings with histological observations. Our studies fell into three parts: 1) investigations of pressure and flow at rest at various levels of the femoral head, 2) investigations of the same parameters during passive joint loading and movements, and 3) histological examinations of the osteonecrotic femoral heads.

*Material.* The patient material—8 men and 7 women, age 43 (34–67) years—comprised only cases classed as idiopathic, alcohol- and steroid-induced osteonecrosis. Further, the examinations were performed only on advanced cases (ARCO Stages 3–4).

For comparison, pressure and flow were measured in 6 hips in 2 men and 4 women, age 50 (28–63) years, without any clinical, radiographic or scintigraphic evidence of hip disorders. These patients were undergoing surgery of the contralateral hip.

*Methods.* Intraosseous pressure (IOP) and flow (LDF) in the bone marrow were measured simultaneously, prior to surgery, with the patients lying supine on the operating table under general anesthesia.

*Intraosseous pressure measurements.* These measurements were performed using slightly conical metal cannulae with an outside diameter of 3.2 mm of the tip, and a lumen measuring 2.0 mm, and according to the principles described by Lemperg and Arnoldi (1978). The cannula was inserted from the lateral side into the trochanteric area under visual control using an image intensifier. After flushing with heparine-saline, the cannula was connected to a pressure transducer (Trantec 60 - 800, American Edwards Lab., Santa Ana, CA, USA.) by means of a polyethylene tube filled with saline. The intraosseous pressure was recorded on a strip chart recorder (BBC, SE 460, Goerz, Austria). As we were concerned with comparisons between pressure levels at various locations in the femoral head, measurements of extraosseous venous pressure were not considered necessary in these studies.

*Laser Doppler flowmetry.* The method, its principles and the procedures used in our experiments are described on p 15.

*Light microscopical examinations.* Cartilage and bone of the femoral heads were decalcified. The following staining methods were used: H&E for all joint structures; Martius scarlet blue (MSB) was also used in all joint components to visualize erythrocytes in interstitial tissues, intravascular erythrocyte stasis (aggregation) and agglutination, as well as fibrin thrombi of different ages, and the presence and structure of collagen; the Safranin-0 stain was used to evaluate changes in cartilage structure, and also to detect cartilage in such abnormal locations as the synovium and the deep structures of the femoral head; Perl's Prussian blue method for ferric iron demonstrated deposits of hemosiderine, especially in the synovium.

### *Intraosseous pressure and flow measurements at different levels in the femoral head with the hip in the neutral position*

*Procedure.* After achieving a steady state, intraosseous pressure and LDF-values were recorded simultaneously in three different places in the osteonecrotic femoral head: 1) in the intertrochanteric region; 2) immediately distal to the rim of the necrotic segment; and 3) in the osseous part of the necrotic area. In the normal femoral heads the points of measurement were the trochanteric area and the centre of the femoral head.

The results of the flow measurements are given as an

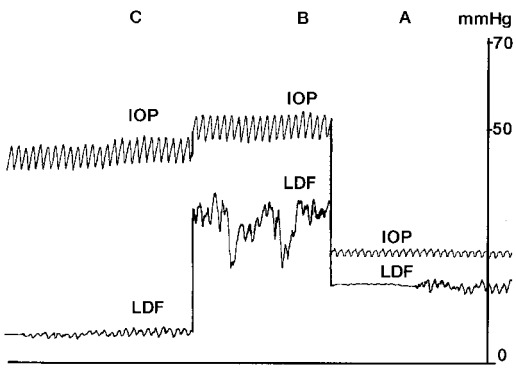



Figure 50. Intraosseous pressure in mmHg and flow (LDF), measured in the trochanteric region (A), at the rim of the necrosis (B), and inside the sequester (C). Patient with idiopathic femoral head necrosis.

average of four measurements in each region. For statistical evaluation, Wilcoxon's test for paired data and Spearman's test for correlation were used, with significance level of 0.05.

*Results.* In all cases and at all points of measurement both intraosseous pressure and laser Doppler flow tracings showed pulsatile excursions synchronous with the patients' electrocardiograms.

In 6 normal femoral heads IOP in the trochanteric area was 21 ± 7 mmHg and in the centre 19 ± 3 mmHg. The corresponding LDF values were 221 ± 63 mV and 224 ± 75 mV, respectively.

In 8 cases with osteonecrosis, measurements were obtained from all three selected areas, intertrochanteric, rim zone and sequester (Figure 50). The mean IOP in the trochanteric region was 38 ± 7 mmHg, compared with 61 ± 9 mmHg in the rim zone, and 55 ± 9 mmHg in the necrotic area. The corresponding mean LDF-values were 165 ± 16 mV in the trochanteric area, 430 ± 77 mV at the rim, and 35 ± 6 mV inside the sequester. The differences in flow values between the various zones were significant at the 0.05 level. The differences in IOP between the rim zone and the trochanteric region, and between this area and the sequester were statistically significant, whereas the difference between rim zone and sequester was not.

### Measurements during simulated joint loading and passive movements

In these experiments the tips of the cannulae were placed in the centre of the femoral head, in osteonecrotic cases outside the sequester. The patient material was identical with that examined in the first part of the study.

*Manoeuvres during the examination.* After measurements at rest, as described above, an assistant put pressure on the straight leg with the patient's foot pressed to the flat surface of a weight-recording device placed on the assistant's chest. A series of brief periods of pressure was than applied to the patient's foot and the force used was recorded in Kp. Total immobility was attempted between each period of loading. With the patient's limb still straight, 2 to 3 brief periods of external and internal rotation were performed. The force used during these manoeuvres was not measured numerically. All were done quickly and forcefully.The next set of manoeuvres, comprising external and internal rotation of the femur and flexion of the hip beyond 70°, was performed with the hip in 70° flexion and with the knee bent 90°.

### Results

*Normal femoral heads during simulated loading.* In normal femoral heads the pressure rose steeply to a moderately high pulsatile plateau, and was dependent on the load applied. The flow showed very moderate changes with a small increase during the initial phase, followed by a slight decrease during sustained loading, and ending with a moderate increase when the loading pressure was released (Figure 11).

*Normal femoral heads during external and internal rotation.* In the normal hip, movements into internal and external rotation were usually accompanied by very small variations in intraosseous pressure, but considerable fluctuations in flow velocity in the bone marrow of the femoral head (Figures 14, 15).

*Osteonecrotic femoral heads during simulated loading.* As in normal femoral heads the pressure rise during loading was dependent on the load applied. The flow variations were modest and the main difference between affected and normal femoral heads was the pressure level, which was considerably higher in the femoral heads with osteonecrosis. Figure 51 is a typical pressure and flow chart from an osteonecrotic femoral head.

*Osteonecrotic femoral heads during external and internal rotation.* In general, the intraosseous pressure showed considerable variations during these joint movements, while the intraosseous flow was only moderately affected (Figure 52). Flexion of the hip joint did not affect the results of these manoeuvres.

In this relatively small material the striking difference in pressure and flow reactions to joint movements between normal and osteonecrotic femoral heads seemed to be characteristic.

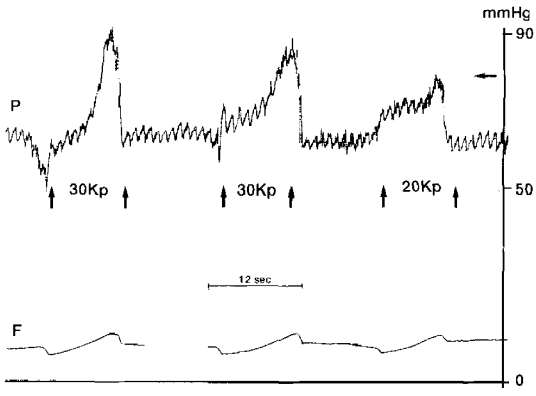



Figure 51. Intraosseous pressure and flow tracings, before, during and after three perods of loading. Osteonecrotic femoral head. Point of measurement: centre of the femoral head (outside the necrotic area).

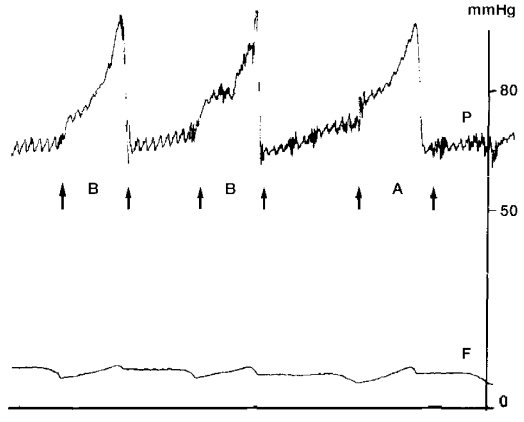



Figure 52. Intraosseous pressure and flow tracings from the centre of the femoral head (outside the necrotic area). Steroid-induced osteonecrosis. A = period of external rotation; B = periods of internal rotation.

### *Results of light microscopy*

*Synovium.* The changes observed in the synovium of affected joints were of the same character in the three types of non-traumatic osteoneocrosis. 3 to 5 rows of synoviocytes were usually observed, and the stroma immediately beneath these lining cells was mostly edematous. In the deeper layers of the thickened membrane, fibrosis was dominant. The vascularity of the membrane varied widely: from a density of vessels reminiscent of arthrotic synovium to fibrous areas with very few vessels. In the more densely vascularized zones erythrocyte aggregations and agglutinations were common, as were extravascular erythrocytes.

Shreds of bone and cartilage were observed in the superficial and deep layers of the membrane in all specimens (Figures 53, 54). In the latter location they were usually surrounded by dense fibrotic tissue. Calcium deposits were common and sometimes massive. Hemosiderin was observed in some specimens and, as in arthrotic synovium, was most prominent in close apposition to collagen strands.

*Femoral cartilage.* Figure 55 shows a typical crescent lesion, in this case from a necrosis classed as alcohol-induced. The cartilage, together with a narrow strip of bone, is separated from the rest of the femoral head, the necrotic area stretching far into the underlying bone marrow. The cartilage surface is mostly smooth and the thickness appears normal. This type of lesion seems common to all three forms of osteonecrosis described here. Figure 56 shows cartilage and bone from the crest

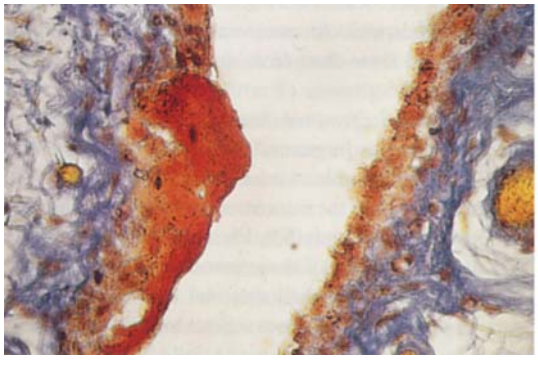


Figure 53. Opposing synovial villi from osteonecrotic hip joint. Several layers of lining cells, and to the left indeterminable inclusion, probably bone shred. Erythrocyte agglutination in several vessels (MSB, x250).

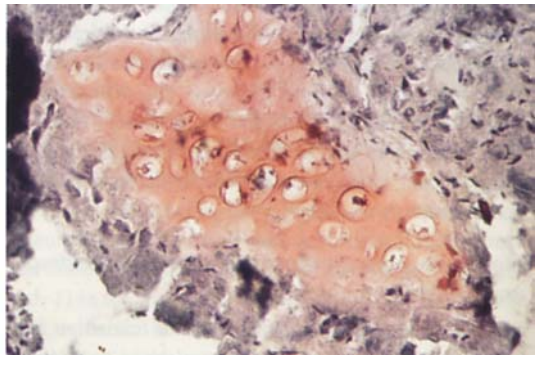


Figure 54. Mainly fibrous synovial membrane from patient with osteonecrosis of the femoral head (idiopathic). Cartilage inclusion (Safranin-0, x250).

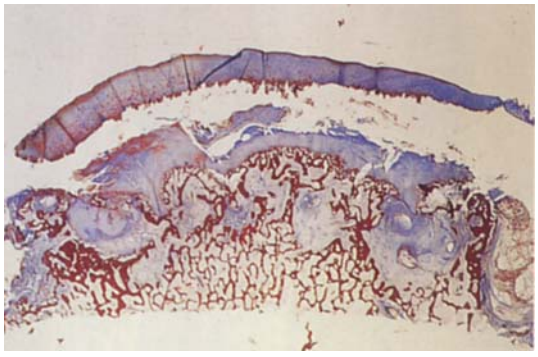


Figure 55. Crescent lesion of femoral head in alcohol-induced non-traumatic femoral head necrosis (MSB, x2.5).

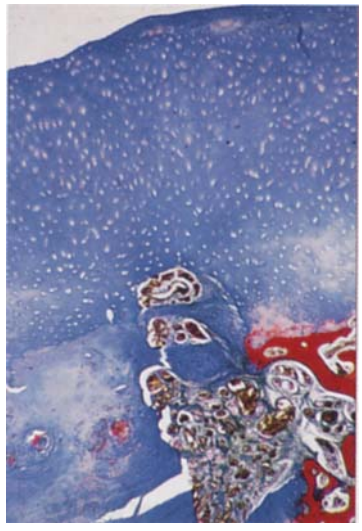


Figure 57. Penetration of vascularized fibrous tissue from subchondral region into largely normal-looking hyaline cartilage. Non-traumatic femoral head necrosis. Rest of subchondral endplate to the right with tidemark (MSB, x25).

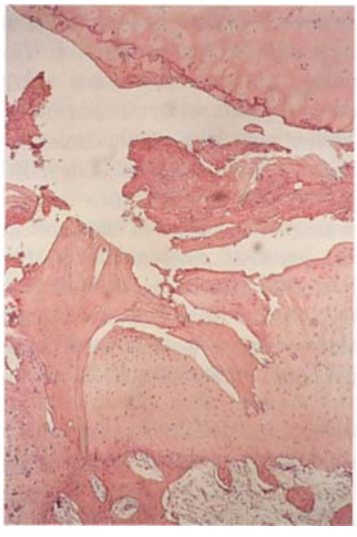


Figure 56. From crescent lesion. Idiopathic non-traumatic osteonecrosis of the femoral head. Normal-appearing hyaline cartilage, single tidemark and attached rim of dead bone. In the cleft, debris, and below that dead and fractured bone trabeculae with ingrowth of fibrocartilage (H&E, x25).

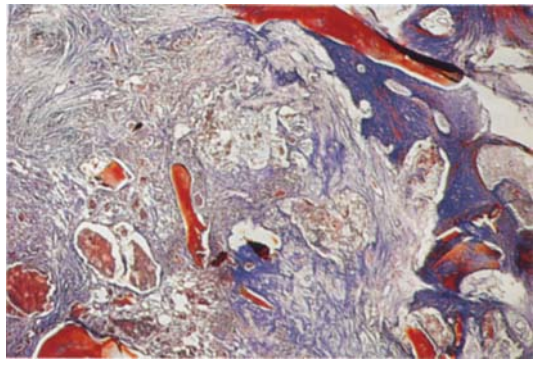


Figure 58. Near centre of necrosis (alcohol-induced). No normal soft tissue in bone marrow. Pieces of dead trabeculae in fibrous and fibrocartilagenous invasive tissue (MSB, x40).

cent, this time from a case of idiopathic necrosis. While the surface cartilage is hyaline in structure, the large and irregular patches of cartilage deep to the cleft are almost wholely fibrocartilagenous in character as are many of the islands of cartilage found deep in the necrotic area of the femoral head. Duplication or lack of tidemark were observed occasionally, and penetration of well-vascularized fibrous tissue from the region of the osteochondral junction was common (Figure 57). Cloning of chondrocytes, although observed in most specimens, was much more modest than in arthrosis, rheumatoid arthritis and hemophilic arthropathy, where the joint changes appear to be secondary to primary changes in the synovial membrane and fluid.

*Bone marrow – soft tissues.* In the necrotic area the characteristic finding in all three types of femoral head necrosis was displacement of normal soft tissue by masses of more or less primitive mesenchymal tissue and fibrocartilage (Figures 58, 59). These invasive tissues were generally well vascularized and their vessels showed numerous areas with intravascular erythrocyte aggregations, agglutinations and newly formed or older fibrin thrombi (Figure 60). Free erythrocytes in the interstitial space were common. In the rim zone distal

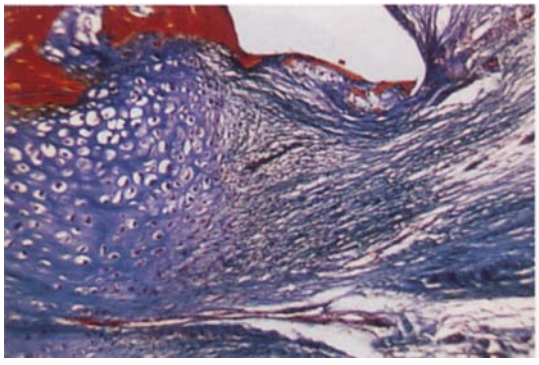


Figure 59. Transition from fibrous to fibrocartilagenous tissue near dead trabeculum. Idiopathic necrosis, centre of lesion (MSB, x100).

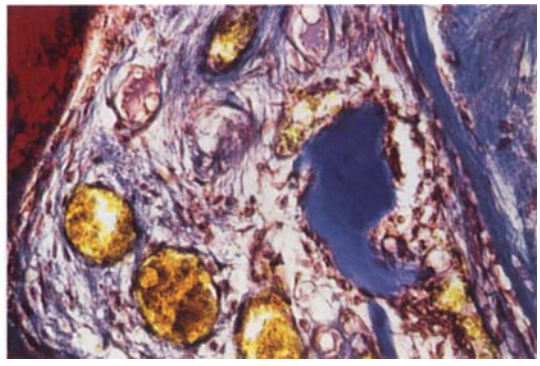


Figure 60. Vascularized fibrous invasive tissue with examples of intravascular stasis and a large old fibrin thrombus (blue), right of centre (MSB, x250).

to the necrosis the soft tissue of the more normal-looking marrow was also well vascularized with the same signs of intravascular stasis or blockage in many vessels, especially veins and venules. These findings were also apparent in areas some distance from the border of the necrosis. Particularly in the subchondral necrosis area, the invasive primitive but recognizable tissues gave way to zones of completely unstructured and non-vascularized debris (Figure 61).

*Bone marrow – trabeculae.* Visibly dead trabeculae, often with fractures and without any osteoblastic or osteoclastic activity, were common in the centre of the necrosis. In large areas, especially in the peripheral part of the necrosis towards the joint cavity, the only traces of bone were debris scattered in the primitive invasive soft tissues, or located among indeterminable soft tissue debris (Figure 61). In the apparently intact trabeculae of the rim zone on both the necrotic and the intact side, fibrin thrombi in the Haversian canals or blockage by fibrous tissue were a characteristic finding with MSB-staining. This method stains newly formed thrombi a bright yellow, older thrombi are coloured red and old thrombi blue. In this limited material, comprising late stages of femoral head necrosis (ARCO, Stages 3 and 4), very old thrombi, often transformed into fibrous tissue, were common in idiopathic and steroid-induced osteonecrosis, whereas most of the Haversian thrombi in alcohol-induced necrosis were younger (yellow or red). Figures 62 and 63 are typical examples. The adjacent osteocyte lacunae were either empty or showed pyknotic degeneration of nuclei.

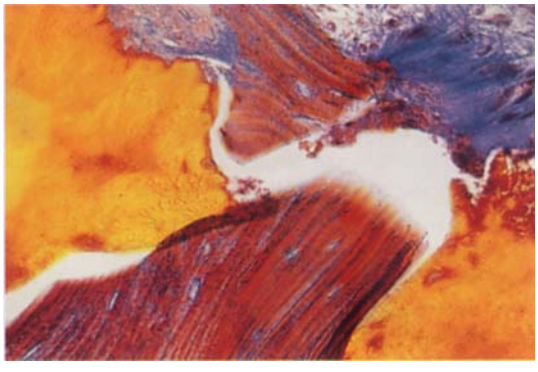


Figure 61. Dead trabeculae in debris, bordered by fibrous invasive tissue. Steroid-induced femoral head osteonecrosis (MSB, x250).

### Comments

*Pressure and flow.* The observations of pressure and flow in normal femoral heads and in late-stage non-traumatic osteonecrosis can be summarized as follows: In the normal femoral head low intraosseous pressure at rest was observed with relatively rapid blood flow. Very slight pressure increases on all joint movements were accompanied by significant increases in flow rate. Conversely, in the osteonecrotic femoral heads high intraosseous pressure at rest was found together with slow intramedullary flow in the necrotic area, and considerable pressure increases during joint manoeuvres were usually accompanied by a slight reduction of flow rate (centre of femoral head).

We interpret the low pressure and high flow at rest and during joint movements as signs of free drainage (intra- as well as extraosseous) from the normal bone marrow. Conversely, the high pressure and slow flow at rest and the marked pressure increases and reduced flow rate during joint manoeuvres indicate impairment of drainage from the bone marrow of the osteonecrotic femoral head.

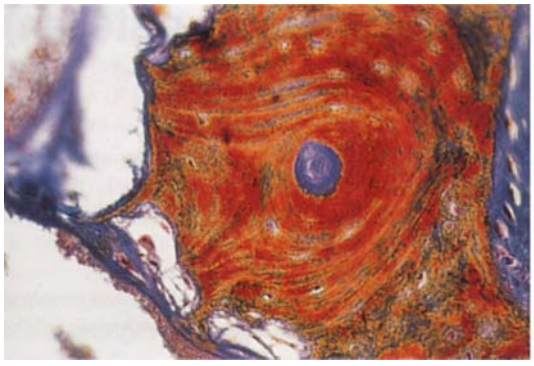


Figure 62. Old thrombus or blockage by fibrous tissue (blue) in Haversian canal. Empty osteocyte lacunae. Rim zone of steroid-induced femoral head necrosis (MSB, x250).

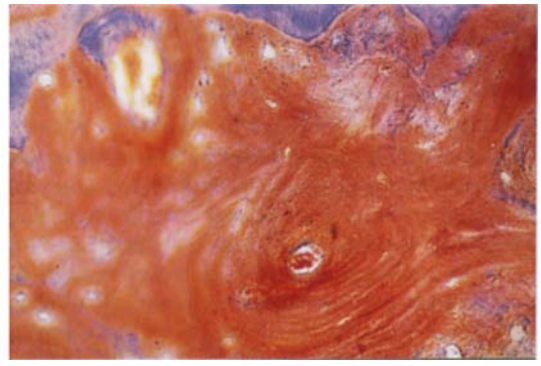


Figure 63. Relatively newly formed (red) fibrin block in Haversian canal at the osteochondral junction. Alcohol-induced femoral head necrosis (MSB, x250).

An interesting finding in these experiments with pressure and flow was that all measurements showed higher pressure in the necrotic area than in the well-vascularized trochanteric region, and that both pressure and flow tracings from this supposedly avascular sequester were pulsatile.

*Histological findings and their relation to changes in flow and pressure.* The light microscopy findings showed that large areas of the "necrosis" are vascularized; indeed, some areas are extremely well supplied with vessels. The findings also indicate that many of these vessels trace their origin to vessels in soft tissues of the foveolar notch and in tissue invading the bone marrow from the border zone between cartilage and bone. The incidence of stasis and blockage in the veins and venules of the more or less primitive invasive tissues is high, and in or near the border zone this tendency to blockage is also marked in the vessels of the Haversian canals. Thus, the remarkably high pressure and the very slow flow in the necrotic area are most logically due to high resistance to venous drainage. The pulsatile pressure and flow tracings, however, indicate that the arterial supply is more or less intact outside the zones of debris. In these late stages of osteonecrosis with secondary synovitis, intra-articular vein compression, known to be important in the pathomechanism of arthrosis (Arnoldi and Reimann 1979), may play an additional role. However, the phenomena observed in this study indicate that intraosseous, intravascular venous blockage is of major importance, and that it may be due to an abnormal local tendency to thrombosis.

# Patellar pain syndromes (chondromalacia patellae)

The term patellar pain syndrome (PP) is used here as a descriptive term for pain in the knee region, characteristically provoked or accentuated by a set of manoeuvres involving either movement in the patello-femoral joint, increased pressure of the patella against the femoral condyles, or a combination of both.

### *Blood supply to and drainage from the patella*

The patella belongs to the "short" bones, consisting of a tight mesh of cancellous bone surrounded by a firm but elastic cortical shell. Relative to the size of the bone, the cartilage plate is large.

### *Arterial supply*

Björkström and Goldie (1980) described the arterial supply thus: in the extraosseous patellar ring a transverse infrapatellar artery runs posterior to the patellar ligament. The other parts of the rete patellae and the branches forming the prepatellar arterial network lie in the thin layer of loose connective tissue that covers the fibrous extension of the quadriceps tendon on the anterior aspect of the patella. This part of the extraosseous arterial system is thus only covered by the subcutaneous fascia and skin.

In addition to these main sources of arterial supply, Björkström and Goldie (1980) described further supply from the quadriceps tendon to the base of the patella, and from the synovial tissue to the margins of the bone and to the apex. They described two main intraosseous arterial systems. One is the mid-patellar branches that stem from the prepatellar network and enter obliquely upwards from below, through the central part of the anterior surface. The second system consists of apical branches from the transverse infrapatellar artery posterior to the patellar ligament. These supply the lower part of the patella and communicate with the mid-patellar arteries.

### *Arterial changes at the osteo-chondral junction in chondromalacia patellae and arthrosis of the patello-femoral joint*

*Normal cartilage.* Björkström and Goldie (1980) observed that the subchondral arteries arose from the apical and mid-patellar arteries as straight or slightly curved branches radiating towards the subchondral region (Figure 64). In all specimens with normal cartilage, the calibre of the arteries gradually diminished to fine terminals. In the over 60s, the main arteries were thinner than in the young and the endings did not reach out as far towards the periphery.

*Chondromalacia patellae.* Björkström and Goldie (1980) observed that the branches reaching normal cartilage zones resembled those of normal patellae, whereas arteries reaching the zones of cartilage degeneration became wider than normal, reached further towards the periphery, ending either straight and abruptly or were bent almost parallel to the cartilage. In the zone of degeneration the arterial pattern might take on an arcade-like design. Within these arcades the arteries were tortuous and wide at the peripheral margin. These vascular changes correlated with the grading of chondromalacia.

*Arthrosis.* Björkström and Goldie (1980) found that the design of intrinsic arterial supply resembled that of severe stages of chondromalacia, but was more pronounced (Figure 65).

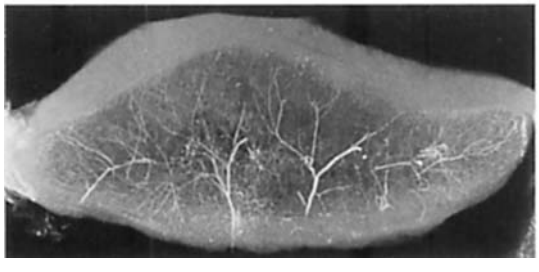


Figure 64. Microangiograph of a transverse section of a normal human patella showing arteries radiating towards the articular cartilage and recurrent branches supplying the patellar cortex centrifugally (Bridgeman and Brookes 1990).

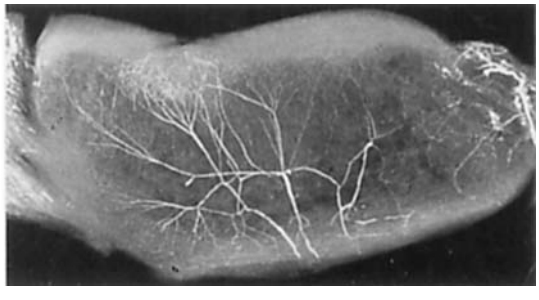


Figure 65. Microangiograph of a sagittal section of an aged human patella showing the auxillary inferior marginal blood supply. A patch of cartilage softening is associated with marked hypervascularity (Bridgeman and Brookes 1990).

### *Venous drainage*

Venous flow from the patella has mainly been studied by means of intraosseous phlebography. The contrast-filled veins seem to correspond to the arteries. Changes in patellar disorders will be described below.

### *Staging of chondromalacia patellae*

In patients with PP-syndromes changes in the knee joint cartilage are observed in a number, but far from all cases. It is noteworthy that these changes are confined to the cartilage of the patella, except in the last stages of chondromalacia when the cartilage of the femoral trochlea may show mirror changes. However, at this stage it is difficult to distinguish between chondromalacia and patello-femoral arthrosis.

We have used Ficat and Hungerford's (1977) staging system:

*Stage 0.* No discernible macroscopic changes in patellar cartilage.

*Stage 1.* Local softening (the blister lesion; Figure 73) of a circumscribed area, commonly, but not always located in the danger zone on the lateral facet near the median ridge. At this stage the surface of the cartilage is intact.

*Stage 2.* Open chondrosis. At this stage the degenerative cellular and ground substance changes predominate. In particular, the superficial layer of cartilage becomes involved by increasing proliferative changes alternating with signs of necrosis and ending in surface ulceration.

*Stage 3.* Open chondrosis with denudation of bone and progression to patello-femoral arthrosis.

### *The juxtapatellar synovial membrane*

At the base of the patella the synovium, extending from the suprapatellar pouch, is densely adherent to the insertion of the quadriceps femoris tendon, while it is separated from the medial and lateral vasti by loose connective tissue (Ficat and Hungerford 1977). The medial, lateral and distal cartilaginous borders are surrounded by a small synovial wall or fold, separated from the patella by a fossa. In patients with PP-syndromes, and especially those with the severe stages of chondromalacia, the peripatellar synovial wall and ditch often show characteristic signs of localized synovitis with inflammatory edema that covers the entire peripheral area of cartilage. Such inflammatory changes may become very pronounced, but rarely exceed the immediate vicinity of the patella. Generalized synovitis of the knee joint with clinically demonstrable exudation is not common in PP-syndromes, arthrosis excepted.

### *The infrapatellar fat pad*

Covered by synovial membrane where it faces the joint cavity, the centre of the structure lies behind the ligamentum patellae, but extends beyond the borders of the ligament medially and laterally. During extreme flexion the centre is compressed by the ligament with the medial and lateral parts appearing as bulges on either side. Proximally, the fat pad covers the entire posterior part of the apex below the border of the patellar cartilage and distally it has a broad connection with the anterior proximal surface of the tibia.

## Investigations by intraosseous pressure measurements, intraosseous phlebography, arthroscopy and $^{99m}$Tc-phosphate scintigraphy

*Previous studies of patellar bone marrow pressure.* Measurements of intramedullary pressure in normal human patellae were performed with subjects in the horizontal position by Ficat and Hungerford (1977), who estimated the normal pressure at 10–15 mmHg. Björkström et al. (1980) found a mean normal pressure of 19 mmHg. In puppies, Bünger et al. (1982) found the patellar pressure to be 12 (8–15) mmHg and observed that this pressure rose significantly (to about 30 mmHg, mean) when the intra-articular knee pressure was raised by injection of fluid. If the fluid-injected knee was flexed beyond 90°, the mean pressure in the patella rose by approximately 20 mmHg.

In painful knee joints with reflex sympathetic dystrophy base line pressure in the patella ranged from 30–50 mmHg (Ficat and Hungerford 1977). Björkström et al. (1980) measured the intramedullary pressure in chondromalacia, graded according to Collins (1949), and found mean values of 41 mmHg in Grade 1, 37 mmHg in Grade 2 and 64 mmHg in Grade 3. The mean pressure in their normal control group was 19 mmHg and in patients with arthrosis of the patello-femoral joint 37 mmHg. In all groups the pressures varied within wide limits.

These studies agree about intraosseous pressure in normal human and animal patellae and they also indicate that painful patello-femoral arthrosis and chondromalacia seem to be associated with increased intrapatellar pressure in the resting horizontal position.

## Own investigations

We (Hejgaard and Arnoldi 1984, Arnoldi 1991) studied the relationship between characteristic pain, the venous drainage system of the patella, and the pressure and pressure variations in the three bones of the knee joint. $^{99m}$Tc-phosphate scintigraphy was also used (Hejgaard and Diemer 1983) to identify possible changes in bone marrow metabolism.

After pressure measurements and phlebography, arthroscopy was performed on the painful knees using a standard infero-lateral approach. The articular surfaces were examined by eye and by probe. Patellar chondromalacia was graded according to Ficat and Hungerford (1977).

### *Intraosseous pressure measurements*

*Material and methods.* The material was 24 men, median age 33 (20–48) years, and 37 women, median age 34 (16–60) years. The symptoms were bilateral in 5 men and 15 women. There were thus 81 painful knees and 41 knees without pain (controls). Patients with arthrosis of the knee joint (radiography) were excluded.

*Pressure measurements.* The patients were examined supine under general anesthesia. Bone marrow biopsy needles, 4 cm long with an outer diameter of 3 mm and a lumen of 1.5 mm, were drilled into the patella close to its base, with the tip directed slightly distally. Similar needles were drilled 2 cm into the medial femoral and tibial condyles. Extraosseous venous pressure was measured through a tube introduced into the internal saphenous vein at the level of the medial malleolus. The tip of the tube was placed at the junction of the saphenous and femoral veins. Heart level, arbitrarily fixed at 5 cm posterior to the sternum at the level of the fourth intercostal space, was used as reference point for all measurements. The needles and the intravenous catheter were connected to a four-channel pressure recording system. Within the range of measurement the recording system gave proportional deflection according to the pressure applied and responded accurately in frequency and amplitude to sine-wave pressure as high as 15 Hz. Intraosseous pressure was defined as the difference between the measured intraosseous pressure and the extraosseous venous pressure. The intramedullary pressure was measured simultaneously in the patella and the femoral and tibial condyles.

*Positions and manoeuvres during measurement.* Two clinical tests, usually positive (i.e. provoking pain) in all severe PP cases regardless of etiology, were used during the measurements: the pressure test and the sustained flexion test.

*The pressure test* is performed with the patient lying supine with the knee in extension. The patella is placed in the trochlea and kept there with one hand, while the examiner puts weight on the patella through the palm of his other hand.

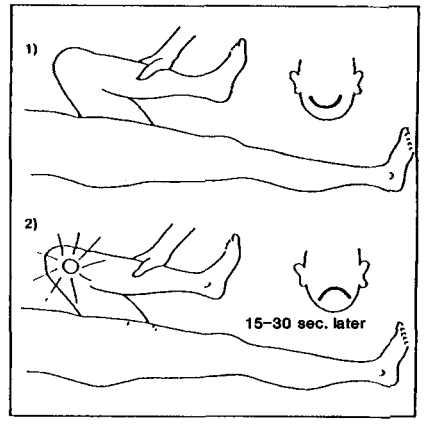



Figure 66. Positive sustained flexion test: pain-free movement into maximal flexion (1); after 15–30 sec in maximal flexion the knee becomes increasingly painful.

*The sustained flexion test* (Hejgaard and Arnoldi 1984). The patient is placed supine with the knee extended and relaxed. The knee is then flexed fully and kept firmly in sustained flexion for up to 45 seconds. The movement to full flexion is pain-free in the absence of arthrosis. The test is positive if the patient complains of increasing pain after a pain-free interlude of 15–30 seconds (Figure 66). The pain may become extremely severe and caution is advocated.

All patients were examined bilaterally with the knees in relaxed extension and in sustained forceful flexion. Groups were further examined bilaterally in the supine position 1) during forceful pressure on the patella against the femur, simulating the pressure test; and 2) during compression of Hoffa's fat pad, by pinching with the thumb and index finger on both sides of the patellar ligament.

***Results.*** *Pressures in the relaxed extended knee.* Intraosseous pressures were measured in the patella, femur and tibia. In a group of 40 patients with long-standing pain, severe enough to warrant operation, Hejgaard and Arnoldi (1984) found a significantly higher patellar pressure in painful knees than in controls ($p < 0.001$, Mann–Whitney) and those with pain at rest had a higher pressure than those without ($p < 0.05$).

Table 13 shows the results from a larger material (Arnoldi 1991) including data from patients treated by conservative means. Thus, the difference in mean patellar pressure between painful and control knees was statistically significant, whereas the differences observed at the two other points of measurement were not. The

mean extraosseous venous pressure was 8 (2–18) mmHg. No difference between pain-free and painful extremities was observed.

*Effect of compression of Hoffa's fat pad on intraosseous pulsatile excursions.* The apical veins are the most important drainage complex from the patellar bone marrow. Figure 67 shows a typical intraosseous pressure reaction at the three points of measurement before, during and after compression of Hoffa's fat pad (patella), and Table 14 the mean pressure rise above rest level in the patella, femur and tibia.

The increase in size of pulse pressure waves was statistically significant in the pain-free patella ($p < 0.001$; Table 15), and in the tibia ($p < 0.01$). There is a tendency to even greater excursions in painful knees, but the difference between controls and painful knees was statistically significant only in the patella ($p < 0.05$, Mann–Whitney).

*Manual compression of the patella against the femur in the extended knee.* The effects on intraosseous pressure of compression of Hoffa's fat pad and of the patella against the femur (pressure test) were compared in 10 controls. The rise in pressure was greater at all points of measurement during compression of the patella than during blockage of drainage through the apical veins (Table 14; Figure 68).

As observed earlier the size of the pulse waves increased during fat pad compression. Patellar compression, however, was always accompanied by total or almost total disappearance of pulse synchronic excursions in the patella (Figure 68; Table 15). In the femur and tibia, where the rise of intraosseous pressure during patellar compression was modest, the tracings remained pulsatile.

*Patellar pressure in extended, relaxed PP knees, with and without chondromalacia.* Table 16 shows pressures from painful patellae with or without arthroscopic signs of chondromalacia (graded acording to Ficat and Hungerford 1977). Taken as a group, the pressure in chondromalacia patellae was not higher than in painful patellae with macroscopically normal cartilage.

*Intraosseous pressures during sustained knee flexion.* Forced maximum flexion of the knee joint caused a sudden rise of intraosseous pressure, in control as well

Table 13. Pressures in the patella, and the femoral and tibial condyles in the relaxed, extended knee in controls and in knees with patello-femoral pain. Mean (range) mmHg above the extraosseous venous pressure

| Groups | n | Patella | Femur | Tibia |
|---|---|---|---|---|
| Controls | 41 | 19 (0–68) | 18 (0–46) | 13 (2–38) |
| With pain | 81 | 24 (3–62) | 18 (0–54) | 15 (2–38) |

Difference in patellar pressure 5.3 mmHg ($p < 0.01$)

Table 14. Pressures in the patella, and the femoral and tibial condyles, during compression of Hoffa's fat pad and patella against the femur in 10 control knees. Mean (range) mmHg above the pressure in the saphenous vein

| Compression | Patella | Femur | Tibia |
|---|---|---|---|
| Hoffa | 44 (22–53) | 25 (8–44) | 27 (13–47) |
| Patella | 73 (44–98) | 44 (24–76) | 36 (10–57) |

Table 15. Mean pulse amplitudes (mmHg) in the patella in 10 control knees in extension, before, during, and after compression of Hoffa's pad and patella against the femur

| Compression | Before | During | After |
|---|---|---|---|
| Hoffa | 8 | 13 | 8 |
| Patella | 8 | 0 | 8 |

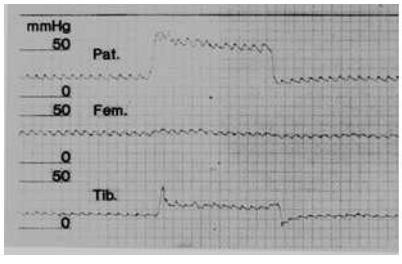



Figure 67. Pressure tracings from the patella and the femoral and tibial condyles, before, during and after compression of Hoffa's fat pad. Pain-free knee in relaxed extension.

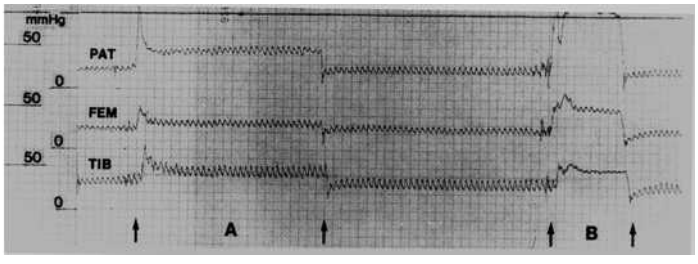



Figure 68. Pressure tracings from the three points of measurements in control knee: A. During compression of Hoffa's fat pad. B. During compression of the patella against the femoral trochlea.

Table 16. Pressure in the patella at rest with the knee in extension, and plateau pressure during sustained maximal knee flexion in knees with patellar pain, with and without arthroscopically verified chondromalacia (staging system, Ficat and Hungerford 1977). Mean (range) mmHg

| Group | n | Pressure at rest | Plateau pressure |
|---|---|---|---|
| With chondromalacia | 27 | 23 (3–46) | 80 (26–250) |
| Without ch. | 41 | 25 (5–62) | 86 (16–161) |
| Stage I + II | 14 | 28 (5–62) | 89 (29–148) |
| Stage III | 27 | 24 (3–46) | 78 (16–161) |

Table 17. Peak and plateau pressure in the patella and the femoral and tibial condyles during sustained maximal knee flexion in controls and in knees with patellar pain. Mean (range) mmHg

| Group | | n | Maximum pressure | Plateau pressure |
|---|---|---|---|---|
| Patella | Control | 33 | 87 (29–172) | 54 (17–92) |
| | Painful | 69 | 143 (36–256) | 78 (16–256) |
| Femur | Control | 34 | 67 (19–118) | 38 (14–62) |
| | Painful | 69 | 77 (20–248) | 43 (10–88) |
| Tibia | Control | 33 | 48 (14–84) | 33 (8–52) |
| | Painful | 67 | 57 (18–120) | 43 (7–72) |

as PP knees, at all points of measurement (Figure 69). After peaking, the pressures fell to plateaus which, as a rule, were level until the knee was stretched; they then fell steeply to points somewhat lower than the original resting levels. Pressure recovery to these levels generally took less than 1 second in the patella and femur, but up to 3 seconds in the tibia.

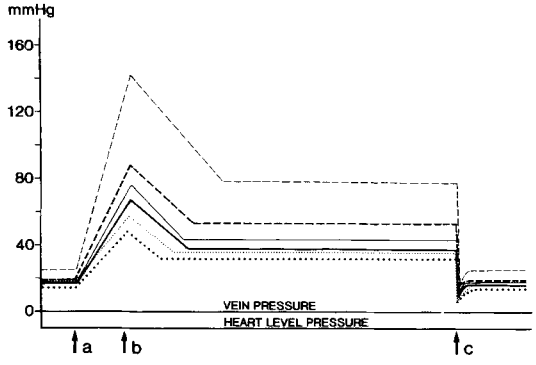
Mean pressures during sustained knee flexion in control and PP knees are shown in Figure 69, which also gives the mean angles of pressure increase and decrease. The differences in maximum and plateau pressure between patellae in control and painful knees are highly significant (Table 17; $p < 0.001$, Mann–Whitney). Femur and tibia pressure differences were not statistically significant.

*Plateau pressure during sustained knee flexion related to the results of the sustained flexion test.* Clinical results of the sustained flexion test were compared with the pressure in the patellar bone marrow during sustained flexion. As painless movement into flexion (arthrosis excluded), followed by a pain-free interlude of 15–30 sec is characteristic of a positive test (Figure 66), it was of special interest to compare plateau pressure with the outcome of the test. Plateau pressure was higher in painful knees with positive clinical tests than in those with negative tests (90 [16–86] vs 46 [29–256] mmHg; $p < 0.001$, Mann–Whitney).

During sustained knee flexion, bone marrow pressure seemed to be largely equal in painful joints with and without chondromalacia (Table 16).

*Pulsatile variations on pressure tracings during sustained knee flexion.* Pulse waves in the patella disappeared completely from the tracings during sustained flexion in 27 of 33 control knees. In 6 knees they became visible when the pressure had reached plateau level. In this subgroup plateau pressure was 30 (28–60) mmHg, compared with 54 (17–92) mmHg in the whole group.

Of the 69 knees with patella-related pain, 6 showed pulsatile plateau pressure, with a mean of 34 (26–61) mmHg, compared with 78 (16–256) mmHg in the whole group.




Pain-free knees: – – – patella, —— femur and ····· tibia; and knees with patellar pain: – – – patella, —— femur and ····· tibia.

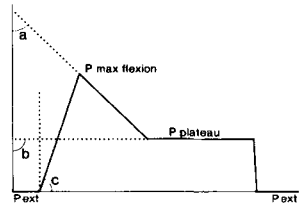



Figure 69. Pressure at rest, peak values and plateau pressures before, during and after sustained maximal knee flexion. Mean values from the three points of measurements in pain-free knees and in knees with patellar pain. The method of assessing the rapidity of pressure rise and fall is illustrated in the upper right section. Mean pressure in the internal saphenous vein is 8 mmHg. Mean interval a–b was 1.2 sec. The interval b–c varied within wide limits.

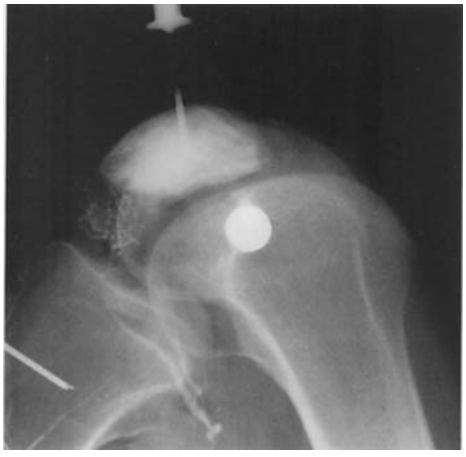


Figure 70. Intraosseous patellar phlebograph from pain-free knee in flexion, exposed 1s after contrast injection. Apical veins are the only ecape route for the injected contrast.

In the femur and tibia all pressure tracings were pulsatile at plateau level, although the excursions were lowered compared with the resting state in some cases.

### *Intraosseous patellar phlebography*

Intraosseous phlebography of normal patellae was performed by Ficat and Hungerford (1977) on subjects lying supine with the knee extended. They found the apical region to be the main hilus of venous drainage from the patella and that the contrast-filled veins seemed to follow the course of the arteries supplying the bone. In a small group of PP patients with reflex sympathetic dystrophy they found intramedullary stasis in the femoral condyles. They do not seem to have performed patellar phlebography in these cases.

### *Own investigations*

*Material and methods.* Intraosseous phlebography was performed on 39 pain-free patellae and 77 patellae from knees with pain (Arnoldi 1991).

Contrast material (2–3 mL) was injected through the needle in the patella and the first exposure was made 1 sec after completion of the injection. Further exposures were made at 1 and 5 min and in a number of cases at 10 or 15 min. In 30 patients the examination of the extended knee was followed by a second series of bilateral phlebographs with the knee in sustained maximal flexion. Lateral exposures were used in both series.

***Results.*** *Extraossous patellar drainage in the extended knee.* The extraosseous course of the veins was observed at 1 sec after injection of contrast. The following vessels were always observed in pain-free knees: 1) a cluster of veins (5–12) leaving the apex in a distal posterior direction, draining into the saphenous system and into the popliteal vein; 2) a varying number of veins leaving the anterior surface of the patella and following it closely in a proximal direction to superficial femoral veins; 3) a varying number of slender veins leaving the basis patellae in a proximal direction to deep and superficial veins of the femur; 4) a few slender veins leaving the medial and lateral margins of the patella.

In painful knees the overall picture corresponded to the description given above. However, in 21/77, one or several of these systems were missing from the phlebographs, usually the veins leaving the basis and the lateral and medial margins. Only in 2 cases had the apical veins disappeared completely, while they were unusually slender in 8 others. On all phlebographs the contrast in extraosseous veins of both control and PP knees had disappeared within 1 minute of injection.

*Extraossous patellar drainage with the knee in sustained maximal flexion.* In almost all knees, with or without pain, the veins emerging from the anterior aspect, the base and the medial and lateral borders had disappeared from the phlebographs. The apical veins thus seemed to be the only drainage channels functioning in this position (Figure 70) and in many patients the picture suggested a decrease of vein diameters, compared with those during knee extension. In all cases the extraosseous veins were not visible on the 1-minute exposure.

*Intraosseous venous patterns.* Two intraosseous venous patterns could be distinguished: Type 1, a tightly woven mesh of minute vessels (Figure 71), and Type 2, a loose network of larger venules and veins. 36/39 controls and 32/77 PP knees were of Type 1. Patients with this pattern were relatively young, and most patients with a history of overuse (sport) showed this pattern, while an analysis of case histories showed that most patients with a history of direct knee trauma showed a Type 2 pattern (Figure 72).

*Patellar bone marrow evacuation of contrast in extension.* In pain-free knees, total or nearly total emptying of intramedullary contrast occurred within 10 min from 28 patellae; in the remaining 11 the contrast distribution remained unchanged.

In painful knees, taken as a group 27/77 emptied completely within 10 min, while no change in contrast distribution could be observed in 50/77. A significant difference was noted between Type 1 and 2 patterns; 25/45 Type 2 patellae emptied within 10 min, the majority within 5 minutes. In contrast only 2/37 patellae with Type 1 pattern were empty of contrast within 10 min.

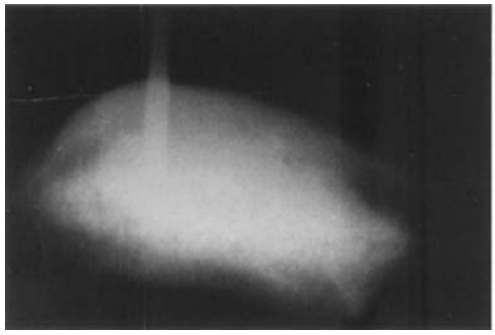


Figure 71. Type 1 intraosseous phlebograph from a knee with patellar pain exposed 10 min after contrast injection with the knee in extension. Extraosseous veins are empty and contrast is only retained in a fine-meshed intraosseous network.

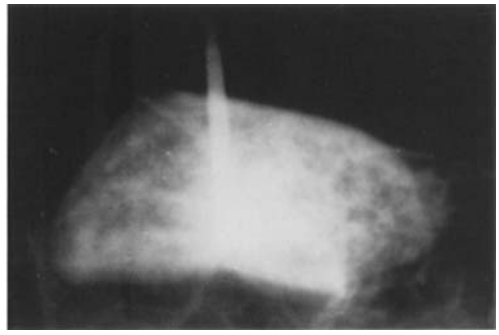


Figure 72. Type 2 intraosseous phlebograph from a knee with patellar pain, exposed 1 sec after contrast injection with the knee in extension. Extraosseous drainage is visible. The contrast fills a loose network of larger venous channels in the patellar bone marrow. The contrast was completely evacuated within 5 min.

*In sustained maximal flexion.* From the 39 painful and 21 control knees examined phlebographically in sustained flexion, no emptying of contrast material from the patellar bone marrow was observed during the 10-minute observation time. There was no difference between pain-free and painful knees or between the two intramedullary vessel patterns.

### *Investigations by $^{99m}$Tc-phosphate scintigraphy*

Darracott and Vernon–Roberts (1971), using Sr-87m, examined 11 patients with chondromalacia patellae. Seven cases with unilateral symptoms exhibited reduced isotope uptake in the affected patella, whereas the other two had moderately increased patellar uptake. Of the two patients with bilateral symptoms, one had reduced uptake in both patellae, the other had markedly increased uptake in one patella and reduced uptake in the other. In all cases lateral scans showed the changes in uptake to be maximal in the region of the patellae, although similar changes of lesser degree were occasionally recorded in the other bones of the knee joint.

### *Investigations of present material*

Hejgaard and Diemer (1983) used $^{99m}$Tc-diphosphonate scintigraphy to examine 80 PP-patients. This material is largely identical with that described in the sections on intraosseous pressure and phlebography. Their bone scans showed that 48 percent of the painful knees had an increased uptake, compared with 9 percent of the controls. A highly significant correlation was evident between an increased uptake and painful Stage 3 chondromalacia.

## Histology

Darracott and Vernon–Roberts (1971) in studies of chondromalacia and control patellae found a thinning of the subchondral osseous plate in all cases of chondromalacia. The trabecular bone showed either diffuse or focal osteopenia. There was also vascular invasion through the osseous plate, and where this was present, the deep zone of patellar cartilage showed hyperplasia of the chondrocytes. Osteopenia was most marked in the regions of vascular supply and this would suggest that the changes in bone were secondary to disturbances of blood supply.

Badalamente and Cherney (1989) compared the vascular and periosteal innervation of the human patella in the normal state and in chondromalacia. In control patellae, arterial and thin-walled venous capillaries were present at the osteochondral junction and deep to the single-layer tidemark. In contrast, patellae with chondromalacia showed arterial and venous capillaries that consistently penetrated the osteochondral junction, the basal calcified layer of cartilage as well as the duplicated or reduplicated tidemark. Further, the number of vessels increased from 1.5 arterial capillaries per 10 µm in control patellae, to 6.0 vessels per 10 µm in chondromalacia. In all cases small myelinated nerves containing Substance P and serotonin were consistently associated with capillaries in subchondral and medullary trabecular bone and in the periosteum. Badalamente and Cherney (1989) suggested that the increase in bone marrow pressure and resultant pain in chondromalacia (and arthrosis) may be related to the increased number of vessels.

Goodfellow et al. (1976) found two distinct lesions affecting the articular cartilage of the patella: surface degeneration, which is age dependent, becoming

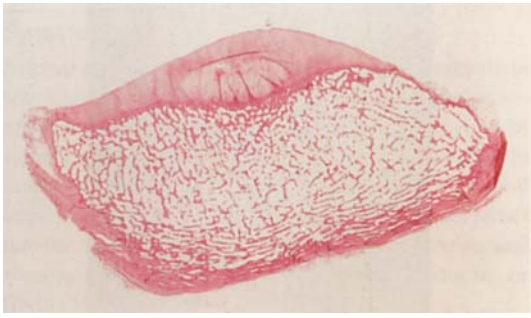


Figure 73. Longitudinal section of painful patella. Cartilage shows blister lesion. The osteopenic structure of the bone marrow is typical (H&E, x2.5)

increasingly more frequent with increasing age. In their opinion it does not cause patellar pain in youth, but may predispose to arthrosis in later years. Goodfellow et al. (1976) introduced the term basal cartilage degeneration to describe another lesion in which there is fasciculation of collagen in the middle and deep zones of cartilage without initially affecting the surface. It was found astride the ridge separating the medial from the odd facet in adolescents who had complained of prolonged patellar pain. They described the macroscopic state of the cartilage in the fasciculation area thus: "articular surface is smoothly intact and the disorder can only be detected by palpation. The cartilage has then an appreciably spongy consistency and exhibits what can be fairly described as 'pitting oedema'."

They also found that in all fasciculated specimens the matrix stained less well with PAS than in normal cartilage. Further, they noticed that synovial effusion was only present where the superficial layer had ruptured and in these cases the synovial fluid was found to contain "innumerable small pieces of shred cartilage."

### *Own investigations*

Our histological investigations (Arnoldi 1991) were directed at normal cartilage and synovium and the changes observed in PP knees and in gonarthrosis. As for the bony structures the interest was centred on vascular changes in or near the osteochondral junction. In all cases the patella was removed together with the adjacent synovial membrane and part of Hoffa's fat pad. In PP knees and patients with arthrosis, a synovial biopsy was also taken at an average 3 cm from the medial patellar margin.

*Methods.* The following staining methods were used: H&E for all joint components; MSB (Martius scarlet blue), the modification by Pusey and Edwards (1978), was used to visualize erythrocytes in the interstitial tissues, intravascular erythrocyte stasis, agglutination and fibrin thrombi, and the presence and structure of collagen; Safranin-0 staining was used to show the conditions in cartilage matrix; Perl's Prussian blue; and von Kossa's staining for demonstrating deposits of hemosiderin and soft tissue calcium deposits, respectively.

***Results.*** *Cancellous bone and osteochondral junction.* The cancellous bone of patellae of PP knees was obviously osteoporotic, compared with normal and arthrotic patellas (Figure 73), and our findings did not differ from those described by Darracott and Vernon–Roberts (1971). The thinning of the osteochondral end plate observed by these authors and Badalamente and Cherney (1989) was also confirmed, as was the increased vascularity of this part of the bone. The most noticeable difference in this region was the almost universal finding of vascular penetration through the bone into the basal calcified layer of cartilage and through the tidemark. Where this had happened a second tidemark had appeared, looking almost like a second line of defence. Up to 6 tidemark lines were observed (Figure 74), but, occasionally, vessels with erythrocyte aggregation, agglutination and fibrin thrombi appeared between the tidemarks or in the matrix of the basal cartilage layer (Figure 75).

A few specimens showed erythrocyte aggregations in the vessels of the Haversian canals in the subchondral zone, but fibrin thrombi in these vessels were extremely rare.

In later studies 5 specimens, removed by patellectomy due to intractable pain, showed variations of vascular configuration in the bone marrow that may explain the 2 types of intraosseous contrast distribution demonstrated by phlebography. In 2 cases the sinusoid diameters were of normal size and in a considerable number their lumen showed erythrocyte stasis to agglutination. In 3 specimens the sinusoids were abnormally wide, contained erythrocytes, but intravascular stasis was rare. One of these patellae had shown a Type 2 pattern by phlebographical examination 7 years previously.

*Matrix and chondrocytes. MSB stain:* In the normal patella, the matrix is stained a uniform clear blue by this method (collagen; Arnoldi 1991). In PP patellae stained by this technique, the characteristic picture was a smaller or greater area near the odd facet where the basal and middle layers had lost their blue colour and taken on a greyish hue, often with reddish variations (Figures 76–78). The demarcation between these areas and normal- looking cartilage was often very sharply defined. The superficial layer retained its dark blue colour as long as it remained intact and sometimes even after fibrillation had set in (Figures 77, 78).

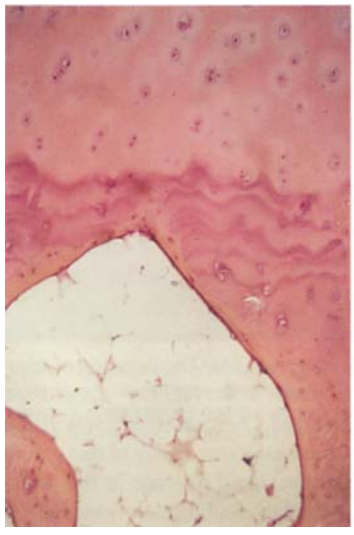


Figure 74. Osteochondral junction from painful patella. Six tidemarks between normal bone and cartilage with widely spaced, but apparently normal chondrocytes (H&E, x100).

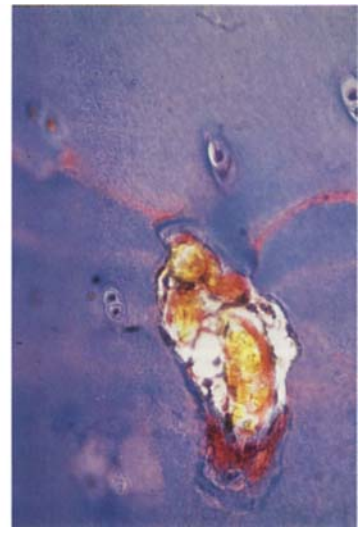
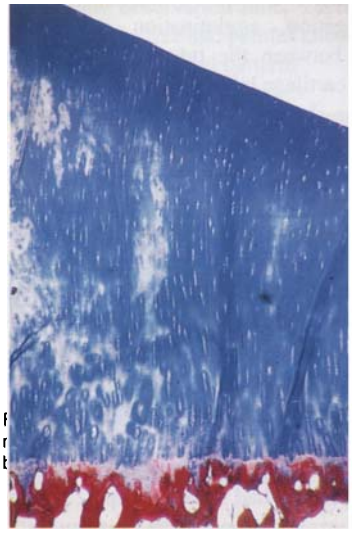
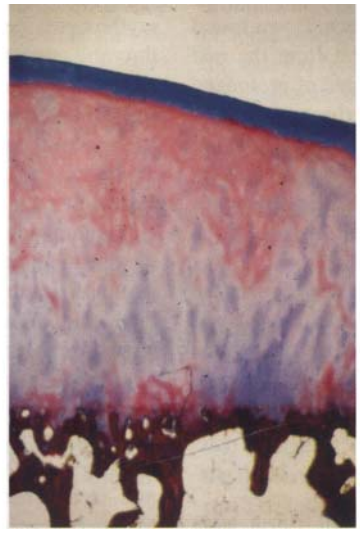


Figure 75. Osteochondral junction from painful patella. Reduplicated tidemark. Vessels in basal cartilage layer, between tidemarks, showing erythrocyte aggregation with transition to fibrin thrombus (red; MSB, x400).





*Safranin-0 stain:* Compared with normal patellae the chondrocytes of PP cartilage and their territorial matrix did not appear affected, where the matrix had kept its normal blue colour (MSB staining). Where this staining showed decolouration, the clusters and pillars of chondrocytes seemed more widely dispersed than under normal circumstances, and in certain areas were scarce. In our material we could not demonstrate the chondrocyte hyperactivity in the basal layer mentioned by Darracott and Vernon–Roberts (1971). Moderate cloning of chondrocytes was observed in a few specimens, but this phenomeon never reached the prominence characteristic of primary arthrosis, rheumatoid arthritis and hemophilic arthropathy (see these sections).

### *Synovium*

*Normal patellae and knee joints.* Biopsies from these specimens showed the same picture as normal synovium in any other normal and painfree joint: 1–2 rows of synoviocytes covering a rather loose stroma, poor in vessels. In all cases, Hoffa's fat pad showed several small and medium-sized normal vessels. In this structure the arteries were of normal thickness and veins and venules contained no erythrocyte agglutinations or fibrin thrombi.

*Gonarthrosis–chondromalacia stage 3.* In this stage the synovium was characterized by an increased number of synoviocytes, 4–6 rows not being unusual. Collections of inflammatory cells were seen occasionally. The stroma was edematous with varying amounts of collagen. Fibrosis could dominate the picture and, generally the synovial membrane was much thicker than normal. Calcium and hemosiderin deposits were not rare, especially in cases where synovial fibrosis was dominant. The most striking change from normal was, however, the greatly increased vascularity and the intravascular blockage by aggregations of erythrocytes, agglutinations and fibrin thrombi, as described in the section on arthrotic and rheumatoid synovitis. This general picture was independent of the location of the biopsy site.

*PP knees–chondromalacia stage 0 – 2.* In all biopsies taken from the parapatellar wall and ditch most of the changes (except hemosiderin deposits) described under arthrosis were present, although mostly in a more modest degree as long as the patellar cartilage surface was intact. In these cases synovial biopsies taken at a distance from the patellar margin all showed normal microscopical structure. In some cases with open chondrosis (stage 2) the outlying biopsies had the same general appearance as described under arthrosis.

### *Hoffa's fat pad*

In 2 of 5 patellae (chondromalacia stage 0–2) removed by patellectomy, intravascular stasis and erythrocyte agglutinations were observed. In the other 3 PP specimens the vessels of the fat pad seemed normal, although the synovial membrane covering the structure showed synovitic changes.

## Comments

### *Pressure at rest, intermittent hypertension, pain and chondromalacia*

*Pressure at rest.* In patients with PP and verified chondromalacia, the intraosseous pressure of the patella at rest and with the knee extended is significantly higher than in pain-free controls (Björkström et al. 1980), and Hejgaard and Arnoldi (1984) found in a material with severe PP that those with pain at rest had a higher pressure than those without. The histological observations (Arnoldi 1991) may indicate that this relatively modest, but significant pressure rise may be due to resistance to venous drainage through some of the drainage systems caused by circumscribed parapatellar synovitis. This assumption is partly supported by the phlebographic examinations (Arnoldi 1991). However, this patellar rest pressure rise rarely reached the levels observed in painful arthrosis and non-traumatic femoral head necrosis.

The material comprised cases both with and without chondromalacia. It is of interest that in the material presented by Arnoldi (1991) there was no patellar rest pressure difference between painful knees with or without visible chondromalacia. This fact, in combination with the histological findings suggest that increased intrapatellar pressure is the cause, rather than the effect of the cartilage changes.

*Intermittent patellar hypertension.* Sustained maximal flexion of the knee joint simulating situations that provoke typical pain, is accompanied by a considerable increase in patellar pressure, greater in painful than in control knees. With plateau pressure above a certain level the sustained flexion test becomes positive, i.e. painful, again independently of the presence or absence of demonstrable chondromalacia. Thus, at rest in extension, as well as during maximal sustained knee flexion, the pain felt seems to be dependent on the height of pressure in the patellar bone marrow, but independent of the state of the cartilage, at least as judged by the criteria used for staging of chondromalacia.

The pathomechanism of patellar pain and the development of chondromalacia will be discussed in greater detail below.

# General discussion

## METHODS AND VALIDITY OF RESULTS

### Phlebography

#### *Long bone drainage demonstrated by intraosseous phlebography*

Until recently, most work has been done on the long bones of the lower extremities. Details of the venous system have been demonstrated both by retrograde filling of the nutrient vein and by intraosseous injection of contrast into the marrow cavity of isolated cadaver bones (Klümper 1976). Two results important to this discussion are: firstly, intraosseous injection of dye through a needle inserted into the bone marrow was shown to fill the venous system and not the extravasal spaces; secondly, the intraosseous route produced a filling pattern identical to retrograde filling via the nutrient vein. The minimal dye pooling around the needle tip was also in accordance with the in vivo experience (Figure 7). Klümper also makes the important observation that the venous pattern can vary considerably in the same bone in different individuals.

The physiological emptying pattern of intramedullary injected radiopaque dye in vivo shows that if injected into the metaphyseal regions, it leaves the bone via larger nutrient veins at the end of the long bones (Figure 7), emptying into the extraosseous deep venous system. These patterns have been described previously and are consistent with other published results (Brookes 1971, Ficat 1985). Sinusoids and other small venous channels are only slightly filled and there is no visible retrograde filling of the central veins of the marrow cavity distal to the site of injection. This drainage pattern results when smaller amounts of contrast material (1–5 mL), are injected over 30–60 sec.

The emptying patterns from different regions of the human diaphysis have been less well studied. Helal (1965) stated a proximal direction of flow in the tibia of a male cadaver. Süsse (1955), however, also working with cadaver material, describes a pattern more closely resembling the short emptying distance to extraosseous and insignificant filling of intraosseous veins found in vivo. Studies of dog femurs showed multiple venous exits, particulary in the metaphyseal areas. It has been claimed that drainage to extraosseous veins of contrast injected into the metaphysis is generally rapid in normal adults though accurate statements are scarce.

According to Arlet et al. (1971) the drainage time for contrast injected into the base of the femoral neck was 5 minutes and Arnoldi et al. (1972), who used the same site, also found it to be less than 6 min. However, in both cases the criterion of "normality" was only the absence of pain and signs of osteoarthrosis in the contralateral hip joint.

#### *Intraosseous angiographic pattern in pathological cases*

The amount of contrast needed to fill the entire intraosseous venous system angiographically in vivo is not known, nor whether it is possible. Klümper (1976) found that 2–20 mL would be needed for the major long cadaveric bones and Brookes and Helal (1968) reported that 5 mL contrast were adequate for displaying the pattern of medullary veins, sinusoids and adjacent deep veins in cadaveric tibiae.

In healthy people, and probably those without pain and arthrosis, dye injected into the metaphyses and epiphyses leaves the bone so rapidly that it is extremely difficult to visualize the intraosseous venous system. Injection of larger amounts of contrast under greater pressure would probably produce the same phlebographical pattern, but must not be performed in vivo as it might prove highly dangerous.

There is, thus, a striking difference between cadaveric and living bone in this respect. While a few mL of radiopaque dye is sufficient to fill the entire venous system of dead bone, it is virtually impossible to fill anything but a very small area around the tip of the cannula in living bone marrow. The prerequisite for more complete filling and, thus, visualization of the intraosseous venous system in vivo appears to be a restriction of the outflow from the bone. In such cases injection of 1 mL of dye into the metaphysis will reveal large parts of the intraosseous venous system including the central diaphyseal veins (Figures 7, 9).

This could mean that what is seen by intraosseous phlebography in patients with painful conditions is the "normal" venous system. If one compares the cadaver angiographies of Klümper with intraosseous phlebographs from patients with painful arthrosis and intraosseous engorgement-pain syndromes the similarities in morphology suggest this as, at least, a possibility.

The suggestion is not invalidated by the report of Philips et al. (1967) which stated that the phlebographic pattern could be normalized after osteotomy. What could have happened is that the drainage from the bone was improved in some way by the osteotomy and

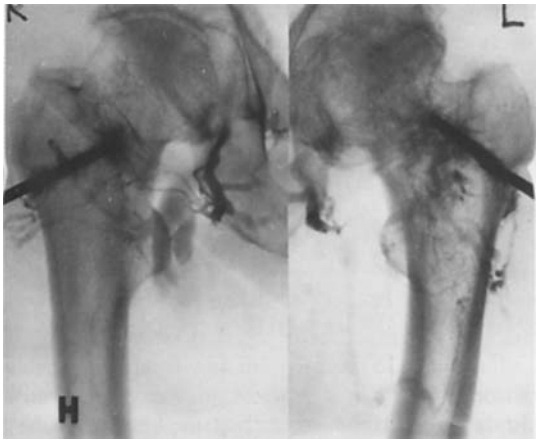


Figure 79. Bilateral simultaneous phlebography in healthy right hip and arthrotic left hip 30 sec after injection of contrast material. Note the differences in size and in calibre of intraosseous veins in the part immediately adjacent to the needle tip (see text).

resistance to outflow decreased. In consequence, the contrast is again drained rapidly and the intramedullary venous system no longer visible. The apparent "normality" of the intraosseous venous system in phlebographs of arthrotic patients compared with Klümpers cadaveric angiograms might also be because our instruments were not sufficiently exact to measure possible differences, the diameters of the larger veins, for example.

A priori it must be assumed that in arthrosis the tissue tension in the non-compliant semi-closed medullary space leaves very little room for venous expansion, in spite of great resistance to flow and increased intraluminar pressure. In one place, however, the difference in vessel calibre between normal bone marrow and that of patients with osteoarthrosis or intraosseous engorgement-pain syndromes is obvious to the naked eye. The calibre of the small vessels around the tip of the cannula is visibly larger in the bone marrow of the disordered joint than in the marrow of the normal side (Figures 7, 79). This constant difference in small vessel calibre is a fairly reliable indication that high resistance to venous flow is accompanied by venous distension as well as intraosseous hypertension.

On the basis of our results and those of many others we conclude that: 1) in normal juxta-articular bone marrow the drainage of intraosseously injected radiopaque dye is always centrifugal and the flow to extraosseous veins is fast (short emptying time); and 2) centripetal filling of intraosseous veins from the injection site is only seen in cases of blockage of venous outflow from bone.

## Intraosseous pressure measurement

Since the first report on intraosseous hypertension in degenerative arthrosis, the interest in measuring intraosseous pressure increased and further reports confirmed the initial results.

Later, our investigations demonstrated that increased pressure is more closely associated with the symptom rest pain than with radiographic arthrotic joint changes (Arnoldi et al. 1975).

Further observations strongly suggested that rest pain, venous distension and intraosseous hypertension are associated with prolonged drainage time of contrast-mixed blood from the medullary space, even in the absence of arthrosis. Finally, intermittent or sustained intraosseous hypertension has been observed in other painful joint disorders, not directly associated with arthrosis (patellar pain syndromes; Arnoldi 1991).

### *Some physiological factors influencing intraosseous pressure values*

In spite of all the work done on this subject during the last three decades, two important points are still not clear: the range of normal pressure in the bone marrow and the limit above which intraosseous hypertension can be said to be present.

Intraosseous pressure measurement in spongious bone by the previously described techniques will cause hematoma in the bone marrow around the tip of the cannula. The pressure within this artificial pool of blood is influenced not only by venous pressure, but also by the arterial pressure in the adjacent intact vessels. This is illustrated by the fact that compression of the supplying artery causes a fall of intraosseous pressure while compression of the draining vein increases the pressure (Arnoldi and Linderholm 1972).

Studies of a number of factors influencing the intraosseous pressure in the calcaneus and the deep veins of the lower leg showed that, with intact arterial supply, the intraosseous pressure is mainly determined by the pressure in the veins draining the bone (Arnoldi and Linderholm 1966, Arnoldi et al. 1972). Furthermore, it was shown that venous pressure and intraosseous pressure are similarly influenced by, for example, muscular exercise and posture (Arnoldi and Linderholm 1966). Therefore, in order to avoid those sources of error emanating from factors that influence venous pressure, intraosseous pressure should be expressed after subtracting the venous pressure measured at the same distance from the level of the heart.

Low intraossous pressure together with non-pulsatile curves can be expected if the arterial supply is interrupted. This was observed in tracings from the femoral

Table 18. Intraosseous pressures (mean, *SD*, range; mmHg) in the tibial and femoral condyles, and venous pressure at the level of the knee joint in 40 healthy humans

| Group | n | $P_{tibia}$ | | | $P_{femur}$ | | | $P_{venous}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total material | 40 | 28 | *15* | (7–71) | 28 | *17* | (3–80) | 9 | *4* | (1–23) |
| Women | 20 | 29 | *15* | (19–71) | 28 | *13* | (9–13) | 9 | *3* | (2–14) |
| Men | 20 | 27 | *16* | (7–71) | 28 | *20* | (3–80) | 9 | *5* | (1–23) |
| Mean age 35 years | 20 | 31 | *14* | (16–71) | 33 | *19* | (13–80) | 10 | *4* | (2–23) |
| Mean age 55 years | 20 | 25 | *16* | (7–71) | 24 | *13* | (3–50) | 8 | *3* | (2–13) |
| Systolic blood pressure > 160 mmHg | 5 | 25 | *12* | (17–44) | 20 | *8* | (9–31) | 6 | *4* | (1–9) |
| Long walking distance before examniation | 11 | 30 | *13* | (14–48) | 27 | *14* | (9–58) | 8 | *3* | (1–10) |
| Short walking distance before examination | 5 | 27 | *13* | (12–49) | 25 | *14* | (6–39) | 8 | *2* | (6–10) |

head in a number of medial fractures of the femoral neck (Arnoldi and Linderholm 1972). High pressure in combination with non-pulsatile tracings is quite common in the femoral head in such cases (Arnoldi and Linderholm 1972), probably due to increased intra-articular pressure caused by bleeding. It is also observed in bone marrow exposed to compression-deformation (Arnoldi 1991), and in the femoral head in non-traumatic necrosis during loading. However, in unloaded joints such a tracing should always be considered an artefact until the whole system has been checked.

### *Normal intraosseous pressure*

This material comprised 40 volunteers randomly selected by computer (Lemperg and Arnoldi 1975). All had clinically normal and painless knee joints. Half had a mean age of 35, the other 55 years. Intraosseous pressure was measured in the metaphyses of the proximal tibia and distal femur, and venous pressure at the level of the knee joint. The measurements were made in local anesthesia on ambulatory patients after 30 minutes rest.

The distribution of intraosseous pressures corrected for the individual venous pressures in the tibia and femur is shown in Table 18. The highest value for intraosseous pressure around the knee in volunteers without pain seems to be 40 mmHg above the venous pressure. The same conclusion can be reached, when pressure values from subjects, with and without painful conditions in the knee joints, are plotted diagrammatically. This was further extended by measuring, at an interval of approximately 30 min, the pressures in both tibiae of 11 normal people. No significant difference between right and left was found, but there was a trend towards somewhat lower values in the second measured leg. In a further 10 normal women, the intraosseous pressures in both legs (femur and tibia) were measured before and after 24 hours bed rest. No significant differences were found, although the values after bed rest were lower. Before rest the mean pressure in tibia was 30 ± 17 (14–71) mmHg; after rest 26 ± 14 (13–61) mmHg.

These measurements from normal pain-free joints are interesting when they are compared with findings from patients. Pressure measurements from two groups with arthrotic hip joints were compared to examine the effect of prolonged bed rest, an age-old therapy for severe rest pain, on intraosseous pressure (Arnoldi and Reimann 1979). The groups were comparable in age and gender, as well as severity of clinical signs and symptoms. One group (31 patients) was examined within 24 hours of admission, the second (38 patients) after 8–22 days in the hospital, where a large part of the time had been in bed. Figure 80 indicates that the degree of activity prior to examination may influence the pressure values obtained.

### *Summary*

The various published reports of intraosseous pressure measurements from juxtachondral bone marrow in nor-

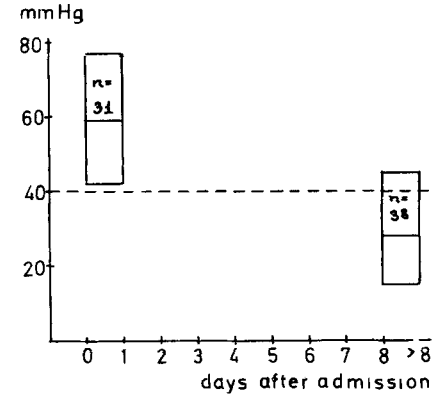



Figure 80. Intraosseous pressures from the femoral neck from patients with arthrosis and a history of severe aching rest pains. Data from 69 hips. Pressure in mmHg, mean and range. 31 hips examined within 24h after the patients were admitted to hospital; 38 examined after 8–22 days bed rest.

mal or non-arthrotic joints seem largely to agree. It must be remembered that these pressures are not strictly comparable for the reasons mentioned previously. However, they give an estimate of the pressure in bone marrow adjacent to painless joints without major arthrosis.

It is difficult to set an upper limit for normal pressure and thus obtain a clear definition of intraosseous hypertension in the unloaded and immobile joint.

### *Pressure and rest pain*

High intraosseous pressure at rest seems to be more closely associated with the symptom of rest pain than with the presence or absence of signs of arthrosis. Attempts have been made to set border values above which rest pain is more frequently present. Arnoldi et al. (1972) suggested 40 mmHg and Lynch (1974) 50 mmHg. However, according to later studies (Arnoldi et al. 1971, Lemperg and Arnoldi 1975) it is clear that individual pressure values overlap considerably, in spite of a highly significant difference between the groups with pain and without. This could mean that there exists an individual critical pressure level above which pain is experienced. This assumption is supported by the observations that intraosseous pressure in the femoral head in arthrosis is immediately lowered by intertrochanteric osteotomy (Arnoldi et al. 1971) or fenestration (Arnoldi et al. 1971, Åstrøm 1975, Hietala and Åstrøm 1977) and that there is immediate relief of pain. Thus, relief was constantly accompanied by a reduction of intraosseous pressure, but not necessarily below any identifiable border value at either 40 or 50 mmHg.

### *Conclusion*

In spite of the highly significant difference between groups of normal subjects and groups with arthrosis or the intraosseous engorgement-pain syndromes, and non-traumatic osteonecrosis, a single intraosseous pressure measurement near the immobile unloaded joint does not seem to have much diagnostic value unless it shows a pressure of 40 mmHg or more, above the pressure in the extraosseous vein.

## $^{99m}$Tc-phosphate scintigraphy

The non-specific character of a positive bone scan is well known. Increased uptake is seen as a result of any process that induces an abnormally increased bone metabolism. The results presented in previous chapters were obtained using the same type of isotope, thus allowing comparison, particularly as many of the scintigraphy studies were combined with measurements of intraosseous pressure and blood flow, and some with histological examinations. Some differences observed between the various disorders are attributable to differences in cause, character and duration of local intraosseous hypertension and disturbances of blood flow.

### *$^{99m}$Tc-phosphate scintigraphy of bone with chronic and intermittent intraosseous stasis and hypertension*

Chronic intraosseous engorgement and hypertension leads to pain and degenerative changes of juxtachondral bone and, as long as the pressure rise is moderate, the area of increased uptake of bone-seeking isotopes corresponds to the area of chronically high bone marrow pressure, indicating a significantly increased bone metabolism (intraosseous engorgement-pain syndromes, radiographically silent and manifest arthrosis, the first stages of non-traumatic osteonecrosis). In areas with extremely high pressure and significantly retarded blood flow, the localized lack of isotope uptake (cold-in-hot spots, crescent lesion) indicates severely diminished bone tissue metabolism or bone death (late stages of non-traumatic osteonecrosis).

The slowly developing and modest bone changes observed in the ankle skeleton of patients with chronic venous insufficiency (Arnoldi et al. 1972) are caused by intermittent intraosseous hypertension only present on walking. Although the presence of bony changes is proof of past or present metabolic activity, increased or pathologically decreased uptake of bone-seeking isotopes is the rare exception.

In the patellar pain syndromes (Arnoldi 1991) patellar pressure in the extended knee at rest is higher than in the pain-free knees. While this chronic intrapatellar hypertension is modest, the considerable pressure differences between control and painful knees appeared during periods of sustained maximal knee flexion. The high intraosseous pressure in these disorders is thus largely intermittent and caused by compression-deformation of the patella. Signs of significantly increased intraosseous metabolism (increased isotope uptake) appeared in all forms and at all stages of chondromalacia (Hejgaard and Diemer 1983), but were only constant in the late stages, i.e. at the transition to arthrosis.

Thus, these investigations indicate a close correlation between the gravity and, especially, the constancy of intraosseous drainage derangement, and the degree of increased or decreased bone metabolism. As shown by Christensen (1985), increased metabolic activity in bone, as indicated by isotope scanning, may be anabolic as well as catabolic. Whatever direction it takes, metabolism demands a supply of blood. Isotope scan-

ning is an important method of investigation in degenerative bone disease, but cannot reveal the cause of the microvascular disorder. It must be remembered that the isotopes used are bone-seeking, and the bone scan does not reflect changes in bone marrow soft tissues.

## KNOWN AND SUSPECTED CAUSES OF INCREASED PRESSURE IN JUXTA-CHONDRAL BONE MARROW

All our investigations indicate that increased intraosseous pressure is nearly always due to increased flow resistance in veins draining joint-bearing bone marrow. Intraosseous hypertension may be intermittent, chronic, or a combination of both with chronically high pressure increasing periodically.

Further, these investigations have shown that the cause of abnormally high resistance to venous flow from the bone marrow is to be found proximally to the joint structures, i.e. between the joint and the heart, in the joint, or in the bone marrow (Arnoldi 1990).

### *Supra-articular causes of increased intraosseous pressure*

The results of pathological changes in supra-articular drainage are best known from ankle conditions in those suffering from severe and long-standing venous insufficiency. Such intraosseous hypertension is strictly intermittent. When measured in the horizontal position and at rest, bone marrow pressure is normal (Arnoldi et al. 1972).

### *Articular and intraosseous changes influencing pressure in joint bearing bone*

Figure 81 shows in schematic form the known and suspected factors influencing bone marrow pressure:

1. Intra-articular blockage of veins draining juxta-articular bone.
2. Compression of the draining veins by structural stretching or torsion as they pass through the fibrous capsule.
3. Compression-deformation of closed or semi-closed intraosseous compartments.
4. Intra- or extravascular blockage of venous circulation inside the bone marrow?

### *Intra-articular blockage (compression and/or obstruction) of veins draining juxta-articular bone*

Anatomical studies and measurements of venous pressure have shown that in arthrosis the extracapsular veins in the hip and knee regions are normal with normal pressure (Arnoldi and Reimann 1979, Ficat and Arlet 1980). The hindrance to venous drainage must, therefore, be sought deep to, or in, the fibrous capsule of the joint.

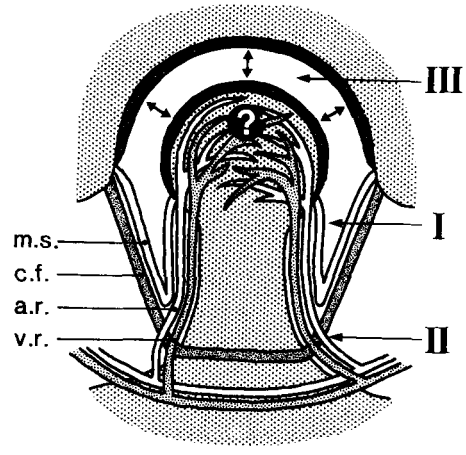



Figure 81. Schematic representation of the relationships between the retinacular vessels and synovial and fibrous capsules of the hip joint. m.s. synovial membrane, c.f. fibrous capsule, a.r. retinacular artery, and v.r. retinacular vein. Roman numerals and question-mark refer to the known and suspected causes of vascular disturbances in the synovium and femoral head bone marrow (see text).

Most of the investigations described below were conducted on the joints proximal and distal to the femur. Both joints are characterized by a subsynovial course of arteries, as well as veins, and the most important drainage from the femoral head and neck and from a large part of the femoral condyles is via these subsynovial channels.

Synovitis is a characteristic early manifestation in experimental arthrosis, in the intraosseous engorgement-pain syndromes and in radiographically silent arthrosis, and is also observed in manifest arthrosis, primary as well as secondary. Further, both clinical and experimental studies have shown that the pressure caused by hemarthrosis may increase the intraosseous pressure and diminish the pulsatile excursions in the bone marrow of the femoral head in cases of intracapsular fractures of the femoral neck, and that aspiration of the hemarthron lowers the intracapital pressure and increases the pulsatile excursions on the pressure tracings.

Thus, increased intra-articular volume gives rise to increased intra-articular pressure, the rise in pressure depending on the degree of volume increase and the strength of the fibrous capsule and its resistance to

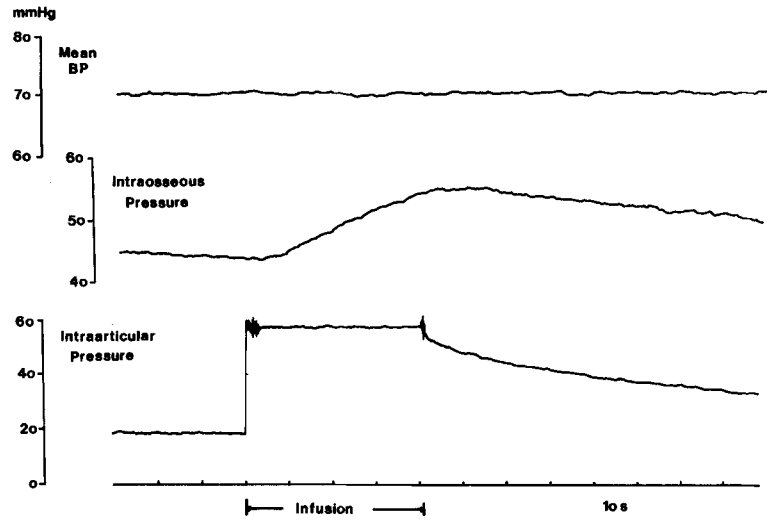



Figure 82. Tracing of intraosseous pressure increase induced by joint infusion of saline. Simultaneous pressure curves from a single experiment on rabbit knee.

stretching (Eyring and Murray 1964). In addition to compression by extravascular forces, our histological examinations showed that intravascular blockage by erythrocyte agglutinations and fibrin thrombi is extremely common in the vessels, mostly venules, of arthrotic as well as rheumatoid arthritic synovium, increasing the resistance to venous flow still further.

### *Experimental tests*

The possibility that intra-articular effusion may influence the pressure in juxta-chondral bone marrow was tested in experiments on rabbits (Arnoldi et al. 1979). In the rabbit knee the femoral condyles are ensheathed by large synovial joint recesses, and the vessels supplying and draining this region have the same subsynovial course as those in human hip and knee joints.

*Material and methods.* Five adult rabbits were used. Experiments were performed under intravenous Mabumal anesthesia. Blood pressure, intra-articular pressure of the knee joint and intraosseous pressure of the lateral femoral condyle were measured simultaneously (Figure 82).

Blood pressure was measured through an 0.6 mm butterfly cannula in an ear artery. Intraosseous pressure was recorded via a 1.5 mm aspiration cannula drilled from the medial side, above the insertion of the medial collateral ligament on the femur, in a distal and lateral direction until the tip reached the lateral femoral condyle. Before connection to the measuring system the cannula was flushed with heparine-saline. The intra-articular pressure of the knee joint was measured via a 0.6 mm butterfly cannula. An image intensifier and an infusion of isotonic Amipaque (Nyegaard & Co., Oslo, Norway) were used to check that the cannula was in the joint cavity. The cannulae were connected to the pressure recording system (Hansen HB 66 manometers, Simonsen & Weel, Albertslund, Denmark) by means of manometer lines (Portex, Hythe, England) and 3-way stop-cocks. For pressure recording, an Ultralette 5671 (Atlas Copco, Bromma, Sweden) was used.

Seven knees were investigated and 30 experiments performed. At five different values of intra-articular pressure, from a few mmHg to above the blood pressure level, corresponding intraosseous pressures were recorded simultanously. Infusion of isotonic saline into the joint was via the measuring cannula via the 3-way stop-cock. During infusion, pressure recorded was determined by the infusion pressure head. After infusion the intra-articular pressure was measured by turning the cock.

*Results.* A rise of intra-articular pressure resulted in a significant pressure rise in the juxta-articular bone marrow ($p < 0.001$). The rise in intraosseous pressure diminished as the level of systemic blood pressure was approached, and a rise above this level did not result in a further rise of bone marrow pressure (Figure 82). The rapid rise of intra-articular pressure induced by infusion of saline is followed by a much slower rise of intraosseous pressure. Lowering of the pressure in the joint was followed by a slower reduction of bone marrow pressure.

*Comments.* Pressure in the marrow of joint-bearing bone is clearly influenced by that in the joint cavity. These experimental results have been subsequently confirmed by other authors (Bünger et al. 1981, 1982, 1983. Lucht et al. 1981). The increase in intraosseous

Table 19. Distribution of pressure differences (mmHg) between points of measurement in femoral head and neck ($P_{caput} - P_{collum}$) in 25 patients with trochanteric fractures and in 36 patients with medial adduction (varus) fractures and pulsatile caput tracings. Number of cases

| Pressure difference | Trochanteric fractures | Cervical fractures |
|---|---|---|
| −20 to −10 | 2 | |
| −10 to 0 | 6 | |
| 0–10 | 12 | 16 |
| 10–20 | 5 | 7 |
| 20–30 | | 3 |
| 30–40 | | 3 |
| 40–50 | | 4 |
| 50–60 | | 1 |
| 60–70 | | 1 |
| 70–80 | | 1 |
| Total | 25 | 36 |

pressure when joint pressure is elevated is probably due to compression of the veins draining the bone marrow. This contention is supported by the observation that an abrupt rise of joint pressure is followed by a gradual increase of intraosseous pressure. This indicates a gradual filling of the semi-closed intraosseous space by initially unimpeded arterial inflow. The maximum intraosseous pressures observed in this study reached a level somewhat below the mean systemic blood pressure. These results correspond to the highest intraosseous pressures observed at rest in painful arthrosis, intraosseous engorgement-pain syndromes and other disorders with synovitic effusion. They also show that the mechanism indicated as "I" in Figure 81 could be a reasonable explanation of the chronic intraosseous stasis and hypertension in these disorders.

### *Clinical observations in fractures of the femoral neck. Joint tamponade by hemarthrosis and synovitis*

In fractures of the femoral neck, hip joint tamponade by blood was suggested as a contributary etiological mechanism in post-traumatic osteonecrosis of the femoral head by Soto-Hall et al. (1964), and the mechanism has been confirmed in animal studies. Strömquist et al. (1988) have reported intracapsular pressures in undisplaced fractures (presumably with intact fibrous capsules) of the femoral neck well above the diastolic systemic blood pressure.

Computer tomography has proved valuable in diagnosing hip joint effusion (Eglund et al. 1986, Wingstrand et al. 1986). Eglund et al. (1988) performed computer tomography in 34 femoral neck fractures 1–32 days after internal fixation. All except one showed an increased distance between the femoral neck and the anterior aspect of the joint capsule compared with the intact side, indicating varying degrees of hip joint hemarthrosis and/or synovitis. Hip joint aspiration in 11 patients revealed increased intracapsular pressure varying between 10 and 112 mmHg, and volumes of aspirated fluid up to 23 mL. The authors conclude that the increased intracapsular pressure may contribute to decreased femoral head vitality.

These investigations indicate that in medial (intracapsular) fractures of the femoral neck joint tamponade by hemarthrosis often stops the flow through the subsynovial veins. This may also explain the high pressures in the femoral head found in many of Arnoldi and Linderholm's cases (1972; Table 19). Sustained increase of intracapsular pressure at levels no higher than 40 mmHg can produce hypoxia and ischemic changes in the femoral head of the rabbit (Swiontkowski et al. 1986, Vegter and Lubsen 1987, Svalastoga et al. 1989). Recently, Kristensen et al. (1989) showed restoration of blood flow after aspiration of hemarthrosis in undisplaced fractures, and Harper et al. (1991) that aspiration of the hip joint in intracapsular fractures produced a significant decrease in intraosseous pressure and an increase in pulse pressure within the femoral head.

## Compression of draining veins during their transcapsular course

Joint effusion, as seen in various type of synovitis or hemarthrosis is accompanied by a rise of intra-articular pressure. In rheumatoid arthritis of the knee joint the intra-articular pressure is least in the mildly flexed position, and further flexion produces extremely high intra-articular pressure (Eyring and Murray 1964, Jayson and Dixon 1970). In most hip joints the first signs of synovitis is pain provoked or accentuated by inward rotation. Thus, in both knee and hip joints, movement that reduces the capacity of the joint cavity results in pain if the joints are the seats of effusion. One of the components of this mechanism may be the compression of subsynovial drainage veins as discussed above and illustrated in the rabbit experiments. To determine whether capsular stretching and/or torsion in joints without effusion may influence the pressure in juxta-articular bone marrow, experiments were conducted on normal fetlock joints in horses (Arnoldi et al. 1980).

*Material and methods.* Six adult horses were used for experiments performed under Halothane anesthesia. Blood pressure, intra-articular pressure of the meta-

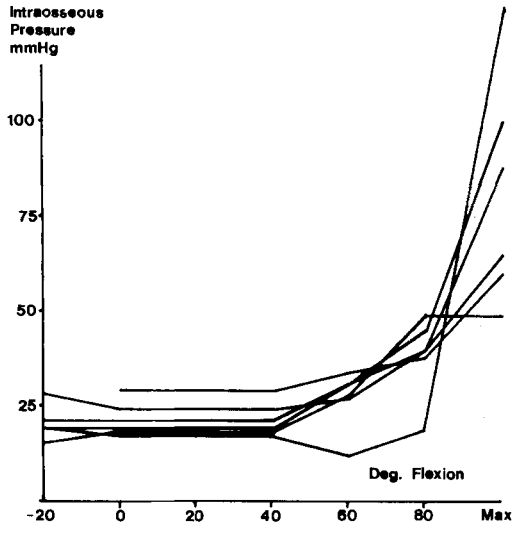



Figure 83. Experiments on horses. Diagram showing the relationship between degree of flexion and intraosseous pressure in juxta-articular bone marrow in the six fetlock joints examined.

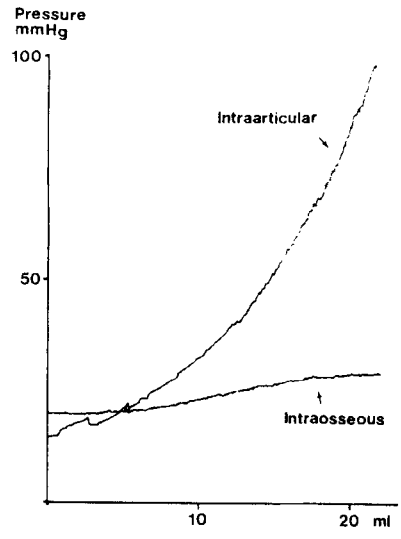



Figure 84. Tracings from a single experiment with simultaneously recorded intra-articular pressure, intraosseous pressure and volume of injected saline in mL. The rate of infusion was 10 mL/min.

carpo-phalangeal joint of the foreleg (fetlock joint) and intraosseous pressure of the juxta-articular bone marrow of the metacarpal bone, were measured simultaneously.

*Experimental procedures.* Blood pressure was measured continuously through a venflon cannula in an artery of the hindleg. The intra-articular pressure of the fetlock joint was measured through a 1.2 mm cannula. An image intensifier and an infusion of isotonic Amipaque were used to check that the cannula was in the joint cavity. In three of the experiments a second cannula was placed in the joint and connected to a perfusor pump to record the simultaneously injected volume of saline. The rate of infusion was 10 mL/min.

Radiographs of the joints were all normal and no pathological symptoms were observed. In the standing position the fetlock joint in the horse is loaded in slight hyperextension.

*Investigations.* 1) Corresponding intraosseous pressures were recorded at different degrees of flexion (from hyperextension to maximal flexion, i.e. approximately 10 degrees above the right-angle position).

2) Corresponding intraosseous pressures were recorded simultaneously for different values of intra-articular pressure obtained by infusion of saline.

3) In three of the six joints the volume of injected saline, the intra-articular pressure and the intraosseous pressure were recorded simultaneously in relation to the rate of infusion.

***Results.*** *Correlation between joint position and intraosseous pressure.* Figure 83 shows intraosseous pressures at different degrees of flexion in six joints without infusion of saline. There was a rise in intraosseous pressure with flexion beyond 40°. At 60° of flexion the rise was significant ($p < 0.05$) and from 60°–80°, the rise was highly significant ($p < 0.01$). Intraosseous pressure approached systemic blood pressure, but was rarely above this level.

*Correlation between intra-articular and intraosseous pressure.* Increasing intra-articular pressure, with saline infusion, was always followed by increasing intraosseous pressure. The values were positively correlated at 0.5077 (Spearmann coefficient) and $p < 0.05$.

*Correlation to the volume of saline injected.* An almost immediate rise in intra-articular pressure was recorded with the saline infusion, followed by a much slower rise in intraosseous pressure after 1 minute, corresponding to 10 mL saline (Figure 84).

*Comments.* The equine fetlock, like the human hip and knee and rabbit knee joints, has large synovial recesses covering the entry and exit of the vessels to and from juxta-chondral bone marrow.The equine experiments confirmed the results in rabbits: increased intra-articular volume and pressure cause a rise in pressure in adjacent bone marrow, probably by compression of the subsynovial draining veins. It was interesting to note the very small amount of saline it took to increase joint, as well as bone-marrow, pressure.

However, in this context the most interesting result was the effect on intraosseous pressure of joint movement per se. One reasonable explanation for the steep rise in pressure on flexion beyond a certain degree is strangulation of the draining veins during their transcapsular course, as suggested in Figure 81 (II).

### Observations on human joints

*Capsular stretching or torsion – venous and arterial compression.* The experiments performed with forceful inward rotation of the arthrotic hip joints with deformed or displaced femoral heads showed characteristic changes of pressure. Following a brief but significant increase the pressure fell to a level below that recorded before the manoeuvre, and during this phase the pressure might reach a very low level.At the same time the pulse amplitudes were reduced but never disappeared completely.

These changes could be a result of increased tension in the fibrous joint capsule. The thin-walled veins with low intraluminar pressure are compressed, causing the brief intraosseous pressure increase. As the tension in the capsule increases, the thick-walled arteries passing though the capsule are also partly compressed, resulting in reduction of arterial pressure and pulse amplitude, as well as intraosseous flow. At cessation of capsular stretching the intraosseous pressure, pulse amplitude and flow rapidly return to the initial levels.

## Compression – deformation

This occurs when a joint is under load, and pressure variations have been studied in both the femoral head (part of a tubular bone) and in the patella, a short bone (Arnoldi 1991).

### Tubular bone

*Normal femoral head.* Femoral head pressure was measured for series of brief periods of loading in anesthetized supine patients. Loading the joint was accompanied by a steep but moderate rise of pressure and an increase of flow rate. The pressure rise was dependent upon the loading force applied. Unloading was followed by a steep drop in pressure below the initial stable level which, however, re-established itself almost immediately.

*Arthrotic femoral head.* In the femoral heads from arthrotic joints the level of loading pressure also seemed to be dependent on the rest pressure level, the degree of deformation and displacement of the femoral head, and the site of measurement: high rest pressure induced high loading pressures and these pressures were higher in the immediate subchondral zone than in the centre of the femoral neck. All pressure tracings from these experiments were pulsatile. With displacement and deformation of the femoral head, the pressure tracings during loading were often similar to those recorded during inward rotation, indicating an increase in capsular tension (see above).

*The femoral head in non-traumatic femoral head necrosis.* Pressure rises during loading depended upon the force applied, and as the resting level was much higher than in normal joints and considerably higher than in arthrosis, the loading-pressure peaks reached values that were higher than in normal and arthrotic joints. At these high levels the pressure tracings could become apulsatile. It should be noted that the forces applied during the experiments (maximum 50–55 kp) fell far short of the forces assumed to develop during ordinary standing or walking. No measurements have been made of conscious subjects during normal activity.

### Short bone compared with tubular bone

*Pressure differences between the patella and the femoral and tibial condyles.* While loading pressures measured in the femoral head were characterized by pulsatile pressure tracings and, with the forces applied, relatively modest pressure increases, measurements from the patella during loading in flexion showed somewhat different results.

In these experiments pressures were recorded simultaneously in the patella and the femoral and tibial condyles (Arnoldi 1991). The measurements were made on pain-free knees and those with patellar pain (PP) syndromes. The measurements generally showed a somewhat higher pressure in the patella than in the femur and tibia in both pain-free controls and in PP knees. Loading during sustained knee flexion accentuated these pressure differences. In pain-free as well as PP knees the peak pressures in the patella during flexion reached values far exceeding 100 mmHg. In PP knees the patellar pressure remained at a level near the diastolic blood pressure during sustained flexion, and the patellar pressure tracings were non-pulsatile. The pressure rises in the femoral and tibial condyles were mostly modest and the pressure curves were always pulsatile.

The results of the various experiments and manoeuvres performed during the investigations, together with the histological findings, indicate that the differences in pressure variations between the patella and the femoral and tibial condyles are due mainly to the following circumstances: 1) difference in bone structure; and 2) different conditions for venous drainage in the three areas of measurement.

### *Anatomy and conditions for venous drainage*

The patella belongs to the group of short bones. It consists of a densely woven cancellous network surrounded on all sides by a solid, but still elastic cortical shell and, in the age group with which we are concerned in PP syndromes, it is highly vascularized. In contrast, the femoral and tibial condyles are parts of tubular bones and their cancellous bone marrow merges into loosely structured diaphyseal bone marrow extending far beyond the knee region and the points of measurement used in our studies. The anatomical structure of tubular bone ensures that an increase in intramedullary pressure, provoked by bone compression and deformation, may disperse over a large area, from the marrow of the condyles upwards through the femur and distally through the tibia. In the closed marrow of the patella this pressure dispersion is negligible. Release of intraosseous pressure is only possible through drainage to extraosseous veins not, as in the two other areas of measurements, through both intra- and extraosseous drainage channels.

## Intravascular blockage of venous circulation inside the bone marrow

The first stages of non-traumatic necrosis of the femoral head are characterized by high pressure in the bone marrow of the femoral head yielding pulsatile pressure tracings. Intraosseous phlebography shows impeded venous drainage and intraosseous stasis, and there is increased uptake of bone-seeking isotopes. In these early stages of necrosis, as in arthrosis, the pressure is higher in the subchondral area than in the trochanter. In the later stages, the pressure tracings from the necrotic area are also pulsatile, although with reduced amplitudes, but the flow is exceedingly slow. The pressure remains high. At all stages, the pressure in the remaining non-necrotic area seems to react to rotation and loading in the same way as in arthrosis. The cause of the intraosseous vascular disorder is but imperfectly known, but it seems that the large number of blocked veins and venules in the Haversian canals as well as in the invasive tissues of the bone marrow, may very well constitute a serious hindrance to drainage flow through venules and veins. (See discussion of non-traumatic femoral head necrosis).

*Comment.* An attempt has been made to isolate some of the factors that appear to influence intraosseous pressure (and flow) in joint-bearing bone by raising the resistance to venous drainage. However, the only pathological factor that is wholely independent in this respect is supra-articularly induced intermittent hypertension of chronic venous insufficiency. The other articular and intraosseous blocking mechanisms are apparently interdependent and occur in various degrees during the activities that produce symptoms in affected joints, and they all seem to play a role in the pathogenesis of pain and degenerative changes of the various disorders examined here.

## CHANGES IN CAPILLARY FLOW—EDEMA

The studies above indicate that extravascular compression or intravascular blockage of the veins draining juxtachondral bone marrow may play an important role in the pathomechanism of the degenerative changes observed in these joint disorders.

Ultimately, the basic pathophysiology is concerned with changes in conditions of capillary flow and their effects on cellular environment. Under normal conditions the capillary membrane is permeable to such hydrophilic solutes as ions, but to a lesser degree to colloid solutes, e.g. plasma proteins. According to Starling the transfer of water, electrolytes and other substances between plasma and interstitial fluid is controlled by the relative hydrostatic and osmotic pressure gradients between the two compartments. Water, electrolytes and non-electrolytes are filtered through the capillary membrane at the arteriolar end of the capillary by hydrostatic pressure. A certain protein osmotic effect is present in the interstitial fluid.

The effective hydrostatic and osmotic pressure are, respectively, higher and lower at the arteriolar end of the capillary than at the venous end, and a small fraction of the plasma fluid with its contents leaves the capillary at the arteriolar end and returns to it at the venous end (approx. 1 percent). Thus, interstitial fluid is a plasma ultrafiltrate.

The normal dynamic balance between intracellular and extracellular fluid and plasma, and thus the cellular environment, is primarily dependent upon the capillary membrane function as described above.

### *Immediate cause of localized edema*

The immediate cause of edema is an imbalance between the transudation of water and electrolytes leaving the circulation through the capillary wall into the interstitial fluid and their return to circulation. The factors controlling these processes are: 1) capillary hydrostatic pressure; 2) concentration of serum protein; 3)

concentration of protein in the interstitial fluid; 4) tissue tension; and 5) lymph flow. Change in any of these forces is followed by the establishment of a new balance by the counteraction of the other forces, i.e. edema tends to be self-limiting. With the establishment of a new balance, water and electrolyte exchange may be normal, though the volume of interstitial fluid is increased. It follows, therefore, that this development is only observed in vascularized tissues.

Studies referred to in this book furnish certain information about the local effects of changes in factors 1, 3 and 4 above.

### *Changes in capillary hydrostatic pressure*

The disorders under consideration are all characterized by chronic or intermittent high resistance to local venous drainage, or chronically high resistance intermittently increased.

High resistance to venous flow results in increased hydrostatic pressure at the venous end of the capillary with increased capillary distension. This has a double effect: the increase in capillary blood pressure augments the transudation of water, electrolytes and serum proteins into the interstitial fluid compartment. This serves to decrease the effective osmotic pressure of plasma. Capillary and venule walls become permeable to even very large protein molecules and the permeation will thus increase at edema formation, as observed in synovia of arthrotic joints and the subcutis in chronic venous insufficiency of the lower limb. There are indications that intermittent venous hypertension is especially prone to increase the permeability of large protein molecules (Boersma and van Limborgh 1967), and of such formed elements as red blood corpuscles (Zweifach 1940).

### *Tissue tension*

Burch and Sodeman (1937) defined tissue tension as the pressure with which tissue structures resist changes in their anatomical relations. Such pressure varies considerably from tissue to tissue. Thus, subcutaneous is always lower than intramuscular tissue tension in the lower leg, and among these muscles those with a tight fascia show a higher tissue tension than those with loose fascial coverings, both at rest and during muscle contraction (Wells et al. 1938). Apart from the structure of the muscle fascia, muscular tissue tension was found to depend on the amount of extravascular fluid present in muscle, and the degree of filling of its blood vessels. Apart from measurements of intraosseous pressure, no measurements of tissue tension in bone and cartilage seem to have been made. Cartilage has a low compliance and its tissue tension must be considerably higher than tension in subcutaneous and muscular tissues at even small increases in tissue volume.

### *Influence of tissue tension on blood flow*

Edema increases tissue tension and it is generally agreed that such increased pressure tends to reduce blood flow, either due to arteriolar closure at high extravascular pressure (Burton and Yamada 1951), or to a reduction of local arteriovenous pressure difference and, hence, blood flow, as local venous pressure increases equal to the rise in the surrounding tissue pressure (Ryder et al. 1944).

In studies of patellar pressure under various experimental conditions (Arnoldi 1991) it was noted that in this limited and non-compliant bone marrow space, increasing intraosseous pressure (tissue tension) affected the pulsatile excursions on the pressure tracings from the marrow. Under the circumstances of the experiments, an increase of intraosseous pressure to 40–60 mmHg enlarged the pulse waves. However, if the pressure increased further the tracings became non-pulsatile. In the arthrotic femoral head we found significantly higher pressures and pulse excursions immediately below the cartilage than in the femoral neck, but never apulsatile pressure tracings.

Nielsen (1984), in experiments on soft tissue arteries of the lower limb, observed that pre-capillary vessels collapsed with cessation of blood flow when the (effective) diastolic transmural arterial pressure was reduced to zero, and Sejrsen (1990) states: "When the tissue pressure reaches values corresponding to diastolic arterial pressure, the arterioles will be compressed during diastole. Under these circumstances the arterioles present a very high resistance to flow and they will not be refilled during systole. The result is a cessation of blood flow."

It is entirely possible that the mechanism described above (intact arterial channels in combination with very extensive, but periodical obstruction of the drainage system combined with high tissue tension) is responsible for the intermittent high pulseless pressure observed in the patella during sustained maximal flexion, particularly in patients with patellar pain syndromes (compression deformation in combination with partial drainage blockage). The same mechanism may equally produce the occasional high peaks of pulseless pressure seen during some joint manoeuvres in non-traumatic femoral head necrosis—intraosseous intravascular venous blockage, capsular strangulation of extraosseous veins by torsion, supplemented by intra-articular venous blockage during the arthrotic end stages.

In these cases of extreme venous flow resistance and high tissue tension, the effect on capillary flow may be

very similar to that of interrupted or severely reduced arterial supply.

The structure of the bone seems to be another important factor governing the level of intraosseous pressure. Thus, compression of the patella against the femoral condyle raised the intraosseous pressure in the condyle, as well as in the patella. However, owing to non-compliance of the closed patellar marrow space, the pressure rise was always greater there than in the "open" marrow of the femoral condyle, where pulseless tracings were never observed. Opening of the bone marrow (osteotomy or fenestration—core decompression) always significantly reduced the intraosseous pressure in the arthrotic and osteonecrotic femoral head and in the painful patella.

Thus, our results indicate that because of increased tissue tension, decreased effective transmural vessel pressure, and arterio-venous pressure difference, impairment of venous drainage from juxtachondral bone marrow always influences capillary flow. Under certain circumstances tissue tension becomes so high that the flow of blood ceases. Hemoconcentration due to increased osmotic pressure of extravascular proteins and the effects on cellular metabolism of abnormal proteins in the interstitial fluid compartment may also be important in the pathogenesis of degenerative tissue changes. In this connection it should be remembered that synovial fluid is essentially a plasma dialysate.

### *Relationship between bone marrow blood flow and pressure*

Pressure and flow rate were determined in anesthetized supine patients with the hip in the neutral position and during various manoeuvres: loading of the femoral head by compression into the acetabulum; internal and external rotation and flexion. The findings from normal, arthrotic and late-stage non-traumatic osteonecrotic femoral heads can be summarized thus:

*Normal femoral head.* Low intraosseous pressure at rest with relatively rapid blood flow. Very slight pressure increases on all joint manoeuvres, usually accompanied by a marked increase of flow rate.

*Arthrotic femoral heads.* Increased intraosseous pressure at rest with relatively slow flow. Marked, and occasionally very considerable, pressure increases on joint manoeuvres, accompanied by a slight reduction in flow rate.

*Late-stage osteonecrotic femoral heads.* High intraosseous pressure at rest in the trochanteric area, and very high pressures in the rim zone of the sequester and inside the sequester. Low flow rate in the trochanteric area and very low inside the sequester. Relatively high flow rate at the rim zone.

We interpret the low pressure at rest, moderate pressure rises but high flow rates during joint manoeuvres as signs of free drainage (intra- and extraosseous) from the normal femoral head marrow. Conversely, the high pressure and slow flow at rest and the marked pressure increases during loading and joint movements, combined with a regular, although modest decrease in flow, indicate impairment of intra- and extraosseous venous drainage in both arthrotic joints and joints with non-traumatic osteonecrosis.

## DIFFERENCES AND SIMILARITIES BETWEEN ARTHROSIS AND NON-TRAUMATIC OSTEONECROSIS OF THE FEMORAL HEAD

Until the appearance of the work by Harrison et al. (1953) it was generally accepted that arthrosis is caused by a deficiency of arterial supply to the femoral head. By now, this concept has few supporters. Non-traumatic femoral head necrosis is, however, generally accepted as an avascular necrosis, implying that the localised bone-tissue death is due to interruption of arterial inflow to the affected bone marrow area.

The results of the investigations mentioned here, together with observations made by many other authors, make it natural to re-examine and discuss the evidence regarding the cause(s) of osteocyte death, the replacement of bone by other mesenchymal tissues, and the progression to secondary arthrosis.

### *Interruption of arterial supply versus blocking of venous drainage*

It is a truism that total interruption of arterial supply to an organ, or part of an organ, leads to infarction (total death due to anoxemia of the tissues involved). Examples are legio. It is, however, also a common observation that cessation of arterial flow is accompanied by lowered tissue tension, in this case lowered pressure in the affected bone marrow, and the pulsatile excursions on the pressure tracings disappear (Arnoldi and Linderholm 1972). On the other hand, with intact arterial inflow blockage of venous outflow will raise the tissue tension in the area affected, and, as reported from many of the experiments cited above, the pulsatile excursions on pressure tracings tend to increase, at least as long as the rise of intraosseous tissue tension does not exceed the local diastolic arteriole pressure.

All published works report increased and pulsatile pressure in the femoral head bone marrow in intraosseous engorgement-pain syndromes, radiographically silent and manifest arthrosis, the early and late stages of non-traumatic osteonecrosis, and also in the late secondary arthrosis of rheumatoid disease (unpublished data), and both pressure and pulse excursions seem to be highest near the subchondral zone. Moreover, both early and late stages of non-traumatic femoral head necrosis generally display intraosseous pressures considerably higher than early and late stages of arthrosis (Ficat and Arlet 1980, Kiær et al. 1986, Pedersen et al. 1989), and the pressure increases during loading and joint movements are also significantly higher in osteonecrosis.

These findings indicate that blockage of drainage is a common feature in these diseases, and also that the resistance to venous drainage from the bone marrow of the femoral head is greater in non-traumatic osteonecrosis than in both early and late arthrosis. The findings do not, however, indicate interruption of arterial supply to the head.

Intraosseous phlebography shows essentially the same disturbances of outflow of venous blood from the femoral head bone marrow in all these hip disorders.

$^{99m}$Tc-phoshate scintigraphy shows increased uptake in the femoral head in early and late arthrosis, early and late rheumatoid arthritis and early and late osteonecrosis. The cold-in-hot spot and the crescent lesion belong to the late stages. Increased uptake indicates increased metabolism of bone tissue, anabolic or catabolic, and that again requires a supply of blood and oxygen. This seems to be sufficient in all disorders, except in circumscribed areas of late-stage osteonecrosis.

### *The histological evidence*

Death and disintegration of large areas of subchondral bone is common in the late stages of osteonecrosis, but focal and even widespread areas of bone death were also found in advanced arthrosis by Wong et al. (1987) and local areas of osteocyte death have been noted by many authors. Pedersen et al. (1989) found no characteristic histological pattern in the bone marrow differentiating arthrosis from osteonecrosis.

In all disorders, from the earliest to the latest stages, bone and bone marrow tissues are replaced by invasions of more primitive mesenchymal tissues, and these areas seem to be larger in osteonecrosis than in arthrosis, as are the areas of avascular disorganized debris. However, histologically, *the character and vascularization of these invasive tissues did not differ in the two disorders.*

### *Histological signs of venous blockage*

In all cases examined—arthrotic, rheumatoid arthritic and osteonecrotic—the synovium showed essentially the same picture of vein and venule dilation with stasis, erythrocyte agglutination and fibrin thrombi of various ages. Early stages of non-traumatic osteonecrosis have not been examined in this way. However, the evidence indicates that synovitis and the vascular changes mentioned are secondary phenomena in osteonecrosis. In the bone marrow the venules and veins of arthrotic and rheumatoid arthritic femoral heads showed the same picture of intravascular blockage, and in both late arthrosis and osteonecrosis this tendency to vessel blockage was prominent in the well-vascularized invasive fibrous tissue. All disorders showed agglutinations and fibrin thrombi in the Haversian vessels. They were even observed in cases of radiographically silent arthrosis. However, Haversian blockage was a much more prominent feature in the late stages of non-traumatic osteonecrosis.

The general impression gained by histological observations is, that in arthrosis and rheumatoid arthritis intravascular blockage is predominantly due to extraosseous causes and the intramedullary blockage is secondary, whereas the vessel blockage in osteonecrosis is primarily intraosseous.

### *Comments on the nature of Haversian blockage*

Whereas the intact endothelium proved that the blockage of veins and venules of soft tissues (synovium, normal bone marrow and invasive primitive tissues) was obviously due to intravascular erythrocyte stasis, erythrocyte agglutinations, or fibrin thrombi, the histological findings presented here indicate that the cause of Haversian blockage may not be quite so easily explained.

In a few cases MSB-staining showed amorphous yellow or red thrombi inside clearly defined Haversian venules, but in the majority the blockage, stained blue, showed no signs of identifiable vascular structures. Further, in many of these cases the blue mass showed typical collagen strands. In fact, in these slides the blockage appeared to be due to fibrous tissue (also stained blue with MSB). The intravascular origin of the blockage which tended to fill the canal space was far from obvious.

If the cause of the blockage is intravascular thrombosis, as seen in soft tissue vessels, the absence of endothelial structures could be due to an early stripping of the vascular lining by e.g. oleic acid from a very early fat embolus, as suggested by Jones (1985; Figure 85), and, from studies on thrombosis of peripheral veins, the

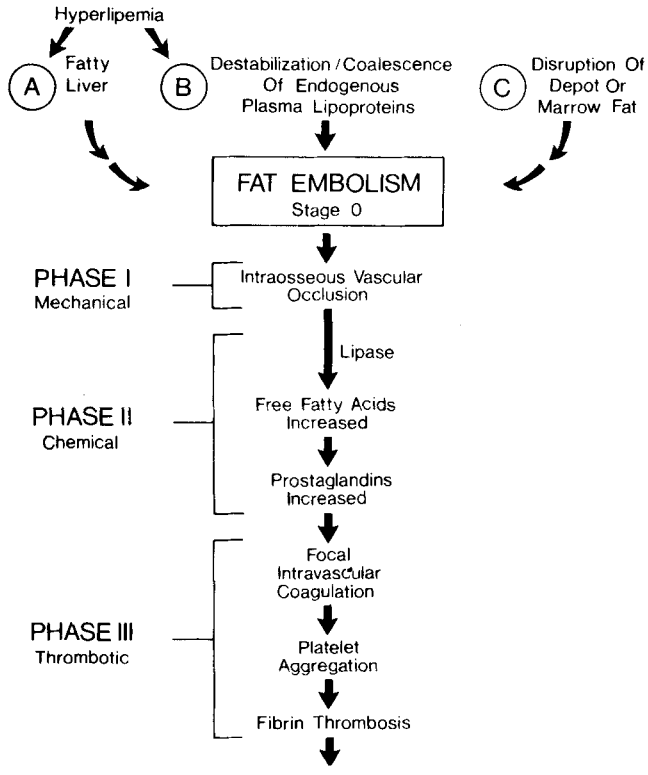



Figure 85. Schematic representation of three mechanisms (A, B and C) capable of producing intraosseous fat embolism and triggering a three-phase process of focal intravascular coagulation resulting in early osteonecrosis (Jones 1985).

transformation of the thrombus into fibrous tissue is a well known observation.

However, the possibility remains that the histologically observed blockage of the canals by fibrous tissue could be a phenomenon parallel to the massive invasions of primitive tissues with low oxygen demands into the bone marrow of the femoral head characteristic of arthrosis as well as non-traumatic femoral head necrosis. For the same reasons, it could also be caused by expansion of the normal extravascular fibrous tissue surrounding the Haversian vessels. If this mechanism is responsible for the histological findings, Haversian blockage would be secondary to vascular changes elsewhere.

Intravascular blockage or extravascular constriction: the fact remains that in the locations where they occur, the osteocytes of the region degenerate or die.

### *Fat embolism as a cause of non-traumatic femoral head necrosis*

The possible association between fat embolism of the subchondral vessels of bone, especially those of the Haversian canals, was suggested by Jones et al. (1965, 1971) and a synthesis of the evidence supporting this concept was published later (Jones 1985).

This hypothesis is based on epidemiological, experimental and clinical research, and as it represents a concept accepted by many students of the disease, it will be summarized here, together with some of the reports with conclusions and observations adverse to the theory. Finally, it will be compared with the observations of our own research.

*Epidemiological studies.* Jacobs (1978) found that 89 percent of 269 patients with non-traumatic femoral head necrosis had concomitant disorders known to be complicated by disturbed fat metabolism.

*Experimental studies.* Fisher et al. (1972), Cruess et al. (1975), Paolaggi (1984), Surat (1984) and Kawai et al. (1985) treated rabbits with corticosteroids and observed hyperlipemia, fatty liver, fat embolism in the vessels of the femoral head and osteocyte death. The observation time varied between 21 and 150 days. Kenzora et al. (1978) confirmed the findings of fatty liver and femoral head fat embolism, but not osteocyte death (observation time 63 and 365 days). Paolaggi (1984) found significant bone marrow necrosis after 3 weeks of corticosteroid medication. Increased intrafemoral head pressure was noted by Wang (1981) with decreased blood flow (Wang et al. 1984) after 6–8 weeks. Jaffe et al. (1972) found fat embolism in the subchondral capillary beds of both the femoral and humeral heads, and Gold et al. (1978) noted a large number of empty lacunae during the second and third weeks, together with an accumulation of necrotic debris within the marrow spaces.

### *From fat embolism to thrombosis*

Figure 85 (Jones 1985) represents his view of the transition from fat embolism to thrombosis in the vessels of the femoral head. Oleic acid, generated by neutral embolic fat, causes a marked stripping of capillary endothelium, passive congestion and edema. It also produces local thrombosis when injected into an isolated vein segment. Platelet aggregation and fibrin deposi-

tion occur in the vicinity of the fat (Sikorski 1983, Sikorski and Bradfield 1983). However, the precise mechanism by which fat produces thrombosis is not known. It has been shown that platelet aggregation and fibrin thrombi are associated with fat emboli (Bradford et al. 1970, Philp 1974) and that intravascular coagulation may be precipitated by endothelial damage and fat embolism.

*Therapeutic experiences based on this theory.* Fat-clearing agents have been tried experimentally to prevent steroid–induced osteonecrosis (Surat 1984, Wang et al. 1983, 1987). So far such agents have not been tried in humans.

### *Opposing views, based mainly on experience with human non-traumatic osteonecrosis*

Glimcher and Kenzora (1979) compared sections of normal femoral heads, arthrotic femoral heads, not involving osteonecrosis, and femoral heads from patients with clear clinical and microscopical osteonecrosis. Using Jones' criteria and staining methods they detected fat "emboli" in the vascular spaces in almost all samples of normal bone. However, the bone adjacent to the presumptive embolus was viable. Also, the capillary endothelial cells in which the fat was located were viable. In their conclusion they find only a negligible role for fat deposits in the pathology of osteonecrosis.

While Jones (1971) could demonstrate deformed fat globules that seemed to be intravascular in the subchondral Haversian canals in necrotic femoral heads from alcoholics, and Fisher and Brickel (1971), Fisher et al. (1972) in patients on high doses of corticosteroids, Solomon (1973) was unconvinced that the fat globules demonstrated in his cases were intravascular, and Catto (1976) and Mulligan et al. (1974) were not able to find them in the osteonecrotic hip and knee, respectively.

### *Own observations*

Our own observations, as described in this book, neither prove nor disprove Jone's hypothesis, as set forth in Figure 85, although we could confirm the findings in "phase III". Our histological observations were performed on late stages of non–traumatic osteonecrosis. Staining by four different lipid-staining methods failed to show intravascular fat globules in the vessels of the Haversian canals or in those of the soft tissues of the femoral head bone marrow. We found, however, a large number of middle-aged and what may have been old fibrin thrombi, also in the Haversian vessels. They may or may not have developed from early fat emboli. However, intravascular fibrin thrombi were also extremely common in the synovium of arthrosis, including the radiographically silent group (early secondary arthrosis) and in the para-patellar synovium of patellar pain syndromes. In PP syndromes Haversian blockage was found, although rarely, in the subchondral bone and the trabeculae. However, it was frequently observed in arthrosis, even in the early stages, and in rheumatoid arthritis, that is cases without signs of non-traumatic osteonecrosis or diseases connected with this disorder.

Our own conclusion is that fat embolism or high lipid contents in the blood could play a role in the very early stages of the disorder, and prepare the ground for the manifest tendency to local thrombosis in non-traumatic femoral head necrosis, but the evidence is far from complete. As yet the ultimate etiology of the hypoxemic state in the affected part of the femoral head remains a mystery.

### *Reaction of bone tissue in arthrosis and osteonecrosis*

The gross morphological differences between arthrosis of the hip joint and the early and late stages of non–traumatic osteonecrosis are easily observed on radiographs and in greater detail by means of MRI (Steinberg et al. 1984). Although the overall picture of non-traumatic osteonecrosis is segmental bone death, histological examinations, isotope and tetracycline labelling have demonstrated reparatory bone processes in the transitional area between the sequestered and normal cancellous bone (Lausten and Christensen 1989, and others). Rebuilding in other areas is rare and is not marked until secondary arthrosis has developed, nor is the acetabulum involved until then.

Conversely, arthrosis is characterized by a mixture of bone destruction and repair. Histological findings of dead bone trabeculae overlaid by new bone formation, growth of osteophytes and a general tendency for the form of the femoral head to adapt to altered mechanical demands, dominate the picture. The acetabulum is involved throughout the pathological process.

## REACTION OF VARIOUS MESENCHYMAL TISSUES TO CHANGES IN BONE MARROW CAPILLARY BLOOD FLOW CONDITIONS

Blockage or retardation of capillary blood flow may be due to interrupted arterial supply or high resistance to

venous drainage. Rösingh and James (1969) demonstrated that complete blockage of arterial inflow to bone results in the death of osteocytes within 8–24 hours. While total blockage of venous drainage has the same effect on capillary flow as a blockage of arterial inflow, in most of the clinical disorders examined here, total venous blockage is of short duration (intermittent venous hypertension). In most conditions the blockage is incomplete, i.e. capillary flow is more or less retarded, but has not entirely ceased. Several authors have stated that a moderately severe reduction of $PO_2$ in bone marrow may induce new bone formation (Harrison et al. 1953, Pistolesi 1962, Abdalla and Harrison 1966, Philips et al. 1967, Arnoldi et al. 1972). Evidence of reduced oxygen tension in juxtachondral bone marrow of arthrotic joints was presented by Brookes and Helal (1968) and Pujol et al. (1973), and, recently, mass spectrometry measurements have confirmed these observations in both arthrosis and non-traumatic femoral head necrosis (Pedersen et al. 1989, Kiær et al. 1986, 1988, Svalastoga 1988).

Hypoxia seems to be a stimulating factor for some mesenchymal tissue activity. Stern et al. (1966) studied the effect of various oxygen tensions on the synthesis and degradation of collagen in bone. With an oxygen content of 10–20 percent in the incubation medium, synthesis exceeded collagen degradation; at 30 percent, both processes increased and at 50 percent were equal. These observations have been severally confirmed. Thus, while anoxia results in tissue death, both experimental and clinical evidence confirm that hypoxia may actually stimulate growth of mesenchymal tissues. However, our histological evidence suggests a considerable difference in the reaction of the various tissues of the juxtachondral bone marrow and the other joint structures.

### *Tissue rivalry in low-oxygen environment*

Arthrosis, rheumatoid arthritis in the late arthrotic stage, and especially the later stages of non-traumatic osteonecrosis were characterized histologically by ingrowth of masses of primitive tissues into the bone marrow. In many cases they seem to have displaced normal soft marrow tissue as well as the bone trabeculae and in those apparently intact, blockage, perhaps by fibrin thrombi in the vessels of the Haversian canals, surrounded by empty cell lacunae, was a common finding, especially in non-traumatic osteonecrosis. The impression gained from these histological studies was dead and dying bone giving place to extremely vital and vascularized primitive fibrous tissues, sometimes transformed into or continuing as broad areas of fibrocartilago.

In non-traumatic osteonecrosis this invasion characteristically took place either from the fovea or from the area just distal to the cartilage border. In the area of a crescent sequester this "lateral" route was especially obvious. As judged by Safranin-0 staining the cartilage of the sequester had generally kept its normal hyaline character, even though the attached rim of bone was dead. However, cartilage on the marrow side of the crack was always fibrocartilago, without tidemark and with a tendency to penetrate far into the bone marrow in conjunction with the even more primitive tissues mentioned above.

The conception of the sequester area as devitalized is thus not entirely correct. Isotope scintigraphy may show the sequester as a cold-in-hot area, but as the isotopes used for diagnostic purpose are bone-seeking, this cold area only indicates a substantial decrease in anabolic and/or catabolic bone metabolism, and does not reflect activity in other tissues.

Revascularization of the sequestered area by vessels in the soft tissue components, and the tendency to clogging of the veins and venules by erythrocyte agglutinations and fibrin thrombi, are probable explanations of the high pressure recorded here and the slow, but pulsatile flow. In the light of experiments by Stern et al. (1966), and the recent findings of low or lowered oxygen tension in the femoral head in these disorders (Kiær et al. 1986, 1988, Svalastoga 1988, Pedersen et al. 1989) the predominance of primitive mesenchymal tissues could be due to their adaptibility to low oxygen tensions in the environment, absent in the more specialized bone marrow cells, including the osteocytes.

### *Conclusion*

The evidence indicates that several etiologies can lead to vascular derangement in juxtachondral bone marrow. These disturbances may be due to arterial inflow difficulties, as is probable in some patients with post-traumatic osteonecrosis of the femoral head. However, in the disorders discussed here, the evidence points to reduced capillary bone marrow blood flow and oxygenation due to impaired venous drainage. The histological examinations have shown essentially the same erythrocyte stasis, agglutinations and fibrin thrombi in the vessels of both normal and invasive primitive bone marrow soft tissues and Haversian canals, from the early stages of radiographically silent arthrosis to the late stages of non-traumatic osteonecrosis. The severity of tissue damage seems to be proportional to the degree of hypoxia in joint-bearing bone marrow and, thus, also dependent upon the location and extension of microcirculatory vessel obstruction.

## CARTILAGE DEGENERATION MORPHOLOGICAL OBSERVATIONS

The experimental and clinical observations described above, in connection with histological findings suggest some conclusions as to the course (and perhaps causes) of cartilage degeneration.

The disorders examined may be divided into three groups:

*Group I.* In experimental arthrosis, intraosseous engorgement-pain syndromes (including radiographically silent arthrosis), arthrosis, rheumatoid arthritis and hemophilic arthropathy, synovitis is a very early feature and may be causative. These disorders have the following features in common: 1) the cartilage disorder is symmetrical, i.e. both opposing cartilage surfaces are involved; 2) the synovial membrane appears to pass through an initial proliferative and productive stage, before it ends up as fibrous and non-productive (the dry joints); 3) especially in the productive phase the chemical composition of the synovial fluid is altered, presumably affecting cartilage components that are dependent on this fluid for normal metabolic activity. The observations from the three disorders selected for examination (arthrosis, rheumatoid arthritis and hemophilic arthropathy) suggest that the severity of changes in the composition of the synovial fluid is proportional to the extent of cartilage damage and to the rapidity of its progress. 4) the histological picture is dominated by degenerative changes, apparently starting from the joint surface, and by conspicuous cloning of chondrocytes; 5) vascularization (and possibly innervation) of cartilage, when present, seems to stem from the vessels in the synovial pannus covering part of the cartilage. Vascularization from the subchondral area is sometimes observed, but rarely; and 6) tidemark is usually single, occasionally absent, but rarely duplicated.

*Group II.* In non-traumatic osteonecrosis macroscopical as well as histological observations indicate 1) an asymmetrical cartilage disorder, i.e. the cartilage lesion is confined to the femoral head, until secondary synovitis has developed. Then the pathomechanism appears to follow the same course as described in Group I; 2) the synovitis seems to be secondary to late stage cartilage breakdown (inclusions; the "Lloyd–Roberts type" of synovitis); 3) the initial cartilage lesions are secondary to degenerative changes in subchondral bone; 4) cartilage vascularisation is rarely seen. Where present it appears to stem from the vessels of primitive invasive tissues in the bone marrow; and 5) cloning of chondrocytes is observed, at least in the late stages. However, compared with the disorders of Group I the clones are extremely modest; 6) tidemark is usually single.

*Group III—basal cartilage degeneration.* This is observed in the patellar pain syndromes (chondromalacia patellae): 1) in this disorder the cartilage lesion is asymmetrical. The femoral cartilage becomes involved only at the last stages, when secondary arthrosis sets in; 2) synovitis is present, but is confined to synovium immediately adjacent to the patellar margin. Generalized synovitis is only observed when secondary arthrosis has developed; 3) vascularisation of cartilage (and possibly innervation) derives from the vessels of the subchondral bone marrow; 4) duplication of tidemark is the rule; as many as 6–7 tidemarks may be present; 5) cloning of chondrocytes is rare and, if present, extremely modest; and 6) at the centre of the cartilage disorders, fibrillation is marked, the chondrocytes are spaced out and, macroscopically, the consistency of the cartilage is edematous.

The development of basal cartilage degeneration is illustrated by Figure 86 (Arnoldi 1991).

Thus, although the end stages of the various disorders discussed here (arthrosis) show many of the same characteristics, they seem to have reached this stage by various routes, i.e., cartilage degeneration may have several causes. Common to all the disorders is weakening of the mechanical properties of the tissue, making it susceptible to destruction by mechanical forces.

## PAIN—RELATION TO INTRAOSSEOUS HYPERTENSION AND VENOUS DISTENTION

Pain is one of the main causes of disability in patients with joint disorders. In fact, pain is the deciding factor for most surgical interventions. Pain is caused by irritation of nocireceptive nervous elements in the joint structures. While hyaline joint cartilage is devoid of such pain receptors, investigations by conventional histological methods, e.g. silver impregnation, have demonstrated nerves in various other joint structures (Kellgren and Samuel 1950, Samuel 1952, Ralston et al. 1960, Kennedy et al. 1982). Although it is generally agreed that fasciae, tendons, ligaments and periosteum are richly supplied with nerves, the results obtained from the synovium have varied. Thus, Harvey (1987) suggested that no pain receptors are present in the synovium, while Kennedy et al. (1982) found this structure

**Figure 86. Basal cartilage degeneration and development of chondromalacia (Arnoldi 1991).** Compare Figures 73 and 76–78.

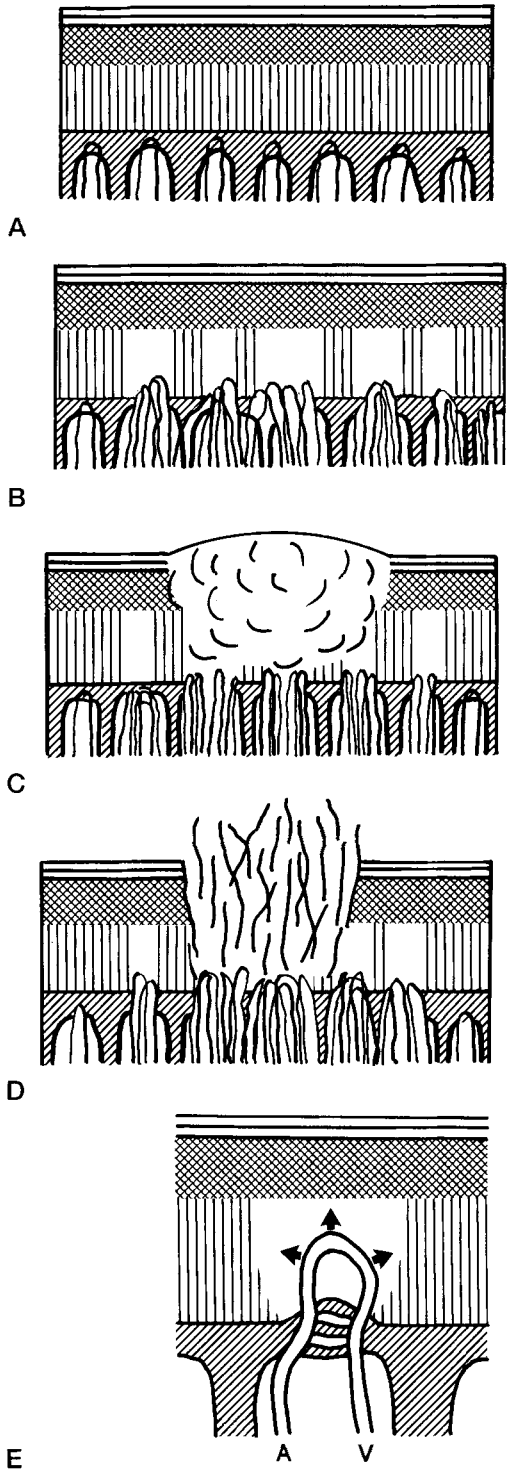
A. Normal stage. The osteochondral bone plate is solid. The relatively few vessels in the area reach the Haversian canals, but do not penetrate into cartilage. The tidemark forms a single layer (Darracott & Vernon-Roberts 1971, Goodfellow et al. 1976, Badalamente and Cherney 1989, own observations).

B. Indicates the osteoporosis of cancellous bone, thinning of the osteochondral bone plate (Darracott and Vernon-Roberts 1971), multiplication of vessels in this region (Badalamente and Cherney 1989), penetration of vessels and nerves into the basal cartilage layer (Darracott and Vernon-Roberts 1971, Badalamente and Cherney 1989, Bridgeman and Brookes 1990, own histological observations) and fasciculation of collagen fibres perpendicular to the joint surface (Goodfellow et al. 1976, Ficat and Hungerford 1977) by matrix edema (own assumption).

C. Expanding edema and changes in matrix and cell quality lead to the circumscribed blister lesion, soft to the touch and probe.

D. The weakened edematous cartilage explodes, due to compressive and shear forces during loaded knee joint movements.

E. The pathological unit. A vessel loop in cartilage during a moment of high resistance to venous flow, e.g. sustained maximal knee flexion. The increased hydrostatic pressure at the venous end of the loop is responsible for edema, and water retention in the matrix is augmented by raised protein osmotic pressure in the interstitial water compartment. The composition of the matrix and chondrocyte environment is probably severely affected and this may well be the fundamental reason for the succeeding cellular degeneration (Arnoldi 1991).




richly innervated. In bone tissue the bone marrow trabeculae and the Haversian canals were reported to contain nerve fibres (Milgram and Robinson 1965, Cooper 1968, Sherman 1963) and in certain pathological states, e.g. arthrosis, the nerves in the bone marrow (femoral head) seem to increase in number (Reimann and Christensen 1977).

Grönblad et al. (1988 a, b) found nerve elements staining with neurofilament antiserum perivascularly in both normal synovium and the synovium from patients with rheumatoid arthritis and arthrosis. Free nerve fibres were also present in these tissues, and some of them stained with antisera to the neuropeptides Substance P (SP) and calcitonin gene-related peptide (CGRP). SP is a sensory transmitter and vasodilator, increases vascular permeability and thus protein extravasation, and stimulates fibroblast proliferation, and CGRP is also a potent vasodilator as well as a sensory transmitter. Levine et al. (1984) suggested that the nervous system, and more specifically the neuropeptide SP, might be involved in the pathophysiology of rheumatoid arthritis. They noted that the joints most affected have the highest concentration of SP, and when SP was infused into these joints the arthritis became more severe. Konttinen et al. (1989) suggest that these neuropeptides may be involved in joint disease, possibly in

both pain and inflammation. The inflammatory effect they attribute to the well-known effects of both SP and CGRP as vasodilators, and on vascular permeability and protein extravasation.

These new observations and suggestions are interesting, both as regards the origin of pain and synovial vascular inflammation. The illustrations given by these authors show the nerve fibres in close contact with the vessel walls. Considering the sometimes extreme vascularisation of the synovial membrane in, e.g. arthrosis (the proliferative stage) and rheumatoid arthritis where most of the vessels are dilated venules, their discoveries suggest a circulus vitiosus starting as in experimental arthritis with traumatic hyperemia, going on to the stasis stages, and perpetuated by the influence of a rising content of vasodilatory neuropeptides.

### *Pain in relation to intraosseous venous distension and hypertension*

Our investigations on patients with non-traumatic osteonecrosis, arthrosis and especially the intraosseous engorgement-pain syndrome indicate that pain at rest is more closely correlated to intraosseous venous stasis and distension than to the height of bone marrow pressure. However, intramedullary hypertension, venous dilation and rest pain are still fairly closely interrelated in most of the degenerative disorders examined.

The connection between pain and venous distension per se is perhaps most convincingly demonstrated by means of phlebography and intravenous pressure measurements in patients with idiopathic dysfunction of the venous pump of the calf or cruralgia orthostatica (Arnoldi 1964, Arnoldi and Linderholm 1969, Arnoldi 1989). In these women the disorder is dominated by severe bursting pain in the calf. The pain is orthostatic, i.e. it is felt when the patient is standing or walking, and disappears after a period of resting with the feet up. Dynamic intraosseous phlebography shows abnormally dilated deep veins of the calf, but with intact valves. The venous pump of the calf functions normally, but with an abnormally large systolic residual blood volume. The contraction pressures during walking are abnormally low, and venous leg ulcers and skeletal changes due to high systolic pressures transmitted to the subcutaneous tissues of the ankle region through incompetent perforating veins, are never seen in these patients.

Thus, in patients with incompetence or dysfunction of the venous pump of the calf it is possible to distinguish quite sharply between the effects of venous hypertension and venous distension. In ambulatory systolic intermittent hypertension of the ankle degenerative changes of mesenchymal tissues dominate (induration, leg ulcers and skeletal changes). In women with cruralgia orthostatica with low systolic ankle vein pressures, degenerative changes are absent, but the abnormal orthostatic deep vein distension is obviously correlated to the pain suffered by these patients.

This typical bursting pain might well be due to activation of pain sensors by vein wall distension. This assumption is strengthened by the fact that any measure that diminishes vein distension (elimination of hydrostatic factor, or application of a compression bandage) also makes the pain disappear.

In arthrosis, non-traumatic osteonecrosis and patellar-pain syndromes it was observed that all the joint manoeuvres that are usually characterised by an increase of pain (loading, flexion, rotation, etc.) were accompanied by a rise in intramedullary pressure above the already high pressure at rest. It is reasonable to assume that these intermittent periods of sharply increased resistance to flow coincide with periods of accentuated distension of veins, venules, sinusoids and capillaries in the joint structures and, as a consequence, by periodically increased activation of sensory transmitters.

In some of the disorders, notably chondromalacia patellae (patellar pain syndromes), arthrosis, rheumatoid arthritis and the late stages of non-traumatic osteonecrosis, the normally avascular and aneural joint cartilage is invaded by vascularized fibrous tissue. This can be either, as in rheumatoid arthritis and hemophilic arthropathy, from the pannus covering the surface facing the joint cavity or, as in arthrosis and particularly chondromalacia, from the tissues of the region of the osteochondral junction. According to Badalamente and Cherney (1989) the invading vessels in the basal layer of the chondromalacial cartilage are accompanied by small myelinated nerves containing Substance P and serotonin. Thus, in many of the disorders dealt with here, the normally aneural and avascular hyaline cartilage may have become innervated as well as partly vascularized.

Finally, when considering the origin of pain, especially in connection with loading and joint movements, it should be remembered that other joint structures, such as the periosteum and synovium, also show an increased number of sensory nerves in arthritic joints.

# Epilogue

In some of the joint disorders dealt with here (hemophilic arthropathy, rheumatoid arthritis) the pathogenesis is more or less clear, whereas in others (arthrosis, non-traumatic osteonecrosis, chondromalacia patellae) it is still obscure. However, since 1953 (Harrison, Schajowicz and Trueta) studies of vascular changes in joint-bearing bone and other joint structures have evoked a steadily increasing understanding of their importance for the pathomechanism of these disorders. It seems as if the mesenchymal tissues of the joints have a very limited range of response to changes in their cellular environment and this is probably why the end stages of the individual diseases and disorders are so similar.

At the moment it appears that whatever the pathogenesis, the primary agent leads to a very early vascular disturbance that, directly or indirectly, exposes the various types of tissue to derangement of their cellular environments. This can be not only a deficient oxygen supply, which is the main theme of this book, but also severe chemical changes, most obvious as regards the non-vascularized cartilage, dependent as it is on the composition of the synovial fluid.

In some diseases, such as hemophilic arthropathy and rheumatoid arthritis, the role of vascular synovitis for joint deterioration has long been accepted. In both diseases the pathological changes in the synovial fluid are so severe that cartilage degeneration follows within a brief period after the synovial involvement. In degenerative arthrosis, however, reversibility seems possible, the changes in synovial fluid are modest compared with the two other disorders, and the development from synovitis to manifest arthrosis takes far longer (often decades). This time factor may have been responsible for the difficulty in accepting the connection.

In the group of joint disorders just mentioned, vascular synovitis can be termed primary. In non-traumatic osteonecrosis and in chondromalacia patellae vascular synovitis is a late phenomenon. It can be termed secondary, but when it appears it seems to have the same deleterious effect on cartilage and is probably responsible for the ultimate joint destruction.

In degenerative arthrosis, one of the more common of these disorders, the rheumatologist or orthopedic surgeon can only wait until the patients pain and joint dysfunction have become unbearable and major surgical intervention defensible. If this disorder is still held to be the inevitable result of age-dependent wear-and-tear, there is not much inducement to further research, except for improved alloplastic devices.

However, the studies cited in this book and dating from many centres give cause for optimism regarding future arrest, or even prevention, of some joint disorders. Hemophilic arthropathy is an example of successful prevention. In Denmark the synovitis of this disease has largely disappeared thanks to efficiently organized factor treatment, and alloplasties for secondary joint degeneration are now rare.

If one is convinced that, within limits, joint use is beneficial to joint health, and that mechanical forces, inherent in all joint functions, will only provoke degeneration of cartilage, if this tissue is already weakened by other processes, then research into these processes becomes interesting and, hopefully, therapeutically rewarding.

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