

ACTA ORTHOPAEDICA SCANDINAVICA
SUPPLEMENTUM NO. 181

From the Department of Orthopaedic Surgery, Rigshospitalet, Copenhagen, Denmark

The Pathomechanism of Human Coxarthrosis

BY

CARL C. ARNOLDI AND INGE REIMANN

MUNKSGAARD . COPENHAGEN

ISBN 87-16-08608-2

ISSN 0300-8827

CONTENTS

ACKNOWLEDGEMENTS	5
INTRODUCTION	6
THE SYNOVIAL MEMBRANE	7
Own Investigations	8
Electron and light microscopic study of the synovial membrane	8
<i>Gross inspection of the synovial membrane in coxarthrosis</i>	8
<i>Light microscopy</i>	8
<i>Electron microscopy</i>	9
Histochemical investigations	9
Discussion	10
THE SYNOVIAL FLUID	11
Own Investigations	11
Protein analysis	11
Discussion	14
VASCULAR CHANGES IN JUXTAARTICULAR BONE MARROW	15
Own Investigations	15
Intraosseous phlebography and measurements of intraosseous pressure	15
<i>Coxarthrosis</i>	15
<i>The intraosseous engorgement-pain syndrome</i>	18
Discussion	20
The cause of intraosseous stasis and hypertension	20
Contracture, joint volume and pain	20

INTERDEPENDENCE BETWEEN INTRAARTICULAR AND INTRAOSSEOUS PRESSURE	21
Own Investigations	21
Discussion	24
CHANGES IN SUBCHONDRAL BONE	24
Own Investigations	24
Quantitative histological analysis of articular cartilage and subchondral bone	26
Histochemical study of alkaline and acid phosphatase activity	26
Distribution of ^{99m}Tc-phosphate compounds in osteoarthritic femoral heads	27
^{99m}Tc-polyphosphate scintigraphy in patients with osteoarthritis, or the intraosseous engorgement-pain syndrome	31
Discussion	33
The conditions for capillary flow in the femoral head in coxarthrosis	33
The effect of reduced nutritive capillary flow on the bone structure of the femoral head	34
Are the vascular changes in subchondral bone marrow an early or late factor in the development of coxarthrosis?	35
ARTICULAR CARTILAGE	35
Own Investigations	36
Differential histochemical staining of glycosaminoglycans in osteoarthritic cartilage	36
Discussion	38
GENERAL DISCUSSION	38
Aetiology and time factor	39
Synovitis and the developments in juxtaarticular bone	40
Synovitis and changes in articular cartilage	41
Other causes of coxarthrosis	41
Correlation of clinical signs and symptoms to the developmental stages of coxarthrosis	41
Future problems	42
REFERENCES	43

ACKNOWLEDGEMENTS

The investigations on which this paper is based were made possible by grants from the Swedish and Danish Medical Research Councils, and economic assistance from the firms Astra-Syntex and Mediscan

Among our many collaborators we are especially indebted to Professor Håkan Linderholm and Professor Rudolf K. Lemperg, both of Umeå, Sweden, Professor Henry Mankin, Boston, USA and to Dr. Steen Bach Christensen and Miss Karen Elisabeth Sønderlev from the Department of Orthopaedic Surgery, Rigshospitalet, Copenhagen.

INTRODUCTION

The pathogenesis of osteoarthritis is still not known. In general the disease is regarded as a result of "degeneration", a wear and tear phenomenon as well as a disorder of advanced age.

Over the years innumerable studies have been concerned with attempts to elucidate this disorder. Most investigators have been engaged in the study of articular cartilage, and alterations in this tissue usually are considered the primary stage of osteoarthritis. Others have entertained the idea that basically osteoarthritis is a vascular disease and that the initial changes are to be found in the subchondral bone. However, the cause of these changes is still obscure. Although general factors may contribute to certain forms of osteoarthritis, it is generally agreed that local factors are of more importance. These may vary from joint to joint.

The present paper deals with the pathomechanism of "primary" osteoarthritis of the hip joint. It has been our intention to analyse the results of a series of investigations on changes in the synovial membrane, the synovial fluid, articular cartilage and the sub- and juxtachondral bone and bone marrow. Our choice of methods depended on the resources of our laboratories, and the subjects of investigation upon a working hypothesis developed during the years 1970-1975 (Fig. 1.). Thus, this work is not intended as a systematic treatise on the pathogenesis of osteoarthritis. Instead, it is first and foremost a synthesis of our findings, a search for internal correlation and an attempt to determine which of the many gaps in our knowledge are of most importance for further studies.

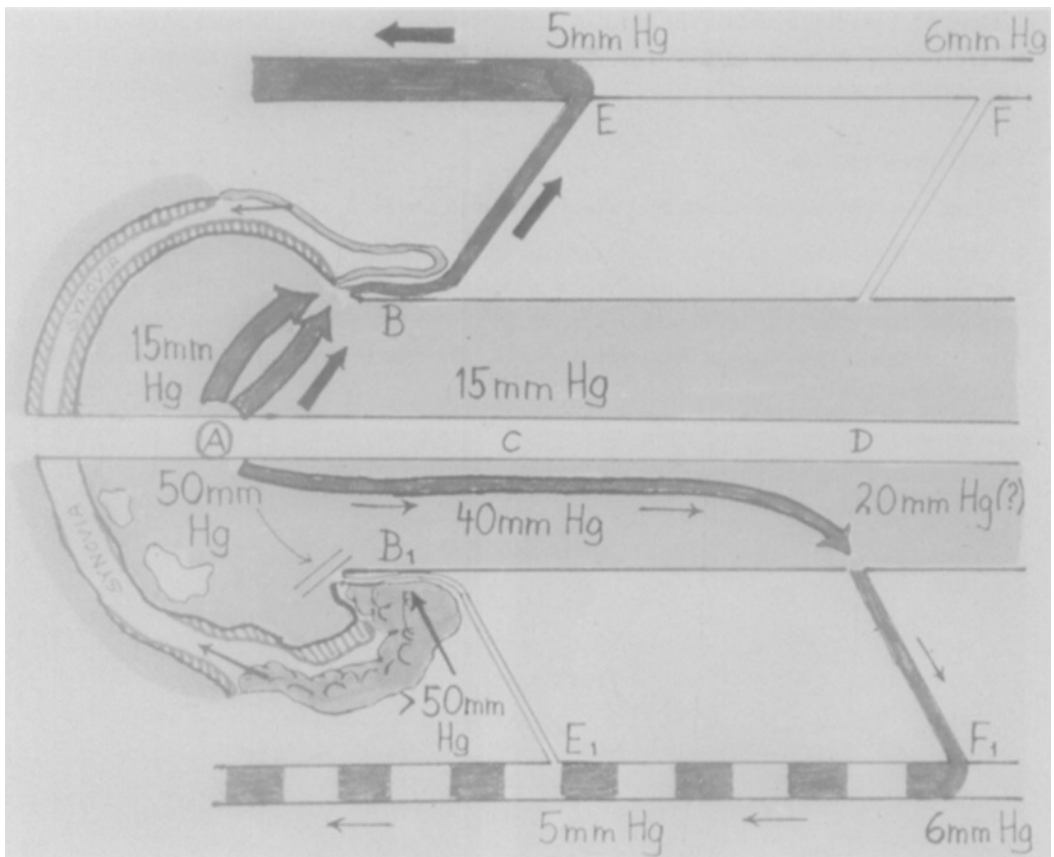


Fig. 1: *The data known from intraosseous pressure measurements and phlebography in 1975, and the basis for the studies represented in this paper.*

THE SYNOVIAL MEMBRANE

The histopathological features of osteoarthritic synovium have been considered non-specific (Roy 1967) and controversy about the role of the synovial membrane has persisted. Though many are of the opinion that changes in the synovium are secondary to cartilage destruction and result from displacement of joint detritus into the synovium (Lloyd-Roberts 1953), it is a clinical experience that synovitis is a very early and consistent feature also in primary osteoarthritis.

In contrast to rheumatoid synovium the changes in the synovial membrane of osteoarthritic joints described in the literature are not very detailed. Proliferation of lining cells, hypertrophy of villi and absence of, or only slight, inflammatory changes have been mentioned (Wilkinson & Jones 1963, Roy 1967, Huth et al. 1973) and vascular changes of the same pattern as observed in rheumatoid arthritis were described by Goldie (1970).

Recently a grading system of the histological criteria for inflammation has been proposed (Salvati et al. 1977) and an increased enzyme level has been demonstrated biochemically (Kar et al. 1976, Salvati et al. 1977).

Own Investigations

Electron and light microscopic study of the synovial membrane

To explore the representative features in osteoarthritic synovium we performed an electron and light microscopic study of the synovial membrane from human hip joints. The material consisted of biopsies from 24 osteoarthritic hip joints, and for comparison, biopsies from twelve patients with rheumatoid arthritis. Biopsies from eight patients with fracture of the femoral neck were used as controls (Arnoldi et al. in press 1979 c).

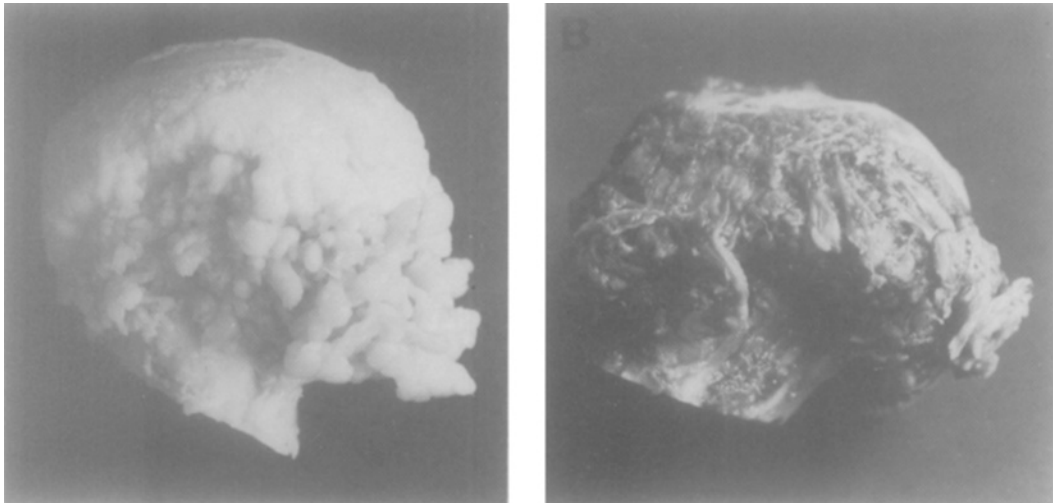


Fig. 2: A: Femoral head from a woman aged 71 with coxarthrosis and proliferative synovitis.
B: Femoral head from a man aged 71 with coxarthrosis and fibrous synovitis.

Gross inspection of the synovial membrane in coxarthrosis. Two relatively distinct types of “synovitis” were observed in patients with coxarthrosis: an early proliferative type and a late fibrous type. The proliferative type was characterized by increase of synovial fluid in the joint and bulky volume of the synovium, the oedematous tissue often having the appearance of a juicy bunch of grapes (Fig. 2 A). In the fibrous type most of these grapelike protuberances had disappeared and been replaced by stringy bands of fibrous scar tissue (Fig. 2 B). In the fibrous type the hip joint usually contained very little fluid.

Light microscopy. The light microscopic examinations revealed that the osteoarthritic synovium as estimated by the grading system introduced by Salvati et al. (1977) only showed slight to moderate degrees of inflammation in contrast to the rheumatoid synovium, which was characterized by pronounced focal as well as diffuse inflammation.

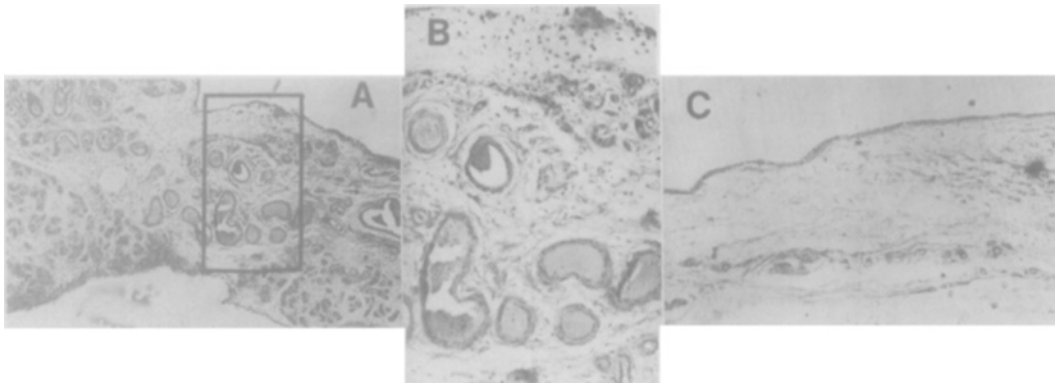


Fig. 3: *A: Synovial membrane from a man aged 63 with coxarthrosis. Marked venous stasis. Haematoxylin/eosin, magnification x 25.*
B: Same as A. Note interstitial oedema. Magnification x 100.
C: Synovial membrane from a woman aged 64 with fracture of the femoral neck. Haematoxylin/eosin, magnification x 25.

Compared with the control group the biopsies from both osteoarthritic and rheumatoid arthritic hip joints showed characteristic vascular changes. The venules and capillaries were dilated and packed with erythrocytes (Fig. 3 A, B and C), hypertrophy of the arterioles was often present and an increased permeability of the capillary wall was suggested by the presence of interstitial oedema, free erythrocytes and haemosiderine deposits in the interstitial tissue (proliferative type). In almost half the cases of osteoarthritis there was an increased amount of fibrosis (fibrous type).

Electron microscopy. Electron microscopy confirmed the changes seen by light microscopy. Free erythrocytes were often seen in the interstitial tissue or penetrating the capillary wall, which was intact and of normal appearance. This is in accordance with the observations by Dryll et al. (1977), who have shown an increased transcapillary migration of circulating blood cells, but a normal structure of the capillary wall.

Histochemical investigations

Compared with rheumatoid arthritis only slightly increased levels of acid and alkaline hydrolase activity have been demonstrated by biochemical methods (Kar et al. 1976). In order to investigate whether this increased activity is consistent with the morphological changes of the synovial membrane seen in our histological studies, a histochemical analysis of alkaline and acid phosphatase in osteoarthritic synovium from human hip joints was carried out (Reimann & Christensen 1979).

Frozen sections of synovial biopsies from 12 osteoarthritic hip joints were studied. Biopsy samples from six patients with fracture of the femoral neck were used as control, together with two biopsies from the knee joints of young patients with torn menisci. The enzyme-histochemical analyses were performed using Burstone's (1959) method for demonstration of non-specific alkaline phosphatase

activity, and Barka & Anderson's (1963) method for demonstration of acid phosphatase activity. For semiquantitative estimation of the enzyme activity the initial time was used, as described by Hopsy & Glenner (1965).

The enzyme levels were significantly increased in the osteoarthritic synovium compared with the controls. The significance of increased alkaline phosphatase activity is not yet clear. However, the alkaline phosphatase was found located in fibroblasts below the lining cells and in capillaries and precapillary arterioles. Thus, the increased activity is presumably consistent with the increased vascularity and fibrosis found by histological examinations.

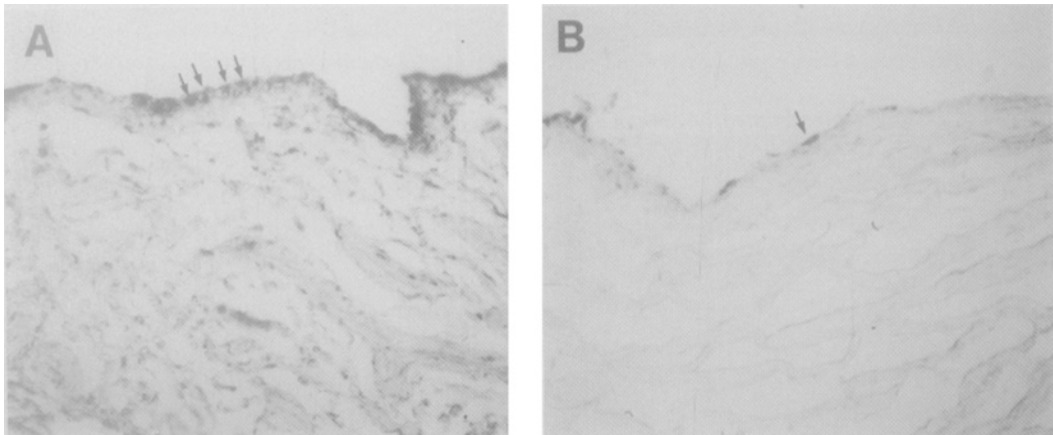


Fig. 4: A: Frozen section from osteoarthritic synovium. The acid phosphatase reaction is seen in superficial lining cells (arrows). Magnification x 100.

B: Frozen section from control synovium. The acid phosphatase reaction is seen in a few of the superficial lining cells. Magnification x 100.

It is generally agreed that increased acid phosphatase activity is involved in the process leading to cartilage damage. Other lysosomal enzymes presumably play a greater role, but acid phosphatase is a good marker enzyme for lysosomal enzymes. As acid phosphatase was found located in the lining cells (Fig. 4 A and B), probably mainly in the A type which is rich in lysosomes, the proliferation of the lining cells – a general histological finding in various types of synovitis – is probably a contributory factor to the increased activity.

The histochemical changes observed in the synovium thus seem to correlate with the histological findings.

Discussion

In patients with coxarthrosis the histological examination of the synovium in proliferative synovitis shows a picture that is dominated by venous stasis and capillary dilation. The few and scattered inflammatory cells could well be explained as a reaction to increased protein content in the

oedematous fluid and to haemosiderine deposits in the interstitial tissue. The subsequent development of fibrosis and scarry transformation of the synovial membrane is probably the long-term reaction of mesenchymal tissue to these changes. This conception is supported by the knowledge of a similar process which develops in the skin and subcutaneous tissues of the ankle region in patients with chronic venous insufficiency. In these patients a purely mechanical disorder of the venous pump of the calf leads to an ambulatory hypertension in the veins and venules of the ankle region with impeded capillary flow (Arnoldi 1966). The early reaction is oedema and increased capillary permeability to proteins and erythrocytes (Zweifach 1940). Large deposits of haemosiderine in the interstitial tissue give rise to the well-known brown discolouration in the lower leg that is so common in these patients. Haemosiderine is a strong tissue irritant and causes an inflammatory reaction in the subcutis which undergoes a scarry transformation. The previously swollen leg shrinks. The scarry tissue is palpable as "induration". The final stage of this "degenerative" process is the chronic venous leg ulcer (Haxthausen 1936, Arnoldi & Linderholm 1968, Arnoldi 1976).

Any process that results in an elevation of intraarticular pressure could probably initiate the changes observed in the osteoarthritic synovium. Examination of pressures in the extraarticular veins of the hip region (Arnoldi et al. 1979 a) indicates that elevation of intraarticular pressure by as little as 5-10 mmHg is sufficient to impede the flow through the synovial veins (see later). The process may begin as an inflammatory reaction caused e.g. by trauma or mechanical dysfunction of the joint with increased production of synovial fluid. Due to the rigid character of the fibrous capsule any increase in volume is accompanied by an increased intraarticular pressure that in its turn will block the venous blood flow and add the effect of venous stasis to the inflammatory reaction (Arnoldi et al. 1979 a). The subsequent effect of further increased capillary permeability could result in a self-perpetuating process.

THE SYNOVIAL FLUID

As synovial fluid is a dialysate of blood plasma to which hyaluronate – synthesized by synovial lining cells – is added, the changes in the synovial membrane in coxarthrosis described above should be reflected in the composition of the synovial fluid. As shown by Lund-Olesen (1970) there seems to be a decreased oxygen tension in synovial fluid from osteoarthritic joints, but to a lesser degree than in rheumatoid synovia. He also observed a significant correlation between PO_2 and pH and between PO_2 and PCO_2 . It is known that the protein concentration in osteoarthritic synovia is slightly increased (Ropes & Bauer 1953), and that there is an abnormal protein pattern (Kushner & Sommerville 1971, Pruzanski et al. 1973, Willumsen & Friis 1975). Further it has been shown that the passage of protein through the synovial vascular walls is affected by molecular size and by presence of inflammation (Kushner & Sommerville 1971).

Own investigations

Protein analysis

To elucidate the permeability of the osteoarthritic synovium to plasma proteins of varying molecular size we performed an analysis of the ratios of synovial fluid concentration to serum concentration (SF/S) for four non-immunoglobulin proteins from osteoarthritic and normal hip joints. We also

investigated whether these changes were correlated to the histological features in the synovial membranes in patients with coxarthrosis (Reimann et al., in press 1979).

The synovial fluid was obtained at the time of replacement surgery from 46 patients with unilateral coxarthrosis. Blood samples from a vein on the forearm were taken simultaneously. Criteria for unilateral coxarthrosis were that the patients showed a radiologically normal contralateral hip without clinical symptoms and that there was no accentuation of the normal uptake pattern at osteoscintigraphy with ^{99m}Tc -polyphosphate (Heerfordt et al. 1976).

The simultaneously aspirated synovial fluids and sera were analysed with electro-immunoassay as described by Laurell (1965). The proteins studied were orosomuroid, molecular weight 44,000; transferrin (74,000); ceruloplasmin (160,000) and α_2 -macroglobulin (820,000). Recently, it has been shown that Stoke's radius, which is a function of molecular weight, volume and shape, is a more appropriate expression of protein size than molecular weight alone (Burnett et al. 1975). However, the size of Stoke's radius for the four proteins investigated roughly correlates with the molecular weight (Burnett et al. 1976, Renkin 1977). Further, local synthesis or destruction in the synovial membrane of these proteins has not been shown (Kushner & Sommerville 1971). The SF/S ratio thus reflects the synovial permeability for the single protein.

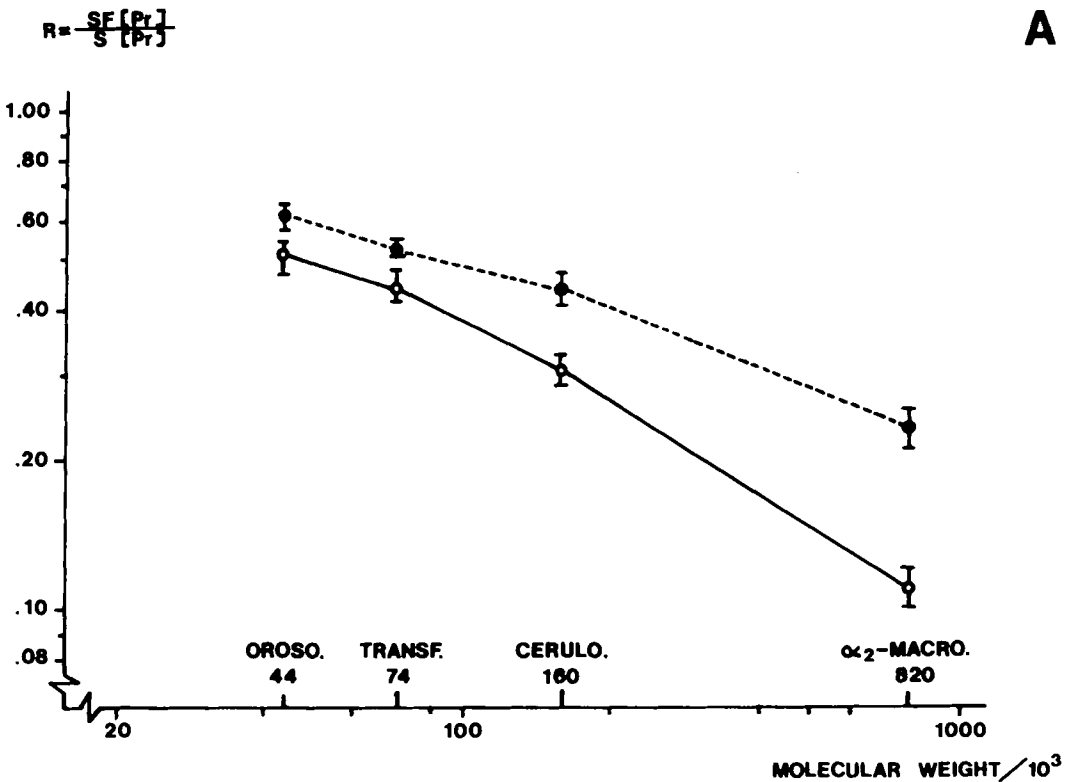
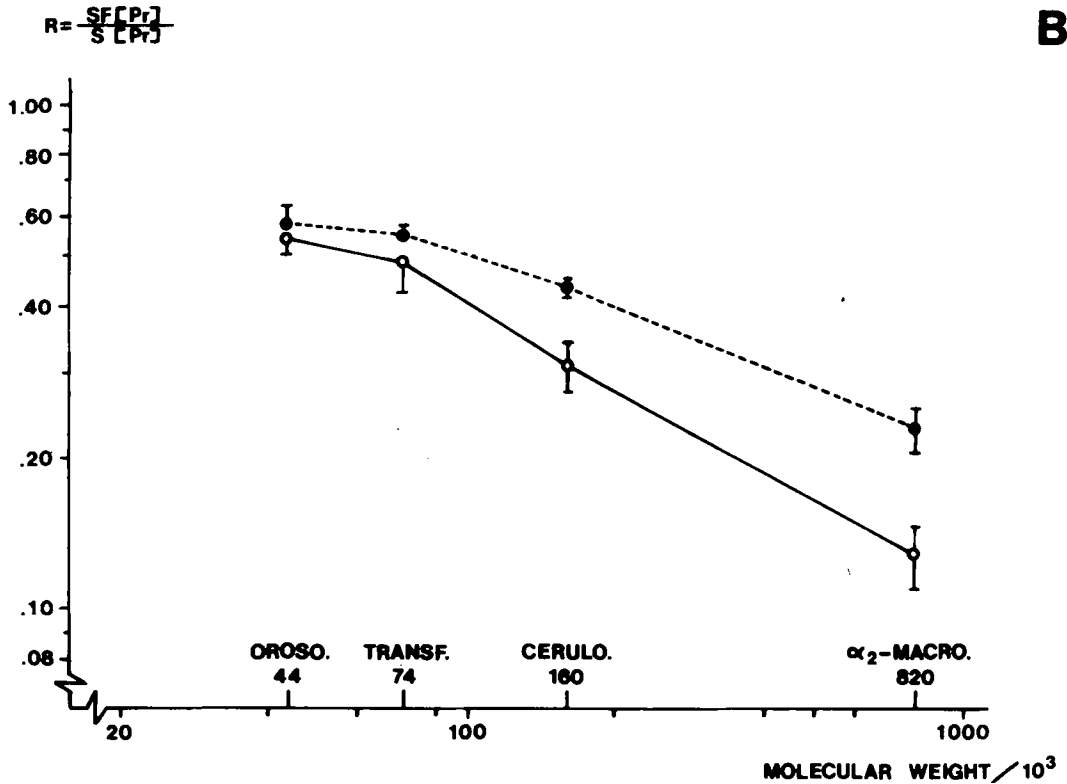


Fig. 5: A: Log/log plot of SF/S ratio and molecular weight from hip joints with osteoarthritis (black circles) and from normal hip joints (open circles). Ratio determined for the four non-immunoglobulin proteins represent the mean \pm SD of 29 and 23 samples respectively.



B: Intraindividual values from eight patients.

Our results showed that the variations in SF/S ratios from the normal hip joints were insignificant. Furthermore, the analyses showed the same pattern in an intraindividual study as when all the samples from the osteoarthritic joints were compared with the normal samples (Fig. 5 A and B).

The analyses showed a relationship between SF/S and molecular weight as described previously (Nettelbladt & Sundblad 1959, Kushner & Sommerville 1971, Pruzanski et al. 1973, Willumsen & Friis 1975). The ratios were higher for osteoarthritic synovia than for normal, and the difference increased with increasing molecular weight and was highly significant for the largest molecules ($p < 0.001$). An almost inverse linear relationship was observed between SF/S ratios of the proteins and their molecular weight (Fig. 5 A and B). These findings indicate an increased capillary permeability in the synovial membrane.

Relationship between protein ratios and inflammation in synovial fluid in different joint diseases has been described by Kushner & Sommerville (1971). They found that increasing degrees of inflammation corresponded to higher SF/S ratios with greatest increases in large molecules. Patients with osteoarthritis showed least evidence of inflammation.

In this series the degree of inflammation was estimated by histological examination of the synovial membrane. It was impossible to correlate the degree of inflammation in the synovium with the protein ratios, owing to the very slight degree of inflammation observed in the osteoarthritic synovium.

As previously described, it is possible to distinguish between a proliferative and a fibrous type of synovitis in coxarthrosis. By comparing the ratios of the four proteins in these two types it was found that patients with proliferative synovitis showed higher SF/S ratios than those with fibrous synovitis. The difference was significant for α_2 -macroglobulin ($p < 0.01$). Thus the abnormal protein pattern in osteoarthritic synovia reflects an increased capillary permeability in the synovial membrane and it seems to correlate with the histological features.

Discussion

Swelling and pain are regular features in all inflammatory joint disease, typified by rheumatoid arthritis. It is also a common symptom after trauma or overloading, more easily noticed, e.g. in the knee than in the hip joint. The patient with primary coxarthrosis is generally in his late fifties or sixties when he is seen by the orthopaedic surgeon. However, a careful history will often reveal periods of intermittent pain in the hip region, combined with limping, during the years preceding the state of manifest osteoarthritis. During this period, when the X-rays are normal, the patients are rarely seen by the orthopaedic surgeon, but by their family physician or a rheumatologist. The treatment – if any – is conservative, mainly consisting of rest, occasionally combined with physical treatment of various kinds, and during the recent decade medication with one or several of the non-steroid antiphlogistica. This conservative regimen is often effective, but in some cases the symptoms return periodically until the diagnosis osteoarthritis becomes obvious. This conservative treatment is essentially a treatment of synovitis.

Thus, there are clinical indications that even primary coxarthrosis does not appear suddenly and without warning sometime after the fifty-fifth birthday. The history is more likely to suggest that clinical osteoarthritis is the final stage of a fairly long-lasting joint disorder. Our clinical experience suggests that many attacks of synovitis disappear without doing permanent damage to the joint. In certain cases the attack leads to manifest coxarthrosis within a short period of time, but in most cases of primary coxarthrosis the synovitic episodes stretch over a number of years before the typical roentgen changes become visible.

Inflammation, joint effusion and subsequent stasis result in a vascular derangement in the synovial membrane. Increased capillary permeability is followed by a change in the protein pattern and the amount of protein in the synovia. One of the functions of the synovial fluid is joint lubrication. As shown by Reimann et al. (1975) and Reimann (1976) boundary lubrication is reduced in rheumatoid arthritis and osteoarthritis. It seems probable that this deterioration is due to the change in the protein pattern of the synovial fluid.

The increased production of acid phosphatase and lysosomes, known to be of importance for the degenerative changes of articular cartilage, and the reduction of oxygen in the synovial fluid (Lund-Olesen 1970) are of special importance as the synovia is the vehicle for supply of oxygen and nutrition to the cartilage. Further, decreased oxygen tension is of significance for release of lysosomal enzymes (de Duve 1964).

The mechanical effect of synovitic joint effusion is discussed on p. 21.

VASCULAR CHANGES IN JUXTAARTICULAR BONE MARROW

The fact that degenerative changes usually are caused by a failure in the supply of oxygen and nutrition to the tissues involved focussed attention on the state of the arterial supply to the joint in many early studies on osteoarthritis. As late as the middle of this century many authors were of the opinion that osteoarthritis of the hip was accompanied or preceded by a state of ischaemia of sub- and juxtachondral bone (Wollenberg 1909, Goldhaft et al. 1930, Plemister 1940, Pridie 1952). This conception was challenged by Harrison et al. (1953). By means of injection studies on cadavers they found a hyperplasia of the intraosseous arteries in the femoral head, and on the basis of this observation they assumed that the arterial inflow to the femoral head was increased instead of reduced in coxarthrosis. The same authors also found signs of venous stasis in the bone marrow.

In the years following this study investigations by means of intraosseous phlebography provided evidence of disturbed venous outflow from the femoral head and neck in patients with coxarthrosis and from the distal part of the femur in patients with gonarthrosis (Mériel et al. 1955, Hulth 1959, Helal 1962, Wardle 1964, Phillips 1966) and increased intramedullary pressure in juxtachondral bone marrow (Arlet et al. 1968).

Own investigations

Intraosseous phlebography and measurements of intraosseous pressure

Coxarthrosis. In a series of 15 patients with unilateral painful primary osteoarthritis of the hip joint, Arnoldi et al. (1972 a) measured the pressure in the bone marrow of both femoral necks and the femoral vein. These examinations were followed by bilateral serial intraosseous phlebography of the proximal part of the femur.

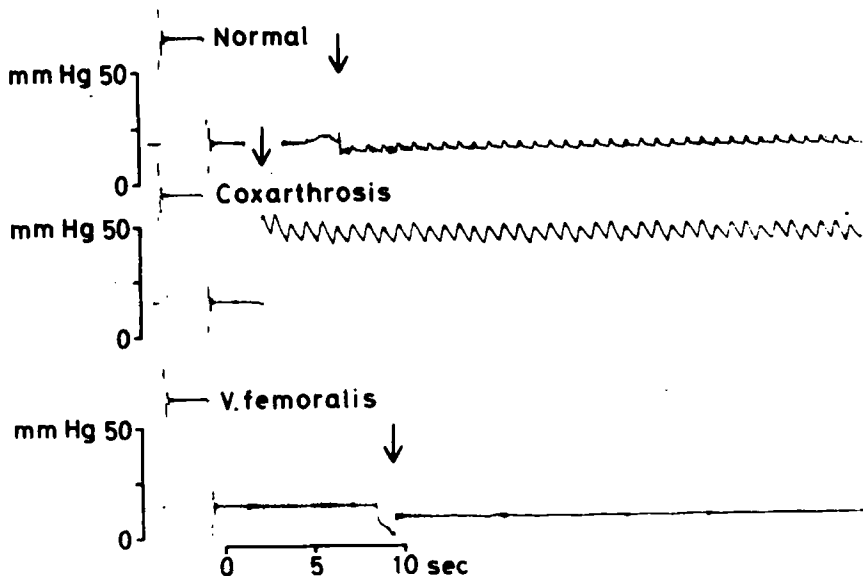


Fig. 6: Bilateral measurements of intraosseous pressure in the femoral neck with simultaneous recording of femoral vein pressure. Patient with unilateral coxarthrosis.

They observed that 1) the intraosseous pressure in normal bone marrow was always higher than the pressure in the extraosseous veins of the region (mean difference 6.8 mmHg). 2) The intraosseous pressure was always higher in the arthritic hip than in the healthy hip (mean difference 29.7 mmHg) (Fig. 6). 3) High intraosseous pressure coincided with phlebographic signs of impaired venous drainage from the upper end of the femur (intramedullary retention of contrast material and disappearance of the veins draining the femoral head (vv. retinaculares) (Fig. 7 and Fig. 8). 4) Patients with high intraosseous pressures (<40 mmHg) always complained of characteristic pain at rest, while patients with lower pressures did not suffer from this symptom.

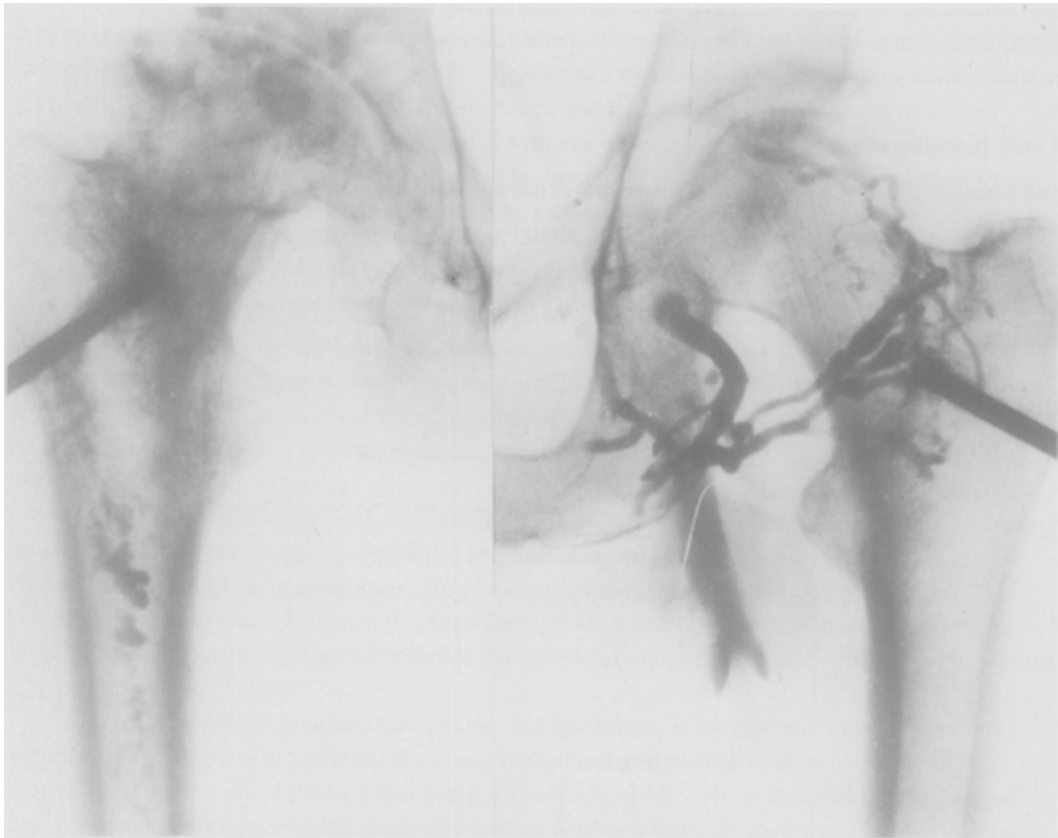


Fig. 7: Bilateral intraosseous phlebography from patient with unilateral coxarthrosis, exposed thirty seconds after bilateral injection of 8 millilitres Isopaque Cerebral. In the normal hip the contrast material leaves the intraosseous space without noticeable filling of intraosseous vessels and is observed in the normal drainage veins. In the hip with severe osteoarthritis the contrast is seen in large, tortuous intraosseous veins extending far down into the femoral shaft.

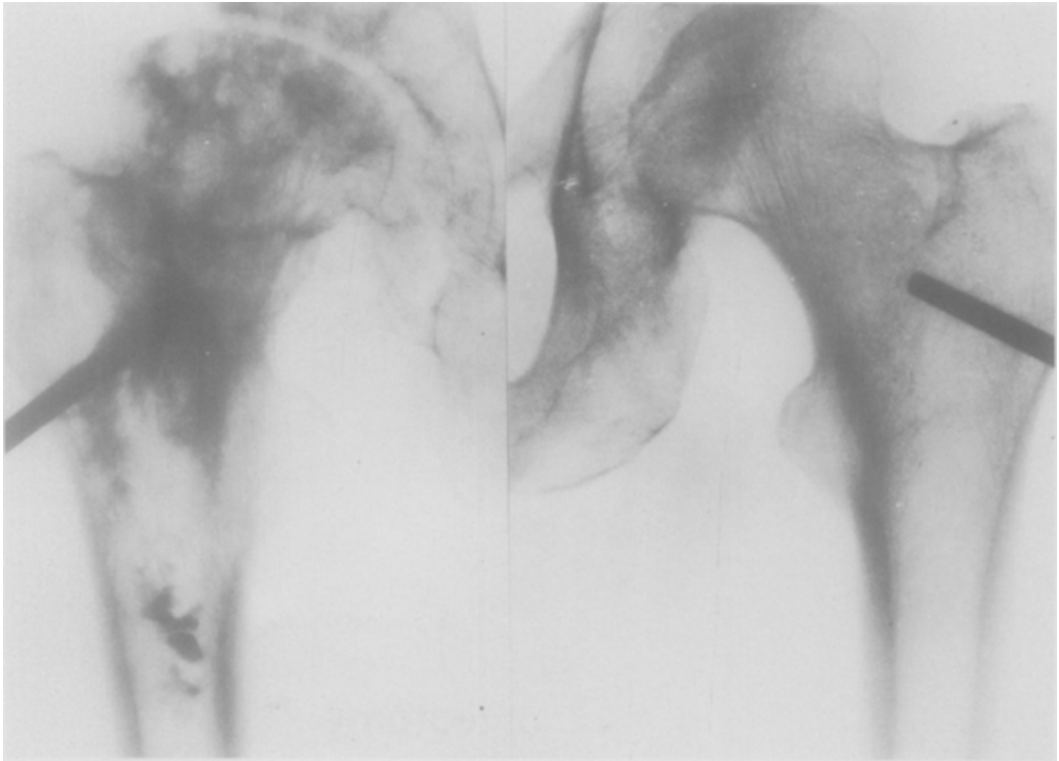


Fig. 8: Exposures of the same patient as in Fig. 7. The film of the normal hip was exposed three minutes after the injection of contrast. The exposure of the hip with osteoarthritis was made thirty minutes later. Large quantities of contrast are left in the medullary space.

In a second series of pressure measurements the same authors showed 5) that in patients with coxarthrosis the intraosseous pressure was always higher in the femoral head than in the neck (mean difference 10.8 mmHg).

In another study Arnoldi et al. (1971) found that 6) in patients with coxarthrosis intertrochanteric osteotomy or cortical fenestration caused an immediate fall of intramedullary pressure in the femoral head and neck (osteotomy 17.6 mmHg and 13.5 mmHg, respectively; fenestration 21.5 mmHg and 15.9 mmHg respectively (mean values)) (Fig. 9). In 10 of the 11 patients who complained of rest pain before the operation these pains had disappeared within 24 hours after the operation.

Thus, these investigations showed that patients with *late stages of painful coxarthrosis* invariably suffered from intraosseous venous stasis and hypertension in the bone marrow of the proximal femur and the changes were most pronounced near the hip joint. The pressure in the extraosseous and extracapsular veins was not affected. Later investigations have shown the same findings in patients with various forms of painful secondary coxarthrosis.

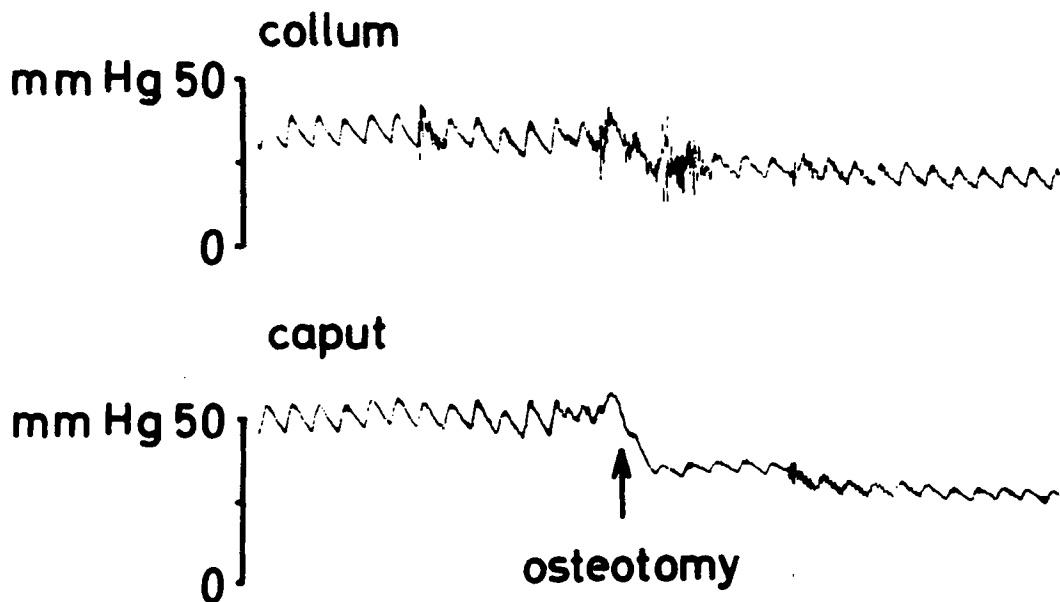


Fig. 9: Pressure tracing from the femoral head and neck, before and after subtotal intertrochanteric osteotomy.

The intraosseous engorgement-pain syndrome. The finding that the characteristic rest pain of coxarthrosis seemed to be connected with intraosseous venous stasis and hypertension focussed our attention on this symptom.

In a series of investigations on patients with various painful conditions in the knee region Arnoldi et al. (1975) found that patients with rest pain (with or without osteoarthritis) showed a higher intraosseous pressure in the proximal part of the tibia or the lower part of the femur than patients without rest pain (with or without osteoarthritis). They observed that the patients with rest pain and high intraosseous pressure, but without visual or clinical signs of osteoarthritis, generally belonged to a younger age group than patients with gonarthrosis. Later studies of this condition (Lempert & Arnoldi 1978, Arnoldi et al. in press 1979 b), showed that the high pressures were accompanied by intraosseous venous stasis, that the intraosseous engorgement-pain syndrome could be located to the hip as well as to the knee region (Fig. 10 and 11), and that roentgen examination often showed a state of juxtaarticular osteopenia in these patients instead of the sclerotic appearance characteristic of osteoarthritis.



Fig. 10: Hip joint from patient with the intraosseous engorgement-pain syndrome after "fenestration" of the femoral neck.

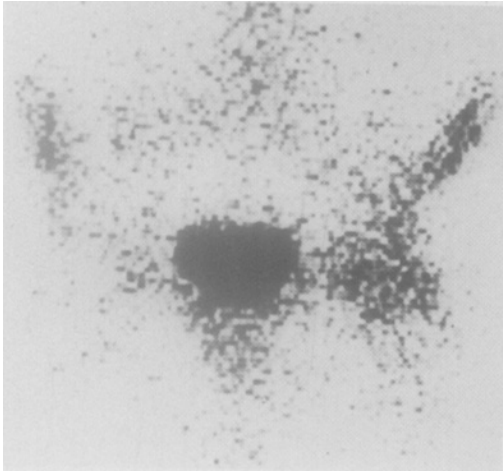


Fig. 11: ^{99m}Tc -polyphosphate scintigraphy of both hips from the patient shown in Fig. 10 (before operation).

Discussion

The cause of intraosseous stasis and hypertension

Our findings by means of intraosseous and intravenous pressure measurements in patients with coxarthrosis indicate that the blockage of venous drainage from the femoral head is located somewhere in or just outside the cortex. Pressure measurements from extraosseous and extracapsular veins, including the circumflex veins, have shown normal findings (Fig. 6 and Fig. 22). The observations by Phillips et al. (1967) seem to exclude venous thrombosis as a cause of blockage. They found that intraosseous phlebography repeated 12-20 months after intertrochanteric osteotomy showed reopening of the normal drainage vessels from the femoral head in a number of patients. Their phlebograms show no signs that this reopening was due to recanalisation of thrombosed veins.

The retinacular veins leave the femoral head just distal to the cartilage border and until they join the circumflex veins their course is intraarticular. The pressure in these veins lies between about 10 mmHg (the pressure in the normal bone marrow) and 5 mmHg (the pressure in the large extraosseous veins). As the studies on the synovium indicated, and as direct measurements from other joints have shown (Eyring & Murray 1964), the intraarticular pressure increases when the volume of synovia increases or when the joint space is reduced. A rise of intraarticular pressure in the order of 10 to 15 mmHg is sufficient to impede the flow through the intraarticular veins, unless the perfusion pressure is raised.

Contracture, joint volume and pain

From experiments on patients with rheumatoid arthritis of the knee joint we know that in the presence of joint effusion the intraarticular pressure is least in the mildly flexed position (Favreau & Laurin 1963, Eyring & Murray 1964, Jayson & Dixon 1970) which is the position spontaneously adopted by patients with effusions in the knee joint and gives least discomfort (Eyring & Murray 1964). In these experiments it was shown that further flexion of the knee produced extremely high intraarticular pressures that actually could rupture the joint capsule. Further, high intraarticular pressure could

inhibit the function of the quadriceps femoris muscle and lead to atrophy and flexion contracture (De Anrade et al. 1965).

In human coxarthrosis the habitual contracture is flexion, outward rotation and adduction, which is also the position with the greatest joint volume due to maximal relaxation of the fibrous capsule. One of the very early clinical signs of coxarthrosis and the intraosseous engorgement-pain syndrome is pain on inward rotation in flexion. If this symptom is analysed carefully it becomes obvious that the pain increases with increasing rotation. The movement from maximum inward rotation back into neutral is accompanied by relief of pain. Inward rotation reduces the volume of the hip joint and if effusion is present the intraarticular pressure should reach its maximum in this position.

INTERDEPENDENCE BETWEEN INTRAARTICULAR AND INTRAOSSEOUS PRESSURE

Theoretically intraosseous stasis and hypertension could be explained as the effect of blockage of flow through the draining vessels from the weight-bearing area of the femoral head, and the haemodynamic changes in the bone marrow might be secondary to high pressure in the joint cavity due to synovitic effusion.

Own investigations

Although the circumstantial evidence of interdependence between intraarticular and intraosseous pressure is impressive, direct experimental evidence of this relationship has been lacking. In order to investigate the reaction of intraosseous pressure to variations in intraarticular pressure we measured the pressure in the bone marrow of the femoral condyle of healthy rabbits before, during and after a known rise of pressure in the knee joint (Arnoldi et al. 1979 b).

As in human subjects the intraosseous pressure is normally somewhat higher than the intraarticular pressure. Injection of fluid into the knee joint was accompanied by an immediate rise of intraarticular pressure and followed by a slower rise of pressure in the bone marrow of the femoral condyle (Fig. 12 and Fig. 13). The results indicated a blockage of venous outflow through the intraarticular drainage vessels with continued arterial inflow to the bone marrow.

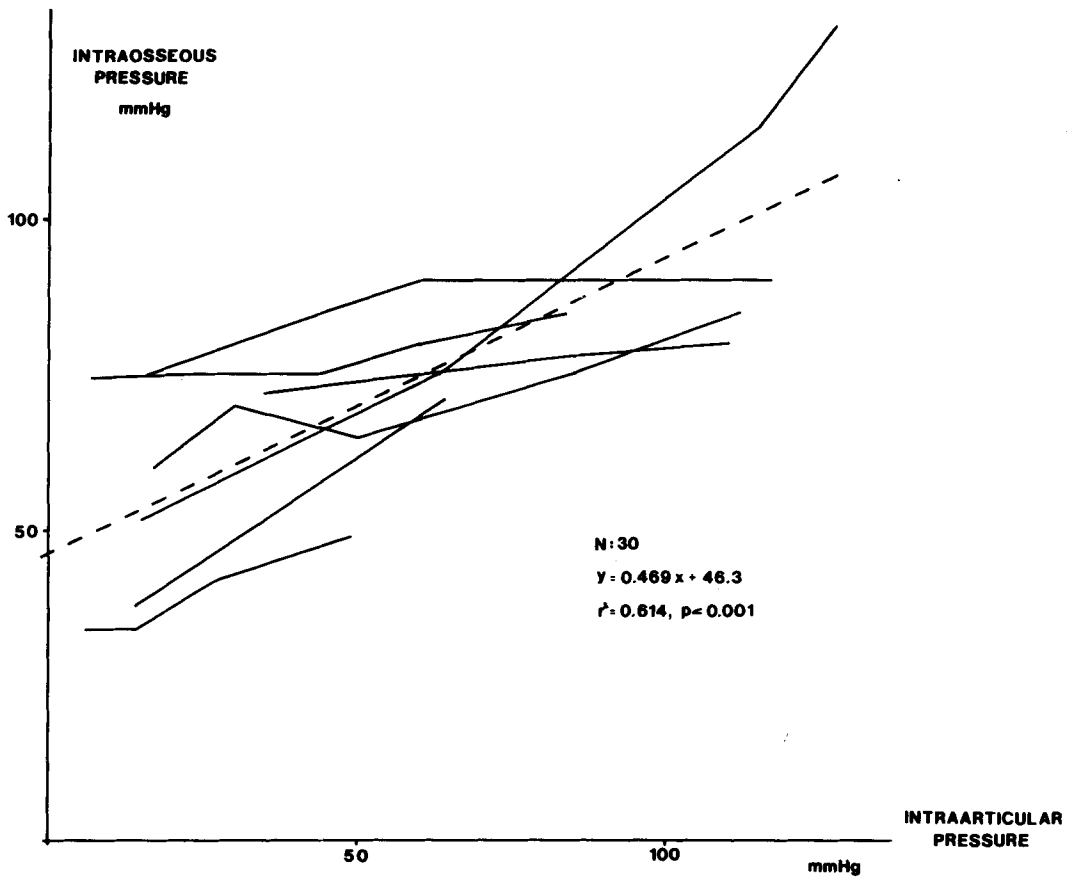


Fig. 12: Intraosseous pressure as a function of intraarticular pressure. A rise of intraarticular pressure resulted in a significant rise of pressure in juxtaarticular bone marrow ($p < 0.001$).

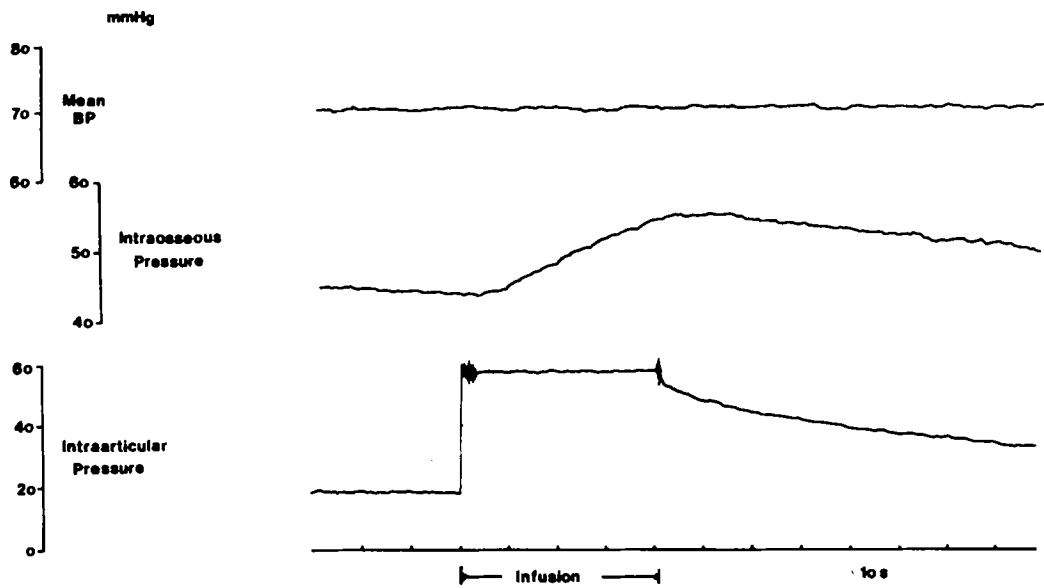


Fig. 13: Tracing of intraosseous pressure increase induced by joint infusion of saline. Simultaneous pressure curves from a single experiment.

Discussion

The experiments described above indicate that intraosseous stasis and hypertension may in fact be secondary to a joint effusion with high intraarticular pressure caused by synovitis.

CHANGES IN SUBCHONDRAL BONE

The structural changes in subchondral bone in the osteoarthritic femoral head are fairly well known (Collins 1949, Sokoloff 1969, Radin et al. 1970, Foss & Byers 1972, Jeffrey 1973). Roughly, they are characterized by an attempt to repair dead trabeculae with increased bone formation. The macroscopic results are seen as deformation of the head, cyst formation, increased radiodensity and building of osteophytes.

Own investigations

Quantitative histological analysis of articular cartilage and subchondral bone

In order to quantify the alterations in subchondral bone and to compare the changes with the severity of the cartilage lesions, a quantitative histological analysis of articular cartilage and subchondral bone from osteoarthritic and normal human hips was performed (Reimann et al. 1977).

The analysis was based on 12 femoral heads, six osteoarthritic and six controls. The cartilage was graded according to the histological-histochemical system of Mankin et al. (1971), using the Safranin O staining method. The subchondral bone was analysed to establish the percentage of trabecular, osteoblastic and osteoclastic areas. The trabecular bone area measurements were made with point-counting method (Harris & Weinberg 1972) and for osteoblastic and osteoclastic area counts the technique described by Melsen et al. (1975) was used.

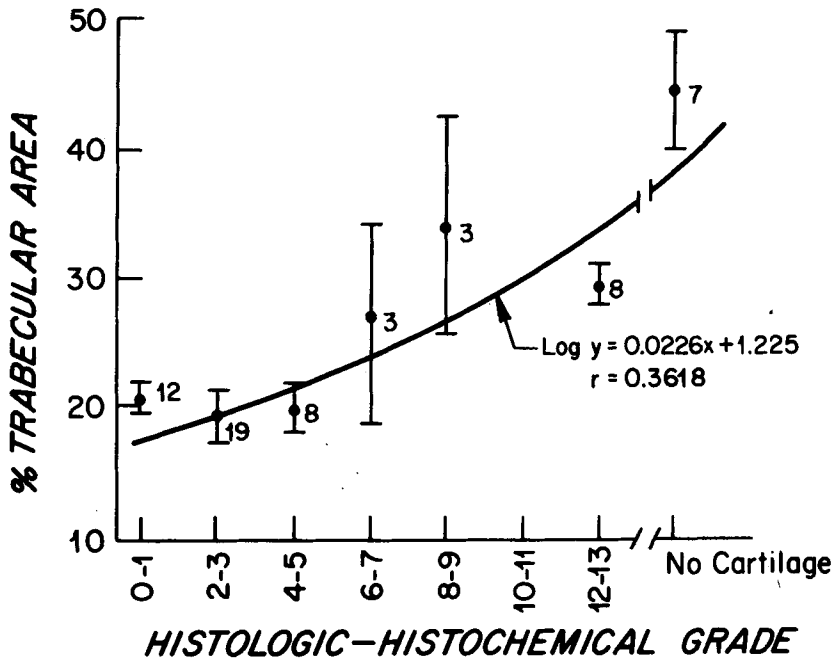


Fig. 14: Diagram illustrating the relationship between the histological-histochemical grade and the per cent of trabecular area.

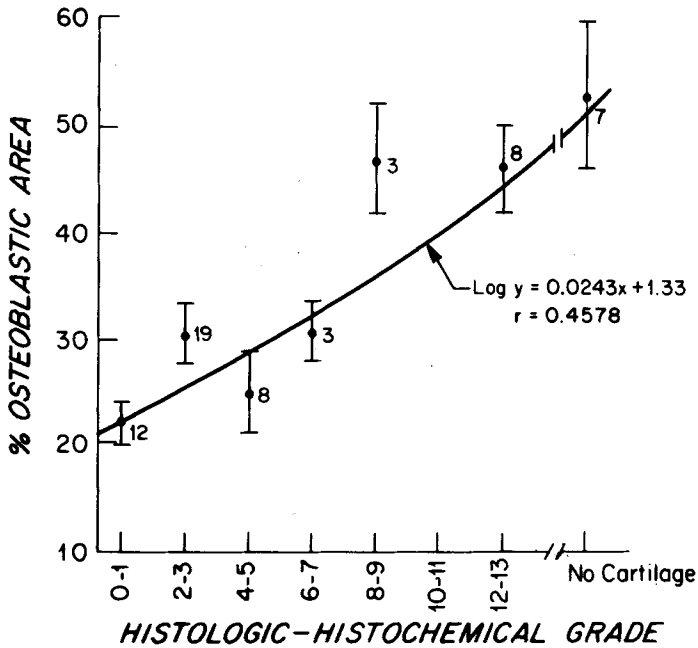


Fig. 15: Diagram showing the relationship between histological-histochemical grade and the per cent of osteoblastic area.

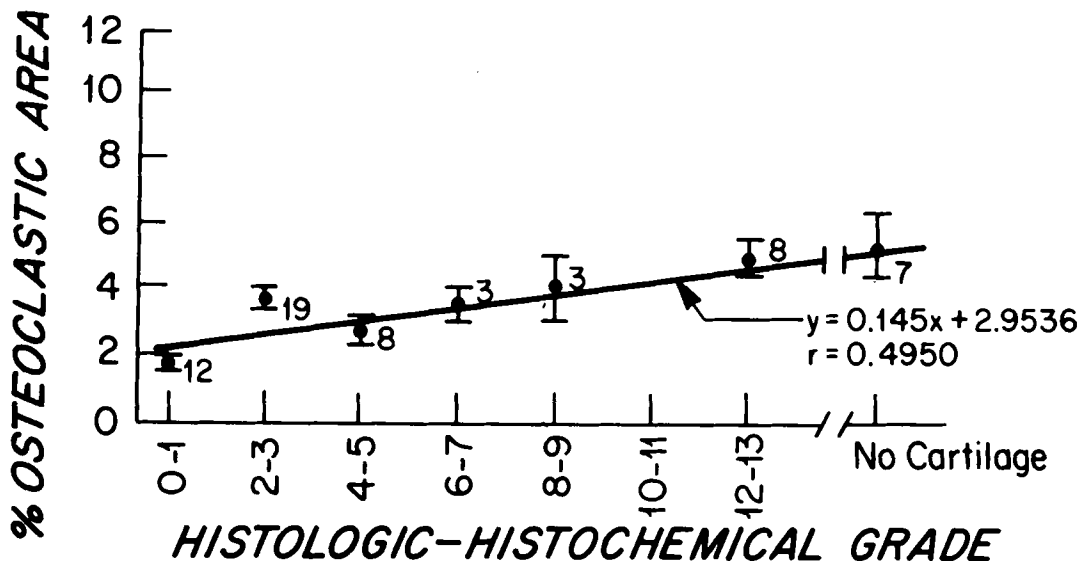


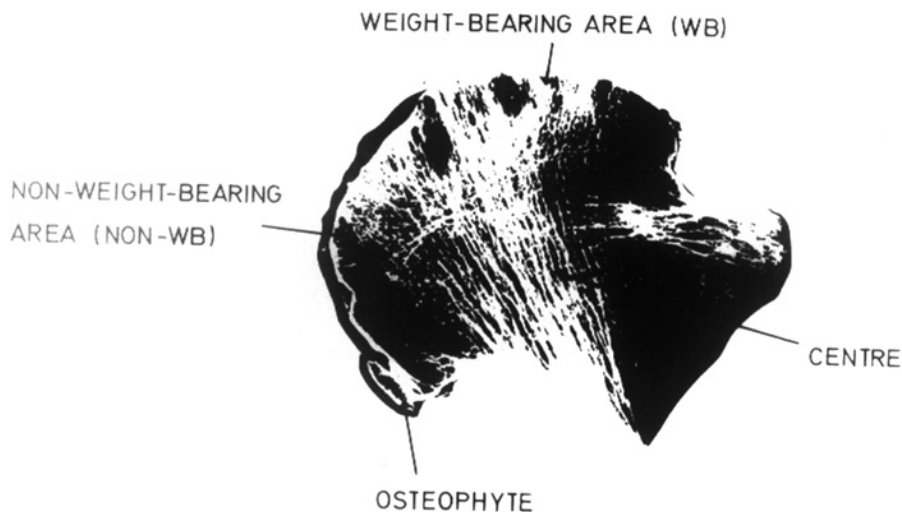
Fig. 16: Graphic representation illustrating the relationship between histological-histochemical grade and per cent of osteoclastic area.

The data obtained showed wide variations in all parameters in the osteoarthritic specimens, but consistently more marked alterations in the weight-bearing areas. The trabecular bone area as well as osteoblastic and osteoclastic areas were significantly larger in the osteoarthritic than in the control group (normal femoral heads obtained at autopsy or femoral heads removed after fracture of the femoral neck) (Fig. 14, Fig. 15 and Fig. 16). By comparing the bony changes with the severity of the cartilage lesions from different areas within the same femoral head a correlation of moderate significance was found between the degeneration of the cartilage and sclerosis and hypermetabolism of the subchondral bone.

Histochemical study of alkaline and acid phosphatase activity

To further elucidate the metabolic changes found in the subchondral osteoarthritic bone by histological examination a histochemical investigation was performed (Reimann & Christensen 1979).

Alkaline phosphatase was used as a marker enzyme for bone regeneration and acid phosphatase as a marker enzyme for bone resorption. These enzymes were chosen as increased alkaline phosphatase activity has been demonstrated in regions of deposition of new bone (Jeffree 1959, Jeffree & Price 1965, Timmer et al. 1968, Andersen 1970) and acid phosphatase – associated with the lysosomes in the osteoclasts – plays an important role in bone resorption (Burstone 1959, Doty & Scofield 1976).



ALKALINE PHOSPHATASE:
 WB ----- 22.1 ± 8.0 sec
 NON-WB ----- 39.8 ± 13.7 sec
 OSTEOPHYTE - 26.6 ± 4.7 sec
 CENTRE ----- 50.7 ± 20.6 sec

ACID PHOSPHATASE:
 WB ----- 41.2 ± 13.8 sec
 NON-WB ----- 94.5 ± 57.4 sec
 OSTEOPHYTE - 69.7 ± 29.0 sec
 CENTRE ----- 126.9 ± 56.6 sec

Fig. 17: Radiographs of femoral head with osteoarthritis showing the different areas estimated. The figures below illustrate the variations in the initial time according to the site studied.

Frozen sections from 24 osteoarthritic femoral heads were prepared for semiquantitative analysis of the enzyme activity using Burstone's (1959) and Barka & Anderson's (1963) enzyme-histochemical methods. The analyses showed that there were wide variations within the same femoral head for both enzymes, with significantly higher activity in weight-bearing than in non-weight-bearing areas and in subchondral bone compared with more central areas (Fig. 17). Further, the enzyme activity correlated directly with the severity of the cartilage lesions. The findings seemed to be consistent with the morphological findings in the histological study.

Distribution of ^{99m}Tc-phosphate compounds in osteoarthritic femoral heads (Christensen & Arnoldi, in press 1979)

Femoral heads from 12 patients with osteoarthritis were examined. Ten mCi ^{99m}Tc-phosphate was given intravenously approximately 2 hours before total hip replacement and frozen sections were prepared. Autoradiograms showed accumulation of ^{99m}Tc-phosphate in the subchondral region of the weight-bearing area of the femoral head and in the osteophytes (Fig. 18 A and B). In the weight-bearing area the uptake was particularly high in the walls of the cysts. In the osteophytes the radionuclide was localized at the osteochondral junction.

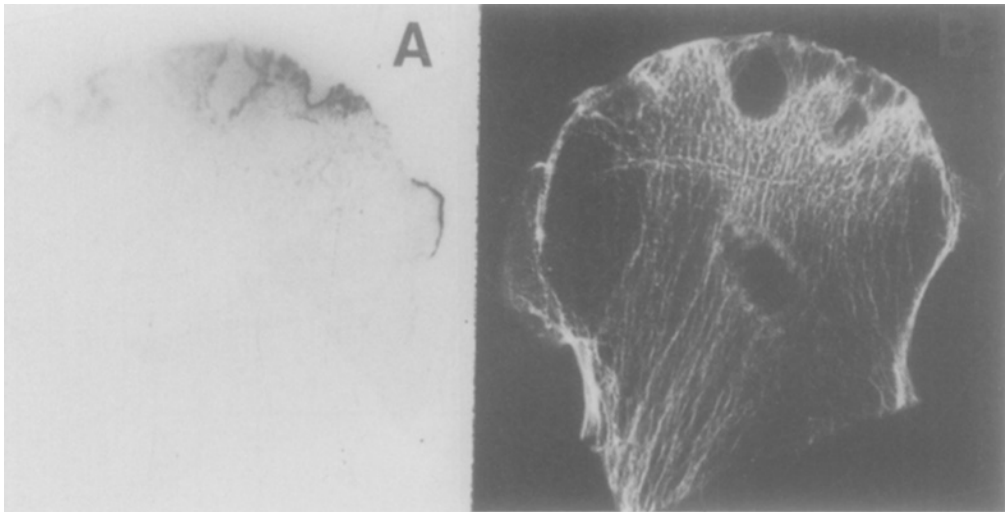


Fig. 18: *A: Autoradiogram from osteoarthritic femoral head from a patient given ^{99m}Tc -polyphosphate preoperatively. The radionuclide is predominantly accumulated at the cyst wall of the weight-bearing area and at the osteochondral junction in the osteophytes.
B: Corresponding roentgenogram of a thin slice of the femoral head.*

A quantitative study was performed from six different zones on a 10-micron thick section from each femoral head, the six zones being the weight-bearing area, the non-weight-bearing area, the osteophytes, the central area, the synovial membrane and the fibrous capsule. These different zones were counted in a well-counter. The areas were determined by planimetry and the uptake per unit volume was expressed in proportion to the uptake per unit volume in the fibrous capsule. The quantitative study confirmed the impression from the autoradiograms. Thus, the highest uptake was in the weight-bearing area and in the osteophytes and the lowest in the synovial membrane and fibrous capsule (Fig. 19).

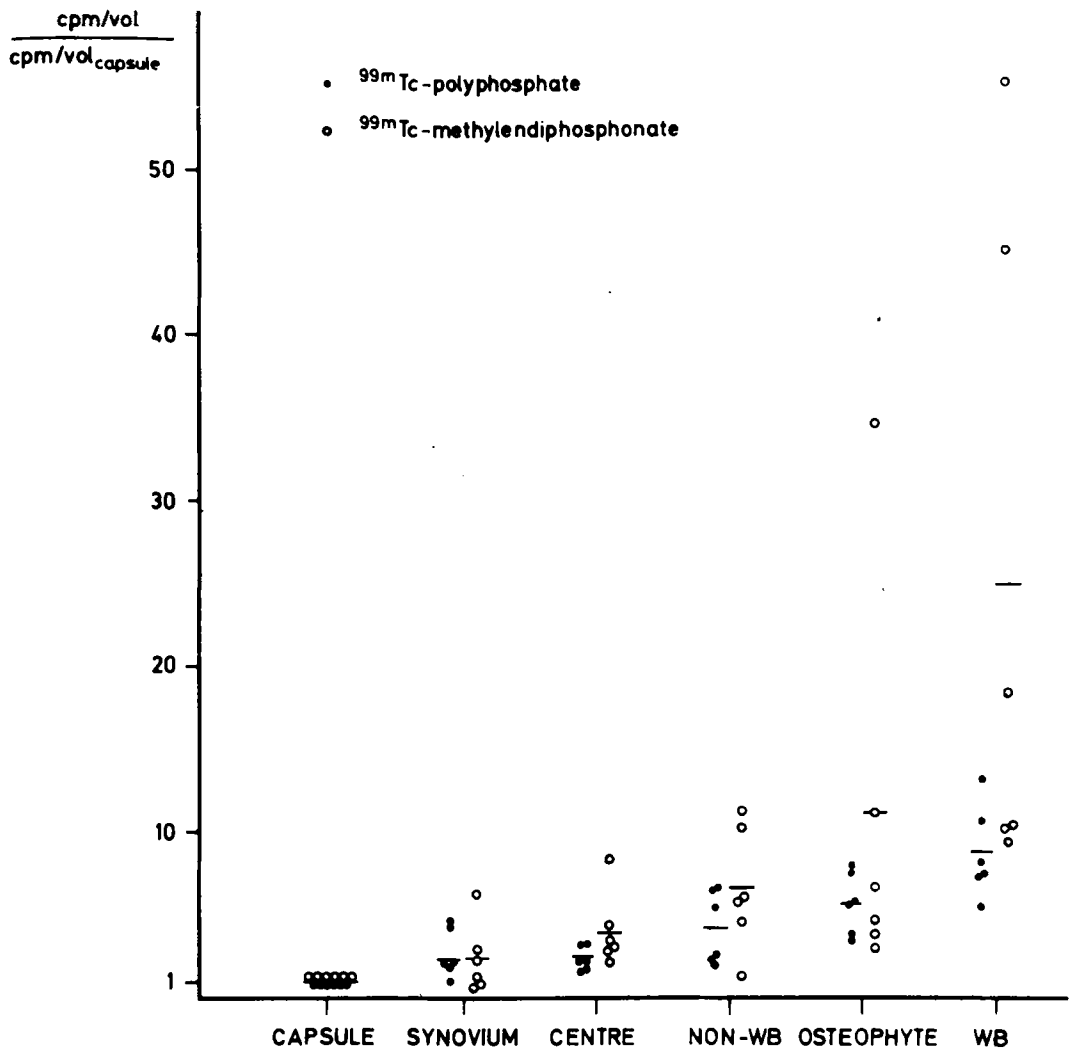


Fig. 19: Target-to-background ratio on different areas in twelve osteoarthritic femoral heads, using the uptake of radionuclide in the fibrous capsule as background.

To compare the distribution of the radionuclide with the morphology, sections were stained with haematoxylin-eosin, with the van Kossa technique for calcium phosphate and by Burstone's method for determination of alkaline phosphatase activity (Fig. 20 A, B and C). The morphological studies showed that the radionuclide accumulated in areas of new bone formation, particularly enchondral ossification. Histochemical staining for alkaline phosphatase activity showed that the distribution of this enzyme roughly corresponded to the deposition of the bone-seeking radionuclide. Incidentally, these investigations failed to produce evidence of callus formation in microfractures of subchondral bone trabeculae.

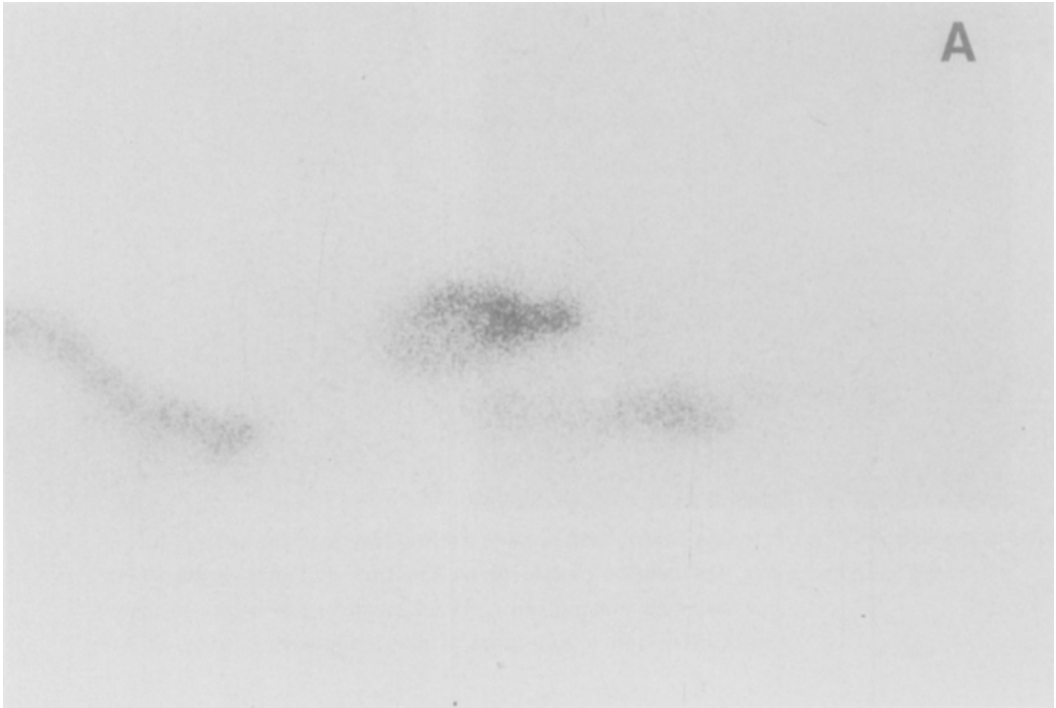
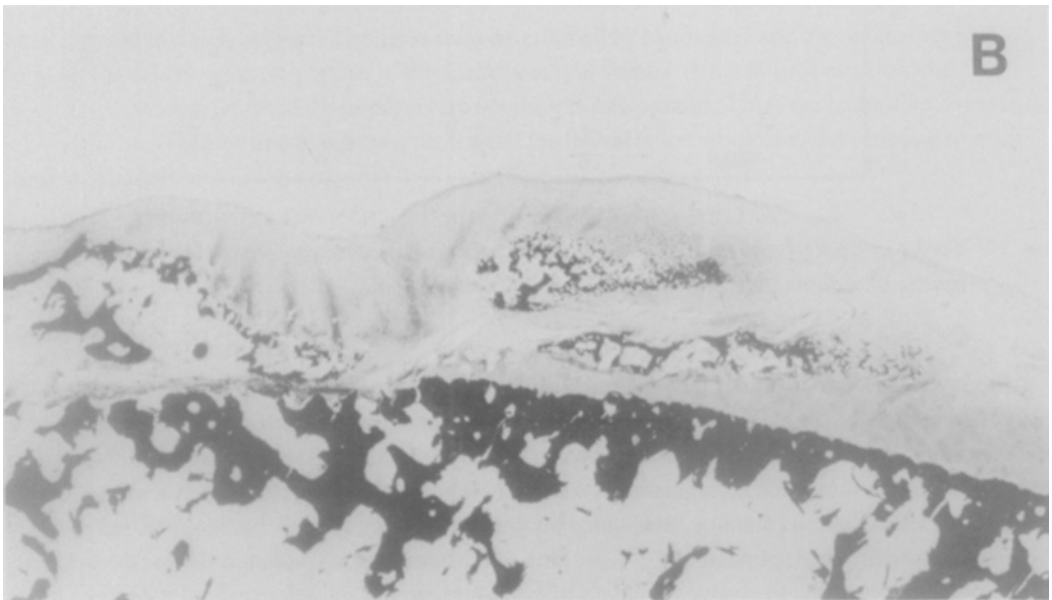


Fig. 20: A: Fibrocartilage at the articular surface with enchondral ossification. Autoradiogram (^{99m}Tc -polyphosphate).





C: Alkaline phosphatase activity. Magnification x 10.

^{99m}Tc-polyphosphate scintigraphy in patients with osteoarthritis, or the intraosseous engorgement-pain syndrome (Arnoldi et al. in press 1979 b)

Twenty-five patients with painful conditions in the hip or knee region were examined by means of ^{99m}Tc-polyphosphate scintigraphy, intraosseous and intravenous pressure measurements and intraosseous phlebography. Seventeen patients complained of typical rest pain in the hip or knee. Ten of these suffered from severe osteoarthritis, whereas seven fulfilled the criteria for the intraosseous engorgement-pain syndrome (Lempert & Arnoldi 1978). In the remaining eight patients the pain had a different character, such as pain on loading or joint movements. These pains were never present when the joint was completely at rest.

All the patients with painful osteoarthritis or the intraosseous engorgement-pain syndrome showed intraosseous venous stasis and hypertension in juxtaarticular bone marrow and increased uptake of the radionuclide over the affected joint (Fig. 11 and Fig. 21). This complete correlation between impaired drainage, increased pressure and increased uptake of the radio tracer was not observed in patients with pain due to other causes.

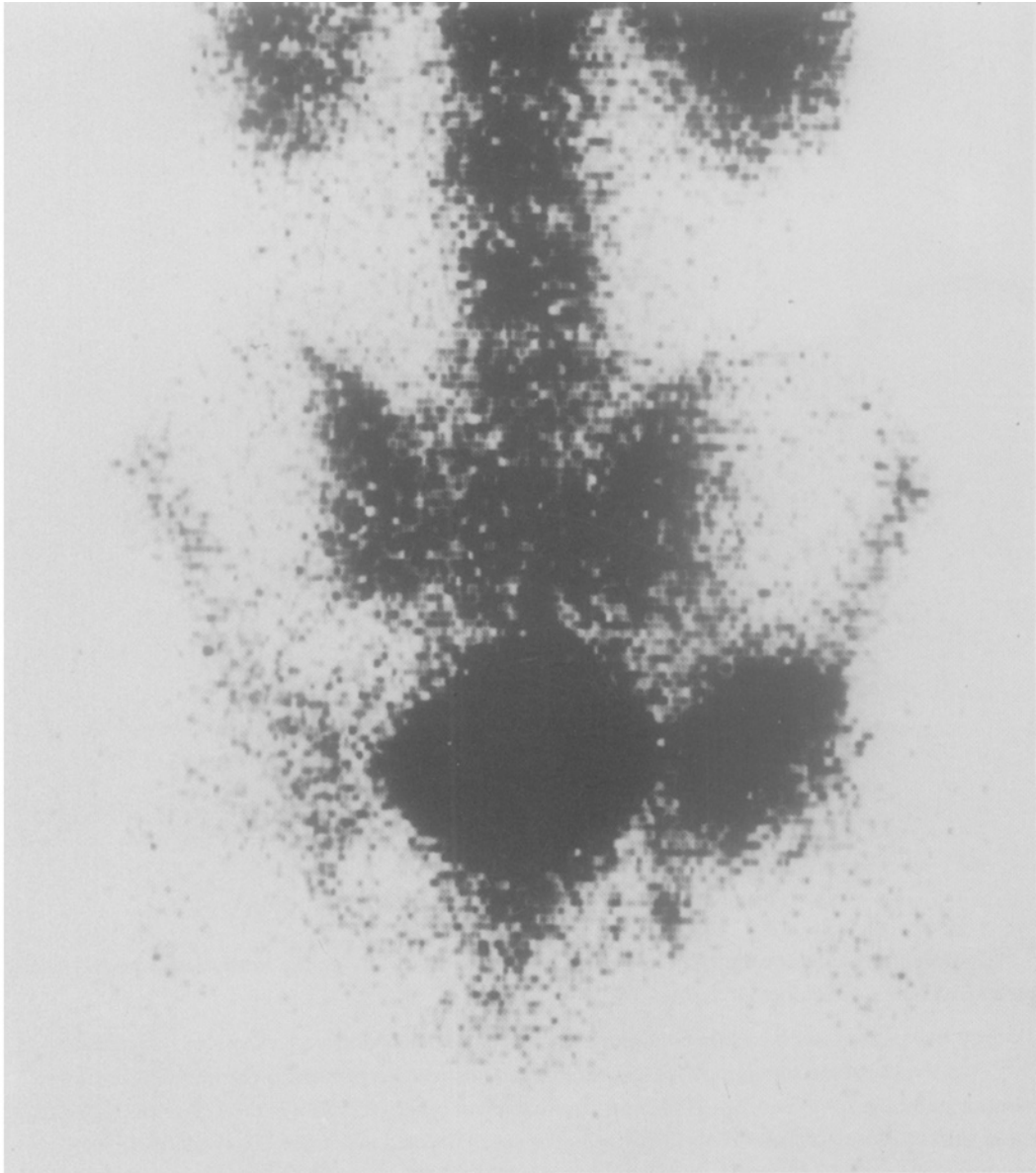


Fig. 21: ^{99m}Tc -polyphosphate scintigraphy from patient with unilateral painful coxarthrosis. Compare Fig. 11.

The authors concluded that the results may be an indication that the intraosseous engorgement-pain syndrome and osteoarthritis are two stages of the same pathological process.

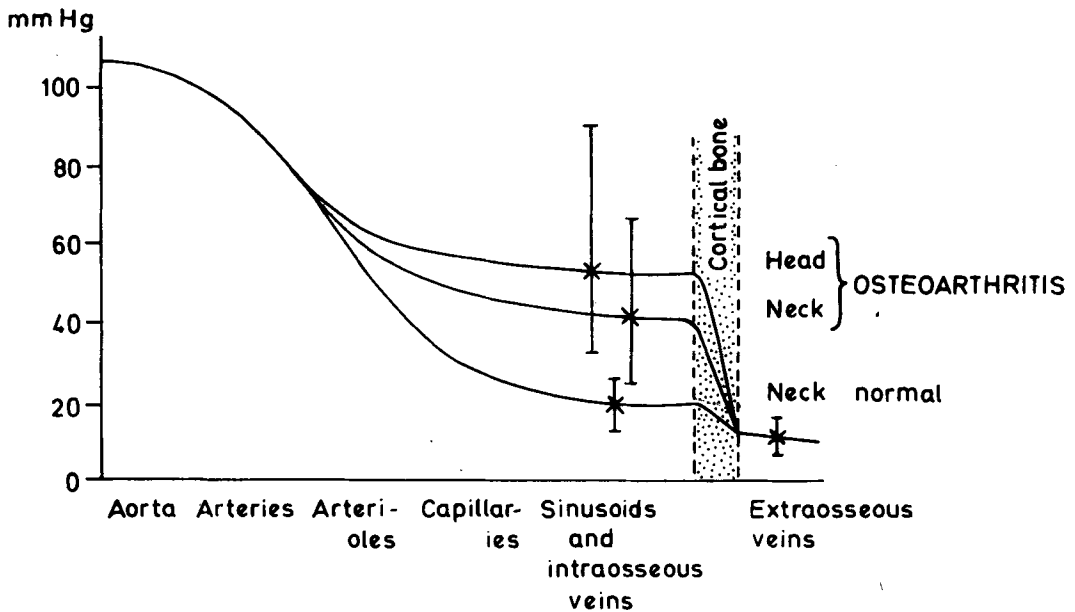


Fig. 22: Schematic representation of intraosseous and extraosseous pressures in patients with unilateral painful coxarthrosis.

Discussion

The conditions for capillary flow in the femoral head in coxarthrosis

Fig. 22 shows intramedullary and intravenous pressures from patients with unilateral coxarthrosis, together with mean arterial blood pressure measured on the upper arm. The findings are inserted into a Landis' curve of pressure distribution through the vascular system (Arnoldi et al. 1972 a). The rate of flow through the capillary depends upon the diameter of the vessel and upon the pressure difference between the arterial and venous end of the capillary. As seen in Fig. 22 this pressure difference decreases in coxarthrosis and more so in the femoral head than in the neck. Hyperplasia of the intramedullary arteries as demonstrated by Harrison et al. (1953) may be a compensatory reaction to the high resistance to flow on the venous side of the circulation. With a pressure distribution as shown in Fig. 22 the end result is probably a reduced nutritional flow to bone tissue, especially to the subchondral bone of the weight-bearing area of the femoral head. The slow clearance of radioactive NaI from the bone marrow of the femoral head demonstrated by Hernborg (1969) may be an indication of this state.

There is, however, both clinical and experimental evidence that the intraosseous pressure – and thus the resistance to capillary flow – may vary considerably with circumstances. If – as our findings induce us to believe – the characteristic rest pain is caused by excessively high pressure in the bone marrow, the appearance of pain after exercise and disappearance after a period of rest indicate variations of pressure depending upon activity. Fig. 23 illustrates the effect of prolonged bed rest upon the marrow pressure.

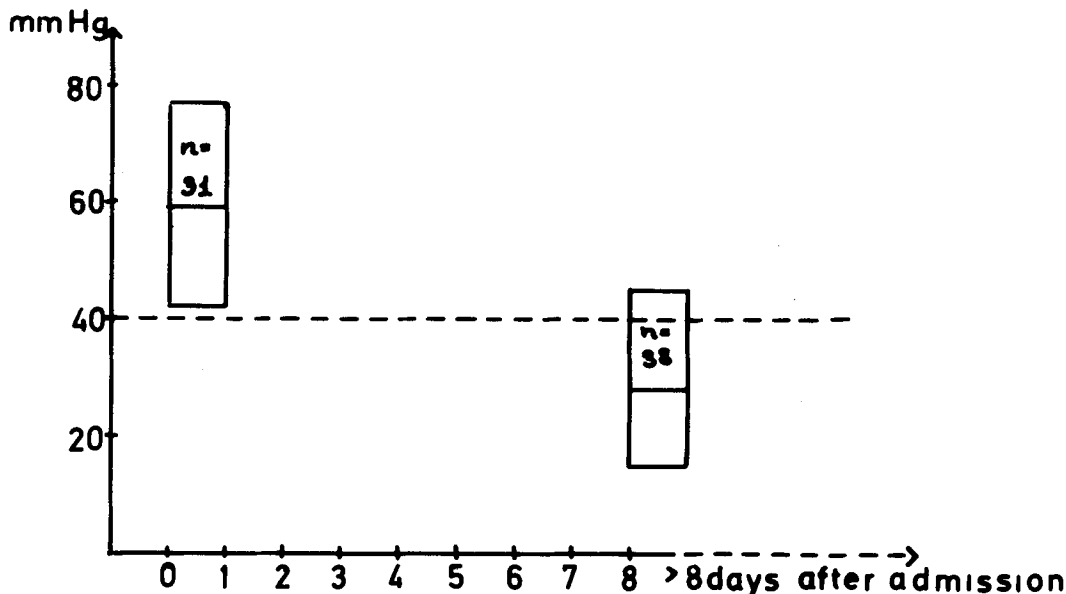


Fig. 23: Intraosseous pressures from the femoral neck of hip joints with coxarthrosis and a history of severe aching rest pains. Data from 69 hips. Pressure in mmHg, means and range. 31 hips examined within 24 hours after the patient was admitted to hospital, 38 examined after 8-22 days bed rest.

Fig. 22 indicates that under extreme circumstances the blood flow through subchondral bone marrow may virtually be at a stand still. The effect upon cellular nutrition would be very much the same as blockage at the arterial end of the system. Complete blockage of arterial inflow to bone results in death of the osteocytes within 8 to 24 hours (Rösingh & James 1969). Thus, clinical observations as well as experimental findings indicate considerable periodical variations in the amount of oxygen available to the cells in the femoral head.

The effect of reduced nutritive capillary flow on the bone structure of the femoral head

The finding of Hernborg (1969) of a reduced clearance of radioactive NaI from the femoral head in osteoarthritis and the intraosseous stasis and hypertension demonstrated by others indicate a reduced blood flow through the bone marrow of the femoral head in spite of continued arterial inflow. This would most probably result in a reduced PO_2 in the region. Direct measurements of oxygen tension in the bone marrow are surprisingly few, but some evidence of reduced oxygen tension has been presented (Brookes 1970, Pujol et al. 1973).

The histological picture of juxtaarticular bone in coxarthrosis is a mixture of bone death and new bone formation. Several authors are of the opinion that venous stasis and reduced oxygen tension are the factors responsible for new bone formation (Harrison et al. 1953, Pistolesi 1962, Abdalla & Harrison 1966, Phillips et al. 1967, Arnoldi et al. 1972 b). The investigations reported here indicate that the various phases of bone death and new bone formation might correlate with varying conditions for

cellular nutrition, which in their turn are dependent upon varying degrees of resistance to flow from the drainage vessels of the weight-bearing area of the femoral head.

Our investigations point to the weight-bearing area as the place where the changes from normal are most pronounced. We are convinced that mechanical factors play an important role in the deformation of the joint that is so obvious in coxarthrosis. However, not all these features are directly explained by the effect of mechanical forces (e.g. osteophytes). Our investigations also stress the fact that the weight-bearing area is the part of the femoral head that is drained by the superior retinacular veins and the part where the effects of venous stasis are most pronounced. In our opinion the question of the relative importance of mechanical forces and weakening of bone structure due to circulatory deficiency for the deformation seen in osteoarthritic joints is still unanswered. Theoretically, it is quite feasible to assume that mechanical forces are only able to cause deformation of a joint if they act upon tissues previously weakened by degenerative changes produced by circulatory derangement.

Are the vascular changes in subchondral bone marrow an early or late factor in the development of coxarthrosis?

Intraosseous stasis and high pressure in the vessels of the subchondral bone marrow are generally regarded as late and secondary manifestations of coxarthrosis which can be explained as a consequence of cartilage and bone changes (Freeman 1972). It is true that demonstration of vascular changes in the late stages of coxarthrosis does not necessarily indicate that these changes initiated the process leading to clinical osteoarthritis.

However, several well-known clinical facts combined with recent findings indicate that haemodynamic changes in juxtaarticular bone may – after all – be a very early and perhaps causative factor in the development of the *skeletal* changes characteristic of osteoarthritis.

- 1) The clinical observation that synovitis is a very common precursor to clinical osteoarthritis, combined with the finding that increased intraarticular volume and pressure is followed by an increase of pressure in juxtaarticular bone marrow (Arnoldi et al. 1979 a).
- 2) The experimental findings by Abdalla & Harrison (1966) that marrow stasis and high intramedullary pressure produced radiological and histological changes in cartilage and subchondral bone in albino rats that were consistent with those of human osteoarthritis.
- 3) The observation that long standing ambulatory hypertension in patients with chronic venous insufficiency leads to skeletal changes of the same character as seen in osteoarthritis (Arnoldi et al. 1972 b).
- 4) The observation that intraosseous stasis and hypertension may be observed in younger people with synovitis and pain, but without signs of cartilage destruction (the intraosseous engorgement-pain syndrome).

ARTICULAR CARTILAGE

The changes of articular cartilage in osteoarthritis are progressive with advancing disease, leading to complete loss of tissue. Most investigators are of the opinion that “degeneration” of this tissue is primary in the pathogenesis of osteoarthritis. Over the years a sizable part of the literature has been

concerned with attempts to analyse these changes. It is not our intention to review this literature as extensive treatises on the subject are available (e.g. Sokoloff 1969).

Numerous reports have been concerned with investigations of biochemical changes in the matrix of articular cartilage and a reduction in the amount of glycosaminoglycans, as well as alterations in quality, have been consistent findings in osteoarthritis (Mathews & Glagov 1966, Mankin & Lippiello 1970 and 1971, Bjelle et al. 1972, Lust & Pronsky 1972 and many others), but parallel with this reduction an increased synthesis of glycosaminoglycans was observed when $^{35}\text{SO}_4$ was incorporated (Collins & McElligot 1960, Mankin et al. 1971, Eronen et al. 1978).

The histological changes in osteoarthritis are characteristic (Collins 1949, Harrison et al. 1953, Sokoloff 1969, Mankin et al. 1971 and others) and a histological-histochemical grading system (Mankin et al. 1971) is available. It has been shown that this grading system correlates with biochemical (Mankin et al. 1972) as well as with enzyme abnormalities (Ehrlich et al. 1973) in the cartilage.

Own investigations

We have used this grading system to define the severity of the changes in articular cartilage from osteoarthritic femoral heads in various studies of the subchondral bone in order to compare the alterations in cartilage and subchondral bone (Reimann et al. 1977, Reimann & Christensen 1979).

Differential histochemical staining of glycosaminoglycans in osteoarthritic cartilage

In another study (Christensen & Reimann, in Press) we performed a histochemical analysis of articular cartilage from osteoarthritic femoral heads, using Safranin O, Alcian Blue-CEC and Toluidine Blue at different pH values. The purpose of the study was to demonstrate the presence and amount of chondroitin sulphate and keratan sulphate in the cartilage matrix and its distribution, compared with normal cartilage.

Safranin O was used to classify the degree of the osteoarthritic changes in cartilage according to the grading system of Mankin et al. (1979). Alcian Blue with critical electrolyte concentration principle (Scott & Dorling 1965) was used to differentiate chondroitin 4/6 sulphate from keratan sulphate (Laurent & Scott 1964, Scott 1967). Toluidine Blue at different pH values is a metachromatic staining and as shown by Krygier & Kasprzyk (1961) and Spicer (1962) persisting metachromasia at pH 1.5 indicates presence of sulphated glycosaminoglycans, while carboxyl groups lose their metachromasia at pH 3.

These investigations showed that the degree of cartilage degeneration in osteoarthritis varied considerably from site to site within the same femoral head. Pronounced changes were seen in weight-bearing areas, whereas less severe changes were present in non-weight-bearing areas. Reduction in staining ability was seen first and most distinctly at the surface. Apart from the loss of staining for glycosaminoglycans the osteoarthritic cartilage was characterized by increased territorial staining of chondroitin sulphate (Alcian Blue with 0.4 M MgCl_2), especially round cell clusters (Fig. 24 A and B). Further, keratan sulphate was found to be located more basally than chondroitin sulphate. In the cartilage of osteophytes practically only chondroitin sulphate was present. The increased territorial staining of chondroitin sulphate reflects an accelerated synthesis, possibly an attempt to repair as seen in immature cartilage.

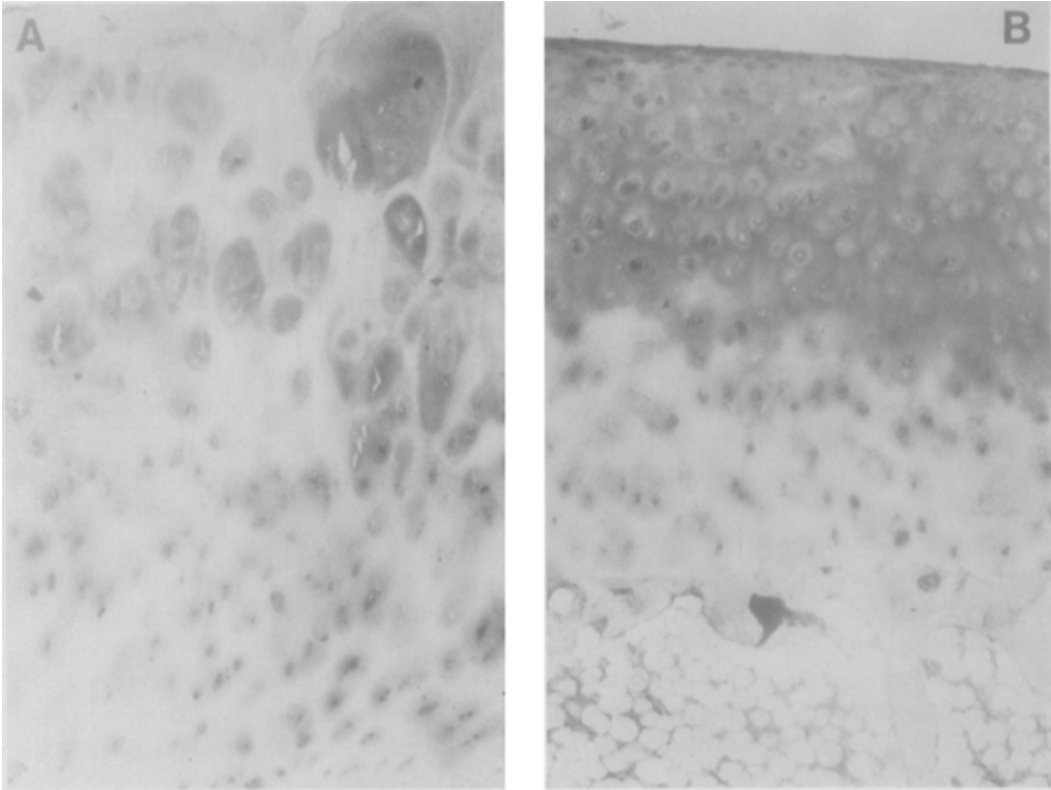


Fig. 24: **A:** *Osteoarthritic cartilage from a patient aged 50 years with intense territorial staining especially high around cell clusters. Alcian Blue with 0.4 M MgCl₂. Magnification x 100.*
B: *Articular cartilage from a patient aged 73 with fracture of the femoral neck. Alcian Blue with 0.4 M MgCl₂. Magnification x 100.*

Discussion

The choice of our investigations on articular cartilage from human osteoarthritic femoral heads was largely determined by our resources and have first and foremost been an attempt to determine whether a relationship exists between changes in cartilage and subchondral bone. Such a relationship has been suggested by means of biomechanical considerations (Radin et al. 1973, Pugh et al. 1974) and demonstrated as described above by quantitative histological analyses (Reimann et al. 1977). Further, it has been shown that the histological changes from osteoarthritic femoral heads, evaluated by the grading system of Mankin et al. (1971), correlate with biochemical and enzyme abnormalities of the osteoarthritic cartilage (Ehrlich et al. 1973). In our studies these correlations were most pronounced in the weight-bearing area.

Articular cartilage has no blood vessels of its own. Most investigators are of the opinion that cartilage is supplied with oxygen and nutrition through the vessels of the synovium via the synovial fluid and that the subchondral intraosseous vessels are of little importance in this respect.

As discussed previously, inflammation and stasis in the synovium reduce the rate of flow through the synovial vessels and increase the permeability of the capillary wall. One result of these changes is a lowering of oxygen tension in the synovial fluid (Lund-Olesen 1970). The protein and enzyme patterns are altered (see above) and striking changes in glycogen metabolism have been noted (Treuhaft & McCarty 1971, Lane et al. 1977). At the same time the lubricating function of the synovia probably is impaired (Reimann 1976).

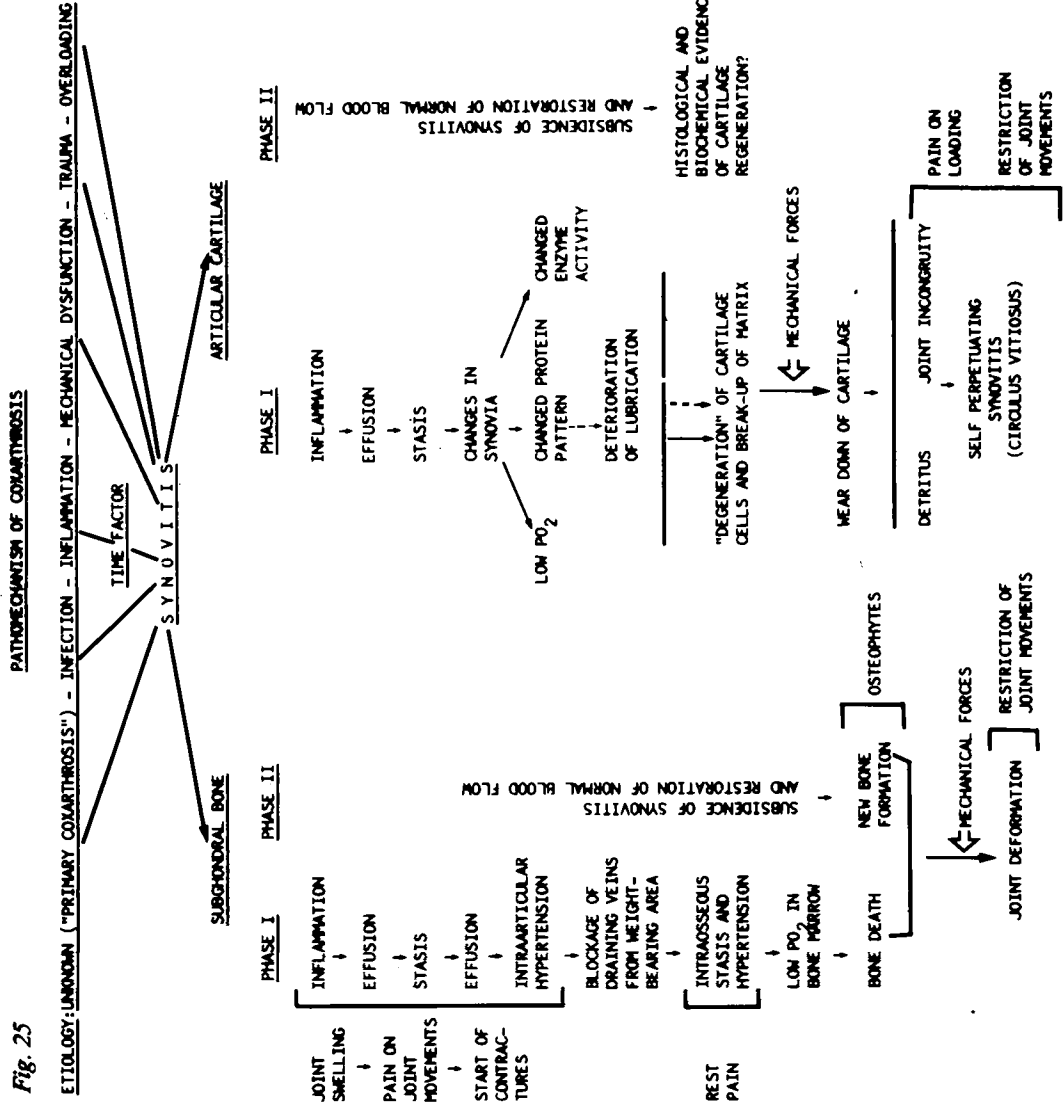
These changes in cartilage environment seem to us a reasonable – if still theoretical – cause of the changes observed in cartilage cells and matrix. Mechanical forces undoubtedly play an important part in the wear and tear that leads to tissue waste, but – as was the case in the question of changes in subchondral bone – we find it difficult to accept mechanical forces as primary causes of cartilage damage. To us the clinical course of osteoarthritis, as well as the experimental evidence, suggest that mechanical force is only able to damage cartilage that is weakened by other causes.

The evidence of our own investigations indicates that the changes observed in articular cartilage and subchondral bone are parallel reactions to the same primary pathological process.

GENERAL DISCUSSION

The findings in patients with osteoarthritis and the engorgement-pain syndrome by means of intraosseous phlebography and pressure measurements, combined with the results of a series of studies on the effects on the mesenchymal tissues of the ankle region of dysfunction of the venous pump of the calf in patients with chronic venous insufficiency (Arnoldi 1964, Arnoldi & Linderholm 1971), especially the changes of the ankle skeleton and joint (Arnoldi et al. 1972 b) led to the working hypothesis sketched in Fig. 1. The results of the studies reported here and reports from the literature are *tentatively* correlated in the hypothesis shown in Fig. 25.

Fig. 25



Aetiology and time factor

The investigations reported here have mainly been concerned with the pathomechanism of "primary" or "idiopathic" coxarthrosis and the intraosseous engorgement-pain syndrome. However, intraosseous pressure measurements and phlebography have been performed on a considerable number of patients

with coxarthrosis secondary to rheumatoid arthritis, Legg-Calvé-Perthe's disease and trauma, and painful secondary coxarthrosis after these disorders shows the same intraosseous stasis and hypertension as found in idiopathic coxarthrosis. We therefore assume the pathomechanism to be more or less identical in primary and most forms of secondary coxarthrosis. Their clinical course may be strikingly different, ranging from the silent period between the congenital hip dislocation and the appearance of clinical osteoarthritis decades later to the rapid development of secondary coxarthrosis after trauma or rheumatoid arthritis. These "time factor" differences have probably something to do with the severity of the aetiological factor. Apart from the specific effect of the rheumatoid inflammation on, e.g. the enzyme activity in the joint, patients with rheumatoid arthritis show the lowest synovial oxygen tension measured. As mentioned above we believe primary coxarthrosis to be the end result of a series of attacks of synovitis, sometimes stretching over a long period of years. In this connection it may be mentioned that in the ankle joint skeletal sclerosis and osteophyte formation, as well as genuine ankle joint osteoarthritis, usually appeared decades after the attack of thrombophlebitis of the deep veins of the extremity responsible for the dysfunction of the venous pump of the calf and the high pressure in the intra- and extraosseous veins of the ankle (Arnoldi et al. 1972 b).

Synovitis and the developments in juxtaarticular bone (Fig. 25)

The synovial membrane seems to react to any abnormal stimulus with essentially the same inflammatory reaction combined with effusion. The clinical examples are legion. The early synovial reaction is combined with a state of arterial hyperaemia, not only of the synovial membrane but also in juxtaarticular bone, where its effect on bone metabolism becomes visible on the isotope scintigram.

In early cases of clinical synovitis the X-rays are usually normal. Occasionally, especially in the more severe cases, they show a state of juxtaarticular osteopenia. The early stage of synovitis is mainly characterized by increased arterial inflow to the structures of the joint, also in cases that later develop into clinical osteoarthritis. This assumption seems to be supported by preliminary results from investigations on artificially induced osteoarthritis on animals (to be published).

The volume increase of synovial membrane and effusion result in increased intraarticular pressure. The effect on the synovial membrane is venous stasis and – as long as the arterial inflow is intact – further joint effusion. As shown in the experiments on rabbit joints a rise of intraarticular pressure is followed by a rise of intraosseous pressure. In the hip joint this must be due to compression of the retinacular veins as they pass from the weight-bearing part of the femoral head through the joint.

In the proximal part of the femur blockage of the draining vessels leads to intraosseous stasis and hypertension. Although the conditions for capillary flow through the femoral head seem to vary, e.g. with physical activity, the findings indicate that the resistance to flow occasionally becomes so great that the oxygen supply to the osteocytes fails. The result is bone death.

Rest, physical treatment and medication seem to be effective in the treatment of many cases of synovitis. Reduction of joint swelling and intraarticular pressure may restore the drainage through the retinacular veins and improve the conditions for bone marrow blood flow. The characteristic histological findings of new bone deposited on dead trabeculae could be the result of this improvement of capillary flow.

Regional bone necrosis and new bone formation leave the femoral head vulnerable to deformation by mechanical forces.

Synovitis and changes in articular cartilage (Fig. 25)

Increased permeability of the capillaries of the synovium caused by inflammation, and later by mechanical stasis, results in important changes in the synovial fluid which is the vehicle for the supply of oxygen and nutrition to the articular cartilage. The changes noted in Fig. 25 are probably just a few of the changes actually taking place. However, if the fact holds true that tissue degeneration and death are the end results of a lack of oxygen, this factor alone should be sufficient to explain the fate of cartilage in osteoarthritis. Even if there should be some foundation for the opinion held by some authors that the basal layers of cartilage are supplied by the subchondral vessels the circulatory derangement in subchondral bone would embarrass this source of supply.

We think that the circumstantial evidence supporting our assumption that cartilage degeneration is due to biochemical changes in the synovial fluid is logically impressive. We are, however, aware that as far as we know this assumption has not been proved by experimental evidence, although Abdalla & Harrison (1966) found signs of cartilage disorganisation as a result of induced venous stasis and hypertension. In our studies of the literature on cartilage research we have noted that, in spite of all the accumulated special knowledge, the ultimate cause of the osteoarthritic changes is generally conceived of as some vague "mechanical dysfunction".

In our opinion mechanical forces are important in the pathomechanism of osteoarthritis, but their main role comes late in the process, when the cartilage is already weakened by tissue degeneration, ultimately due to changes in cellular environment. If this course of events is accepted it is easier to explain why idiopathic coxarthrosis is so often unilateral, why the ankle joints are so rarely affected, etc.

When the mechanical forces become effective the devitalized cartilage is exposed to the wear and tear that results in complete tissue waste, erosion and denudation of the joint surface. The detritus of the worn-down cartilage is caught in the plicae of the synovium and helps to perpetuate the pathological process in this membrane.

Other causes of coxarthrosis

We would like to emphasize here that the pathomechanism suggested in this paper and schematically presented in Fig. 25 is but one of several pathological processes that may lead to coxarthrosis. In this mechanism the key feature is vascular derangement due to high resistance on the venous side of the capillary network, but with intact arterial inflow to the structures of the joint.

In certain forms of osteoarthritis a local arterial failure plays an important role in the pathomechanism. This is the case in coxarthrosis secondary to necrosis of the femoral head after intracapsular fracture of the neck. Bone necrosis due to arterial blockage is probably also important for the development of osteoarthritis after transplantation surgery and steroid medication in immunosuppression, in certain cases of osteoarthritis in alcoholics, and possibly in other diseases.

Correlation of clinical signs and symptoms to the developmental stages of coxarthrosis

In Fig. 25 we have made an attempt to correlate the clinical signs and symptoms of coxarthrosis with the various stages of the pathological process. While some of these correlations are too obvious to deserve comment a few words on the subject of pain seem necessary.

Patients with coxarthrosis may suffer from different qualities of pain. Most of them complain of pain when the joint is moved, especially when the limits of movements are approached. Pain on loading is equally common. Rest pain is especially typical of coxarthrosis. It is characteristic for the pain in coxarthrosis that it tends to radiate down the thigh to the knee region.

Cartilage does not contain nerves, but sensitive nerve endings are found in the synovium and the fibrous capsule as well as in the bone marrow, where the nerves are found together with the blood vessels. Recently, Reimann & Christensen (1977) demonstrated a higher density of nerves in osteoarthritic subchondral bone marrow than in normal and ascribed the increase to the hyper-vascularity of osteoarthritis.

Joint distension by effusion may in itself be painful and the pain increases when the swollen joint is moved. Stretching of the capsule and pinching of swollen synovium are obvious causes of pain. However, the reaction of intraosseous pressure to rise in intraarticular pressure brings another pain mechanism into focus. By now most authors agree that rest pain is due to intraosseous stasis and hypertension (Arnoldi et al. 1971, Bulstrode 1976). The threshold for pain seems to vary individually (Lempert & Arnoldi 1978), but in most cases a rise above 40 mmHg will produce the characteristic rest pain.

In a joint with effusion, forced movements raise the pressure in the joint and may increase the intraosseous pressure above the threshold of pain.

The intraosseous phlebograms showed dilation of all veins in the bone marrow of patients with painful coxarthrosis and the intraosseous engorgement-pain syndrome. Distension of veins is known to be connected with the "bursting pain" characteristic of patients with chronic venous insufficiency of the lower leg or idiopathic dysfunction of the venous pump of the calf (cruralgia orthostatica) (Arnoldi 1964 and 1976). Thus, there are some indications that the distension of the veins caused by intraosseous venous stasis may be the factor responsible for the rest pain of osteoarthritis. The findings that venous dilation and increased intraosseous pressure can be demonstrated not only in the femoral head and neck, but also – although less pronounced – throughout the bone marrow of the femur, might explain the pain radiating towards the knee joint characteristic of coxarthrosis.

Future problems

In our opinion the results of the investigations presented in this paper give a reasonable basis for most of the developments sketched in Fig. 25. The changes represent disturbances of an interacting mechanism and we have attached importance to the internal correlation of our findings. At the time of writing our main problem – still poorly supported by experimental evidence – is the effect of changes in the composition of the synovial fluid upon articular cartilage. However, our choice of investigations has been determined by the resources of our laboratories and are not a result of any bias.

One good reason for publishing the paper now is that it might provoke critical inquiry in centres with greater resources in the field of cartilage research.

REFERENCES

- Abdalla, A. B. E. & Harrison, R. G. (1966) Observations on the reaction of tubular bone to venous stasis. *J. Anat.* 100, 627-638.
- Andersen, H. (1970) Histochemical investigations on the development of the joint and bone systems of the human foetus during the first half of prenatal period, pp. 48-69. Thesis, Axelholm, Copenhagen.
- Arlet, J., Ficat, P. & Sebbag, D. (1968) Intéret de la mesure de la pression intramédullaire dans la massif trochantérien chez l'homme, en particulier pour le diagnostic de l'ostéonécrose fémoro-capitale. *Rev. Rhum.* 35, 250-256.
- Arnoldi, C. C. (1964) The venous return from the lower leg in health and in chronic venous insufficiency. *Acta Orthop. Scand.*, Suppl. 64.
- Arnoldi, C. C. (1966) Venous pressure in patients with valvular incompetence of the veins of the lower limb. *Acta Chir. Scand.* 132, 628-645.
- Arnoldi, C. C. & Linderholm, H. (1968) On the pathogenesis of the venous leg ulcer. *Acta Chir. Scand.* 134, 427-440.
- Arnoldi, C. C., Lemperg, R. K. & Linderholm, H. (1971) Immediate effect of osteotomy on the intramedullary pressure of the femoral head and neck in patients with degenerative osteoarthritis. *Acta Orthop. Scand.* 42, 357-365.
- Arnoldi, C. C. & Linderholm, H. (1971) Intracalcaneal pressure in patients with different forms of dysfunction of the venous pump of the calf. *Acta Chir. Scand.* 137, 21-27.
- Arnoldi, C. C., Linderholm, H. & Müssbichler, H. (1972 a) Venous engorgement and intraosseous hypertension in osteoarthritis of the hip. *J. Bone Jt Surg.* 54-B, 409-421.
- Arnoldi, C. C., Linderholm, H. & Vinnerberg, Å. (1972 b) Skeletal and soft tissue changes in the lower leg in patients with intracalcaneal hypertension *Acta Chir. Scand.* 138, 25-37.
- Arnoldi, C. C., Lemperg, R. K. & Linderholm, H. (1975) Intraosseous hypertension and pain in the knee. *J. Bone Jt Surg.* 57-B, 360-363.
- Arnoldi, C. C. (1976). Physiologie und Pathophysiologie des venösen Rückstromes aus der unteren Extremität. In Karl Sigg: *Varizen Ulcus Cruris und Thrombose*. 4. aufl., pp. 6-17 Springer-Verlag, Berlin-Heidelberg-New York.
- Arnoldi, C. C., Reimann, I., Christensen, S. Bach & Mortensen, S. (1979 a) The effect of increased intraarticular pressure on juxtaarticular bone marrow pressure. *IRCS Med. Sci.* 7, 471.
- Arnoldi, C. C., Djourhuus, J. C., Heerfordt, J. & Karle, A. (1979 b) Intraosseous phlebography, intraosseous pressure measurements and ^{99m}Tc-polyphosphate scintigraphy in patients with various painful conditions in the hip and knee. *Acta Orthop. Scand.* (in Press).
- Arnoldi, C. C., Reimann, I. & Bretlau, P. (1979 c) The synovial membrane in human coxarthrosis. Light and electron microscopic studies. *Clin. Orthop.* (in Press).
- Barka, T. & Anderson, P. J. (1963) *Histochemistry*, p. 25. Harper and Row, New York.
- Bjelle, A. O., Antonopoulos, C. A., Engfeldt, B. & Hjertquist, S. O. (1972) Fractioning of the glycosaminoglycans of human articular cartilage on Ecteola cellulose in ageing and in osteoarthritis. *Calc. Tiss. Res.* 8, 237-246.
- Brookes, M. (1970) Personal communication.
- Bulstrode, C. J. (1976) Why are osteoarthritic joints painful? *J. Roy. Nav. Med. Serv.* 62, 5-16.

- Burnett, D., Wood, S. M. & Bradwell, A. R. (1976) Estimation of the Stokes radii of serum proteins for a study of protein movement from blood to amniotic fluid. *Biochim. Biophys. Acta* 427, 231-237.
- Burstone, M. S. (1959) Histochemical demonstration of acid phosphatase activity in osteoclasts. *J. Histochem. Cytochem* 7, 39-41.
- Christensen, S. Bach & Arnoldi, C. C. (1979) Distribution of ^{99m}Tc-phosphate compounds in osteoarthritic femoral heads. *J. Bone Jt Surg. (Am. Vol)* in Press.
- Christensen, S. Bach & Reimann, I. Differential histochemical staining of glycosaminoglycans in the matrix of osteoarthritic cartilage. *Acta Path. Microbiol. A* (in Press).
- Collins, D. H. (1949) *The pathology of articular and spinal diseases*, pp. 74-115. Edward Arnold & Co., London.
- Collins, D. H. & McElligot, T. F. (1960) Sulphate (³⁵SO₄) uptake by chondrocytes in relation to histological changes in osteoarthritic human articular cartilage. *Ann. Rheum. Dis.* 19, 318-330.
- De Anrade, J. R., Grant, C. & Dixon, St. J. (1965) Joint distension and reflex muscle inhibition in the knee. *J. Bone Jt Surg.* 47, 313-322.
- De Duve, C. (1964) Lysosomes and cell-injury. *Symposium on injury, inflammations and immunity*. Ed. by L. Thomas, J. W. Uhre & L. Grant, Baltimore.
- Doty, S. B. & Scofield, B. H. (1976) Enzyme histochemistry of bone and cartilage cells. *Prog. Histochem. Cytochem.* 8, 1-38.
- Dryll, A., Lansaman, J., Cazalis, P., Peltier, A. P. & De Seze, S. (1977) Light and electron microscopy study of capillaries in normal and inflammatory human synovial membrane. *J. Clin. Path.* 30, 556-562.
- Erlich, M. G., Mankin, H. J. & Treadwell, B. A. (1973) Acid hydrolase activity in osteoarthritic and normal human cartilage. *J. Bone Jt Surg.* 55-A, 1068-1076.
- Eronen, I., Videman, T., Friman, C. & Michelsson, J-E. (1978) Glycosaminoglycan metabolism in experimental osteoarthrosis caused by immobilization. *Acta Orthop. Scand.* 49, 329-334.
- Eyring, E. J. & Murray, W. R. (1964) The effect of joint position on the pressure of intra-articular effusion. *J. Bone Jt Surg.* 46-A, 1235-1241.
- Favreau, J. C. & Laurin, C. A. (1963) Joint effusions and flexion deformities. *Can. Med. Assoc. J.* 88, 575-576.
- Foss, M. V. & Byers, P. D. (1972) Bone density, osteoarthrosis of the hip and fracture of the upper end of femur. *Ann. Rheum. Dis.* 31, 259-264.
- Freeman, M. A. (1972) The pathogenesis of primary osteoarthrosis: An hypothesis. In: *Modern Trends in Orthopaedics* - 6, pp. 40-94. Ed. by Graham Apley. Butterworths, London.
- Goldhaft, A. D., Wright, L. M. & Pemberton, R. (1930) The production of hypertrophic arthritis by interference with the blood supply. *Am. J. Med. Sci.* 180, 386-397.
- Goldie, I. (1970) The synovial microvascular derangement in rheumatoid arthritis and osteoarthritis. *Acta Orthop. Scand.* 40, 751-764.
- Harris, W. H. & Weinberg, E. H. (1972) Microscopic method of measuring increase in cortical bone volume and mass. *Calc. Tiss. Res.* 8, 191-196.
- Harrison, M. H. M., Schajowicz, F. & Trueta, J. (1953) Osteoarthritis of the hip: A study of the nature and evolution of the disease. *J. Bone Jt Surg.* 35-B, 598-626.
- Haxthausen, H. (1936) Om pathogenesisen af ulcer cruris varicosum. *Nord. Med.* 12, 1665-1670.

- Heerfordt, J., Vistisen, L. & Bohr, H. (1976) Comparison of ^{18}F and $^{99\text{m}}\text{Tc}$ -polyphosphate in orthopaedic bone scintigraphy. *J. Nucl. Med.* 17, 98-103.
- Helal, B. (1962) Osteoarthritis of the knee. Thesis, University of Liverpool.
- Herborg, J. (1969) Elimination of $\text{Na }^{131}\text{I}$ from the head and the neck of the femur in unaffected and osteoarthritic hip joints. *Arthr. Rheum.* 12, 30-33.
- Hopsu, V. K. & Glenner, G. G. (1965) A histochemical enzyme kinetic system applied to the trypsin-like amidase and esterase activity in human mast cells. *J. Cell. Biol.* 17, 503-520.
- Hulth, A. (1959) Circulatory disturbances in osteoarthritis of the hip. *Acta Orthop. Scand.* 28, 81-89.
- Huth, F., Soren, A., Rosenbauer, K. A. & Klein, W. (1973) Fine-structural changes of the synovial membrane in arthrosis deformans. *Virch. Arch. A. Path.* 359, 201-211.
- Jayson, M. I. V. & Dixon, A. St. J. (1970) Intra-articular pressure in rheumatoid arthritis of the knee. III. Pressure changes during joint use. *Ann. Rheum. Dis.* 29, 401-408.
- Jeffrey, A. K. (1973) Osteogenesis in the osteoarthritic femoral head. *J. Bone Jt Surg.* 55-B, 262-272.
- Jeffrey, G. M. (1959) Phosphatase activity in the limb bones of growing rabbits. *J. Bone Jt Surg.* 41-B, 401-412.
- Jeffrey, G. M. & Price, C. H. (1965) Bone tumours and their enzymes. *J. Bone Jt Surg.* 47-B, 120-136.
- Kar, N. C., Cracchiolo, A., Mirra, J. & Pearson, C. M. (1976) Acid, neutral and alkaline hydrolases in arthritic synovium. *Am. J. Clin. Path.* 65, 220-228.
- Krygier, A. & Kazimierz, K. (1961) The influence of hydrogen-ion concentrations and some other ions on metachromasia in staining mucopolysaccharides with toluidine blue. *Acta Med. Polona* 2, 123-145.
- Kushner, I. & Sommerville, A. (1971) Permeability of human synovial membrane to plasma proteins. Relationship to molecular size and inflammation. *Arthr. Rheum.* 14, 560-570.
- Lane, J. M., Brighton, C. T. & Menkowitz, B. J. (1977) Anaerobic and aerobic metabolism in articular cartilage. *J. Rheum.* 4, 334-342.
- Laurell, C-B. (1966) Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Anal. Biochem.* 15, 45-52.
- Laurent, T. C. & Scott, J. E. (1964) Molecular weight fractionation of polyanion by cetylpyridinium chloride in salt solutions. *Nature* 202, 661-662.
- Lempert, R. K. & Arnoldi, C. C. (1978) The significance of intraosseous pressure in normal and diseased states with special reference to the intraosseous engorgement-pain syndrome. *Clin. Orthop.* 136, 143-156.
- Lloyd-Roberts, G. C. (1953) The role of capsule changes in osteoarthritis of the hip joint. *J. Bone Jt Surg.* 35-B, 627-642.
- Lund-Olesen, K. (1970) Oxygen tension in synovial fluids. *Arthr. Rheum.* 13, 769-776.
- Lust, C. & Pronsky, W. (1972) Glycosaminoglycan content of normal and degenerative articular cartilage from dogs. *Clin. Chim. Acta* 39, 281-286.
- Mankin, H. J. & Lippiello, L. (1970) Biochemical and metabolic abnormalities in articular cartilage from human osteoarthritic hips. *J. Bone Jt Surg.* 52-A, 424-434.
- Mankin, H. J. & Lippiello, L. (1971) The glycosaminoglycans in normal and arthritic cartilage. *J. Clin. Invest.* 50, 1712-1719.

- Mankin, H. J., Dorfman, H., Lipiello, L. & Zarins, A. (1972) Biochemical and metabolic abnormalities in articular cartilage from osteoarthritic human hips. II. Correlation of morphology with biochemical and metabolic data. *J. Bone Jt Surg.* 53-A, 523-537.
- Mathews, B. F. & Glagov, S. (1966) Acid mucopolysaccharide pattern in aging human cartilage. *J. Clin. Invest.* 45, 1103-1111.
- Melsen, F., Mosekilde, L. & Beck-Nielsen, H. (1975) Kvantitativ histologisk undersøgelse ved metaboliske knoglelidelser. *Ugeskr. Læg.* 137, 933-935.
- Mériel, P., Ruffié, R. & Fournié, A. (1955) La phlébographie de la hanche dans les coxarthroses. *Rev. Rhum.* 22, 238-241.
- Nettelblad, E. & Sundblad, L. (1959) Protein patterns in synovial fluid and serum in rheumatoid arthritis and osteoarthritis. *Arthr. Rheum.* 2, 144-151.
- Phemister, D. B. (1940) Changes in bones and joints resulting from interruption of circulation. *Arch. Surg.* 41, 436-472.
- Phillips, R. S. (1966) Phlebography in osteoarthritis of the hip. *J. Bone Jt Surg.* 48-B, 280-288.
- Phillips, R. S., Bulmer, J. H., Hoyle, G. & Davies, W. (1967) Venous drainage in osteoarthritis of the hip. *J. Bone Jt Surg.* 49-B, 301-309.
- Pistolessi, G. F. (1962) Il circolo venoso profondo dell'anca nell'artrosi. 9^oRussegna internazionale del film scientifico-diduttio. Università di Padova, Italy.
- Pridie, K. H. (1952) The development of osteoarthritis of the hip joint. *J. Bone Jt Surg.* 34-B, 153.
- Pruzanski, W., Russel, M. L., Gordon, D. A. & Ogryzlo, M. A. (1973) Serum and synovial fluid proteins in rheumatoid arthritis and degenerative joint diseases. *Amer. J. Med. Sci.* 265, 483-490.
- Pugh, J. W., Radin, E. & Rose, R. M. (1974) Quantitative studies of human subchondral cancellous bone. Its relationship to the state of its overlying cartilage. *J. Bone Jt Surg.* 56-A, 313-321.
- Pujol, M., Tran, M-A. & Arlet, J. (1973) Premiers résultats d'une étude gasométrique de sang osseux trochantérien dans les coxopathies. *Rev. Rhum.* 40, 515-519.
- Radin, E. L., Paul, I. L. & Tolkoff, M. J. (1970) Subchondral bone changes in patients with early degenerative joint disease. *Arthr. Rheum.* 13, 400-405.
- Radin, E. L., Parker, G. H. & Pugh, J. W. (1973) Response of joints to impact loading. III. Relationships between trabecular microfracture and cartilage degeneration. *J. Biomech.* 6, 51-57.
- Reimann, I., Stougaard, J., Northeved, A. & Johnsen, S. J. (1975) Demonstration of boundary lubrication by synovial fluid. *Acta Orthop. Scand.* 46, 1-10.
- Reimann, I. (1976) Pathological human synovial fluids, viscosity and boundary lubricating properties. *Clin. Orthop.* 119, 237-241.
- Reimann, I. & Christensen, S. Bach (1977) A histological demonstration of nerves in subchondral bone. *Acta Orthop. Scand.* 48, 345-352.
- Reimann, I., Mankin, H. J. & Trahan, C. (1977) Quantitative histologic analyses of articular cartilage and subchondral bone from osteoarthritic and normal human hips. *Acta Orthop. Scand.* 48, 63-73.
- Reimann, I. & Christensen, S. Bach (1979) A histochemical study of alkaline and acid phosphatase activity in osteoarthritic synovial membrane. *Scand. J. Rheum.* 8, 39-42.
- Reimann, I. & Christensen, S. Bach (1979) A histochemical study of alkaline and acid phosphatase activity in subchondral bone from osteoarthrotic human hips. *Clin. Orthop.* 140, 85-91.

- Reimann, I., Arnoldi, C. C. & Nielsen, O. Saxtrup. Permeability of synovial membrane to plasma proteins in human coxarthrosis. Relation to molecular size and histological changes. *Clin. Orthop.* (in Press).
- Renkin, E. M. (1977) Multiple pathways of capillary permeability. *Circul. Res.* 41, 735-743.
- Ropes, M. W. & Bauer, W. (1953) *Synovial fluid changes in joint disease*, pp. 6-8. Harvard University Press, New York.
- Roy, S. (1967) Ultrastructure of synovial membrane in osteoarthritis. *Ann. Rheum. Dis.* 26, 517-527.
- Rösingh, G. E. & James, J. (1969) Early phases of avascular necrosis of the femoral head in rabbits. *J. Bone Jt Surg.* 51-B, 165-174.
- Salvati, E. A., Granda, J. L., Mirra, J. & Wilson, P. D. (1977) Clinical, enzymatic and histological study of synovium in coxarthrosis. *Internat. Orthop.* 1, 39-42.
- Scott, J. E. & Dorling, J. (1965) Differential staining of acid glycosaminoglycans (mucopolysaccharides) by Alcian Blue in salt solutions. *Histochemie* 5, 211-233.
- Scott, J. E. (1967) On the use and abuse of the critical electrolyte concentration approach to the localization of tissue polyanions. *J. Histochem. Cytochem.* 15, 11-113.
- Sokoloff, L. (1969) *The biology of degenerative joint disease*. The University of Chicago Press, Chicago.
- Spicer, S. S. (1962) Histochemical differentiation of sulfated rodent mucins. *Ann. Histochem.* 7, 23-28.
- Timmer, J., Hadders, H. N., Dardonk, M. J. & Kondstaal, J. (1968) An experimental investigation into the development of callus and induced tumours in mice studies by histological and enzyme histochemical methods. *Brit. J. Cancer* 22, 422-436.
- Treuhart, P. S. & McCarty, D. J. (1971) Synovial fluid pH, lactate, oxygen and carbon dioxide partial pressure in various joint diseases. *Arthr. Rheum.* 14, 475-484.
- Wardle, E. N. (1964) Osteotomy of the tibia and fibula in the treatment of chronic osteoarthritis of the knee. *Postgrad. Med. J.* 40, 536-542.
- Wilkinson, M. & Jones, B. S. (1963) Evaluation of needle biopsy of synovial membrane. *Ann. Rheum. Dis.* 22, 100-105.
- Willumsen, L. & Friis, J. (1975) A comparative study of the protein pattern in serum and synovial fluid. *Scand. J. Rheum.* 4, 234-240.
- Wollenberg, G. A. (1909) Die ätiologie der arthritus deformans im lichte des experimentes. *Arch. Orthop. Mech. Therp. Unfallchir.* 7, 226-234.
- Zweifach, B. W. (1940) The structural basis of permeability and other functions of blood capillaries. *Cold. Spr. Harb. Symposia. Quant. Biol.* 8, 216-223.