MEDICAL GRAND ROUNDS

Southwestern Medical School

# "OSTEOARTHRITIS: THE SYNDROME OF CARTILAGE FAILURE"

October 30, 1975

# OSTEOARTHRITIS: THE SYNDROME OF CARTILAGE FAILURE

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## I. INTRODUCTION

Since the primary lesion in osteoarthritis consists of the functional and anatomic breakdown of articular cartilage, we may consider this pathologic entity as the syndrome of articular cartilage failure. This suggests that osteoarthritis is not a disease entity, drawing a parallel with cardiac failure, cartilage failure may be brought about either by an increase in the functional demands on essentially healthy tissue, by primary deterioration of the functional capacity of the tissues themselves or by a combination of both. Therefore, in order to understand how the joint breaks down it is necessary to consider the structure and function of the normal articular cartilage.

## II. NORMAL ARTICULAR CARTILAGE

*a. STRUCTURE.* The cartilage covering the ends of the bones of diarthrodial joints consist of a highly specialized form of connective tissue with properties well suited to its dual role as a shock absorber and a bearing surface. Cartilage is composed mainly of water, collagen fibers, matrix proteoglycan and chondrocytes. The cell density of articular cartilage is low as compared with many other tissues and most of its mass consists of the macromolecular extracellular matrix. Features of the adult cartilage cells observed by light microscopy such as their small size and shrunken appearance, a pyknotic, irregularly shaped nucleus suggested to early investigators that cartilage was an inert, hypometabolic structure. Despite their appearance, there is now ample evidence that chondrocytes are metabolically very active (1,9,10), utilizing both anaerobic and aerobic degradative pathways (11). As a matter of fact, oxygen utilization and metabolic activity per cell is quite high, comparing favorably with the activity of liver cells (12, 13). The collagen fibers, responsible for the cartilage's shape and strength are anchored to subchondral bone and ascend through the calcified boundary layer, run perpendicularly toward the surface and then course tangentially below the surface (14). It has been recently shown that cartilage collagen is of a different species than that of skin and bone (15,16) whereas the triple helix of skin and bone collagen (type I) consists of two $\alpha 1$ and one $\alpha 2$ chain, the collagen of cartilage (type II) contains three $\alpha 1$ chains (17). Furthermore, cartilage collagen is richer in hydroxylysine and glycosyl residues as well as in the pattern of intramolecular and intermolecular crosslinks.

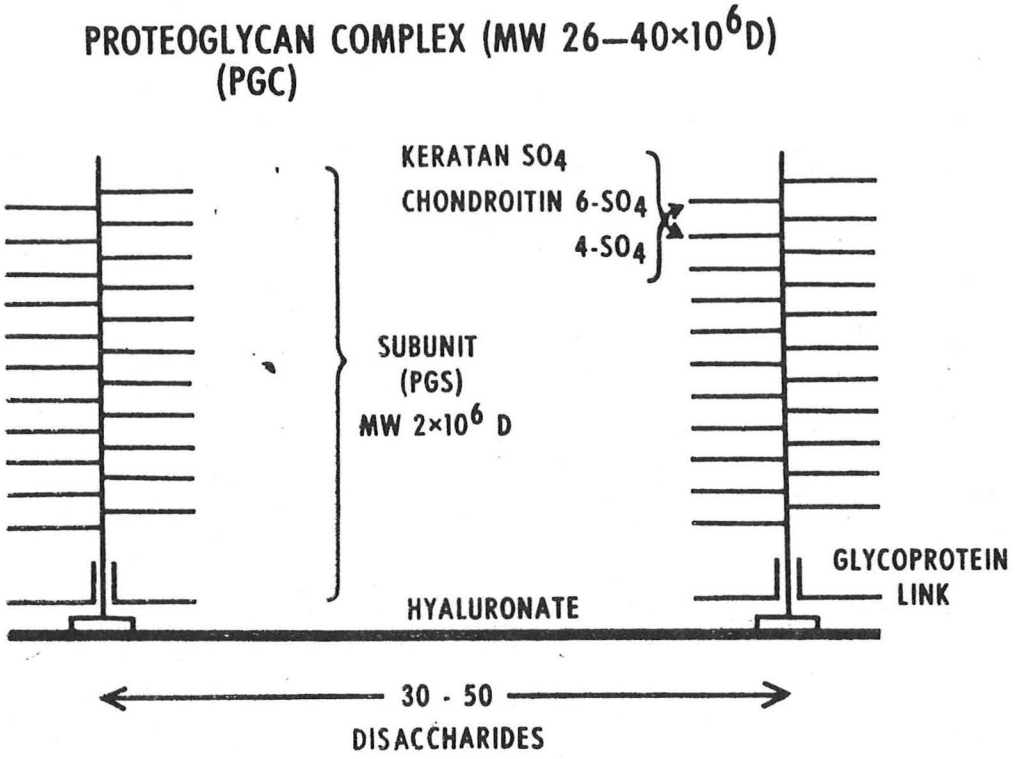


Figure 1 - Structure of the matrix proteoglycan.

In between the fiber mesh and intimately attached to the collagen lies the intercellular proteoglycan matrix. When cartilage is stained with dyes specific for the matrix proteoglycan it is seen that the articular surface and the zone underlying it fail to stain for anionic polysaccharides. Further work has demonstrated low concentration of acidic charges (18) and low proteoglycan synthetic activity by the chondrocytes lying near the articular surface (19). The matrix of articular cartilage has some extraordinary biochemical characteristics. Cartilage is a hyperhydrated tissue with estimates of water content ranging from 70 to 80 percent. The remaining constituents are macromolecular organic solids consisting of about equal parts of collagen and proteoglycan. The proteoglycan is in the form of very large aggregates synthesized by the chondrocytes and subsequently linked to the collagen fiber in the extracellular stage. The proteoglycan subunit has a linear protein approximately 200 um. in length to which are attached at right angles 50 or more long side chains of polymeric sugars known as glycosaminoglycans (20-22). The sugar units are highly charged containing one or two negatively charged groups per unit ($COO^-$ and $SO^{3-}$). The negative charges repel one another causing the macromolecule

to remain stiffly extended in space and establishing an electrostatic "domain" of a considerable magnitude (Figure 1). Glycosaminoglycan subunits do not remain separate but become linked together by a long hyaluronate molecule and two glycoprotein linkage materials to form large stellate aggregates of molecular weight of several million Daltons (23-25). These enormous, stiffly extended hydrophilic macromolecules are bonded to the collagen fibers which together with their physical properties make them ideal "stuffing" for the interstices between the collagen fibers. Thus, it has been shown by Harris (26) that the proteoglycan is responsible for the elastic properties of cartilage while the collagen fibers provide for the integrity of its shape. Proteoglycans are also responsible for the diffusion characteristics of cartilage. The extended acidic chains prevent passage of all but select small molecules so that proteins of molecular weight 40,000 or over are totally excluded (27).

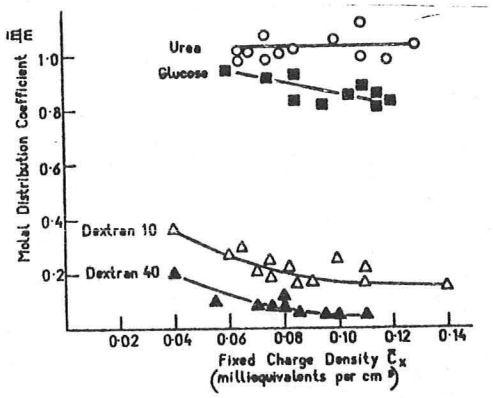


Figure 2 - Penetration of molecules of different sizes into cartilage.

*b. PHYSIOLOGY. 1. Metabolic studies.* As mentioned above, despite their appearance on light microscopy, the cartilage chondrocytes are metabolically very active. Numerous metabolic studies using radioactive isotopes have shown that these cells synthesize the macromolecular proteoglycans and collagen, assemble them intracellularly and rapidly extrude them into the surrounding matrix (10,28,29). This synthetic

activity appears to be almost entirely devoted to renewal of the extracellular matrix and experimental work has shown that a small portion of the proteoglycan in adult rabbit cartilage has a half-life of approximately 8 days (30) while collagen and other proteoglycan are also metabolically active but turnover occurs at a slower rate, from 20 to 500 days (31). In view of the large size of the proteoglycan molecules trapped within the collagen fiber meshwork, it is very likely that the physiologic loss of matrix involves breakdown of the large molecules by neutral and acidic proteases known to exist in chondrocytes and the intercellular matrix itself (32-35).

The chondrocytes of immature cartilage have been shown to replicate actively (36,37) being responsible for the gradual enlargement of the cartilage mass associated with skeletal growth and for growth by enchondral ossification of the bony nucleus of the epiphysis. With maturity, DNA synthetic activity appears to cease (38,39) and mitotic figures are never seen in the adult articular cartilage under normal conditions (37,38,40). Nevertheless, under certain circumstances such as cartilage laceration (41) and as we will see later, osteoarthritis, the articular chondrocyte can reinitiate DNA synthesis and cell division.

2. *Nutrition.* Vascular channels and capillary loops have been observed to pass from epiphyseal bone marrow through canals in the subchondral bone to the calcified zone of the articular cartilage and return to the marrow (42). In the adult, articular cartilage is avascular, approximately the outermost two-thirds, the portion affected by the early events in osteoarthritis, receives its nutrition through exchange of substances between synovial fluid and matrix. This exchange is augmented by normal use of a joint, compression of cartilage squeezes fluid out of it, then sucking the fluid back when the compression is released (43). In contrast, when all joint motion is prevented, cartilage degenerates, apparently because of lack of nutrition (28).

3. *Lubrication.* It is now widely accepted that normal articular cartilage surfaces are irregular when examined in the nonloaded state, *in vivo* and *in vitro* (44-46). The most prominent features include undulations of 200 to 400 um diameter and small ovoid hollows measuring 20 to 45 um. In spite of this degree of roughness, the joint surfaces have been shown to have a friction coefficient about one order of magnitude lower than that of industrial bearings (47-48).

FRICTION COEFFICIENTS OF DIFFERENT SURFACES

| Material | Friction Coefficient |
|---|---|
| Plastic on plastic | 0.1 - 0.3 |
| Metal on metal | 0.3 - 0.8 |
| Lubricated bearing | 0.05 - 0.01 |
| Joint surfaces | 0.01 - 0.001 |

It was first thought that the mechanism of lubrication of the joints was similar to that of machine bearings i.e.: hydrodynamic lubrication (49). In this process, movement of part of the bearing against the other drags a film of fluid across, separating the articular surfaces. It was pointed out by Charnley in 1959 (50) that this mechanism was totally unsuited for the joints. Hydrodynamic lubrication is notoriously difficult to achieve with slow moving surfaces under heavy loads. Moreover, hydrodynamic lubrication would be impossible in view of the reciprocating motion of joints. When the coefficient of friction was measured in joints, it was apparent that as the cartilage became dry, the friction coefficient increased precipitously and the joint surface wore rapidly. Jones (48) suggested that a boundary phenomenon might be responsible for the low friction in wet joints. In boundary lubrication, the lubricant molecules stick to the bearing surfaces preventing direct contact between the metal surfaces. Synovial fluid solutions lubricate joint surfaces better than serum, buffer or machine oil. This is thought to be due to the fact that synovial fluid sticks firmly to the surfaces producing the boundary effect. This mechanism is believed to be important during slow motion and under light loads, under heavy loads the boundary films break and other lubricating processes may play a role. It was Charles McCutchen, as a young postdoctoral student at the Cavendish Laboratories, who suggested another lubricating mechanism. McCutchen, initially a nuclear physicist, had a friend who was working with rubazote, a kind of sponge whose pores interconnect in such a way that the fluid is squeezed out of it only in certain directions. Apparently, having pilfered a piece of rubazote to add to his ablutions,

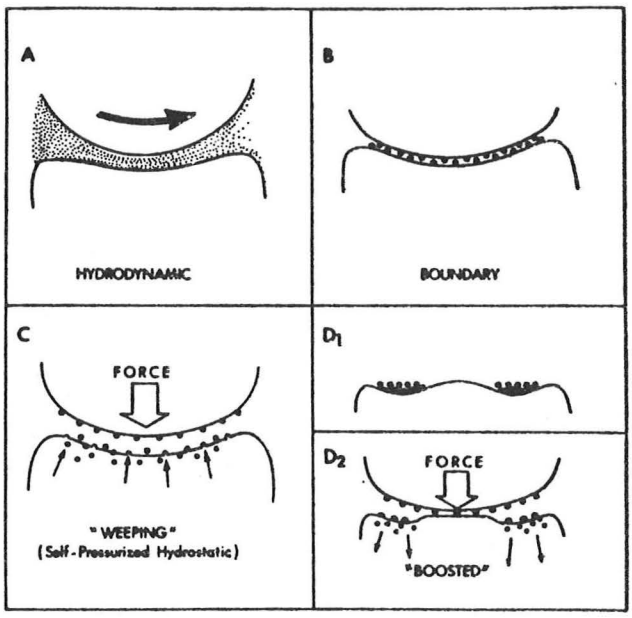


Fig.3 . Diagrams of lubrication theories as applied to joints.

A. In hydrodynamic lubrication, a wedge of viscous synovial fluid forms in the non-congruent area of opposing cartilage surfaces (left). Relative motion in the direction of the arrow, drags a film of viscous fluid across the cartilage surfaces, which are separated by the fluid film.

B. Under boundary conditions, closely approximated and congruent cartilage surfaces are separated only by an adsorbed molecular layer of fluid.

C. Heavy loads imposed on cartilage express fluid from the interstices of the cartilage (small arrows), a process called by McCutchen (1962, 1966) "weeping lubrication", or more precisely, self-pressurized hydrostatic lubrication. The non-viscous fluid film is thought to supplement the boundary conditions prevailing under low loads.

$D_1$. Electron microscopic observations of cartilage suggest a rough surface compared to metal bearings. Synovial fluid may pool in areas of relative depression. Hyaluronic acid molecules are indicated by larger stippled circles.

$D_2$. During joint motion, boundary conditions occur at points of contact, but lubricant properties of synovial fluid are said to be "boosted" when water and small molecules are forced into the cartilage (small arrows), presumably concentrating the hyaluronic acid on the surface, and thereby providing a viscous fluid film (Walker et al., 1968).

McCutchen noted that this sponge, when filled with soapy water had remarkably low friction against the sink rim. Further experiments, which probably caused McCutchen to be the cleanest he has ever been, unquestionably established that this sponge which permitted fluid to flow out of it only on one surface provided an extremely low friction bearing (51,52). McCutchen was really suggesting that cartilage wept fluid when under pressure; he called this phenomenon weeping or self-pressurized hydrostatic lubrication. Indeed, experimental work by him and Sokoloff showed that cartilage compression and loss of fluid are related, and that when the pressure was reduced and the cartilage was allowed to resume its original shape, the fluid was sucked back into the tissue (53,54). It is now believed that fluid does not flow out into the surface in the immediate area of contact but probably contributes to the fluid film created in the next area of impending contact as the joint slides along.

There are other mechanisms playing an important role in joint lubrication under heavy loads. Dawson et al (44) proposed the squeeze-film phenomenon, a concept that depends on a flow of water out of joint fluid into cartilage as the opposing surfaces come together and generate pressure in the lubricant. The passage of hyaluronic acid from synovial fluid into cartilage is restricted by its large molecular size, and as we mentioned previously, the pore size of articular cartilage will only permit passage of water and small solutes. The movement of water out of synovial fluid would therefore tend to produce a concentrated gel of hyaluronic acid which would act as a better cushion. This concept was supported by the work of a group of investigators at the University of Leeds. Walker et al, proposed the concept of boosted lubrication to supplement the squeeze-film principle (55). Upon loading of the joint, lakes of synovial fluid are trapped within the surface irregularities present in normal articular cartilage and become concentrated with increasing pressure. Finally, the compliance or elasticity of articular cartilage may allow its surface irregularities to flatten out under load, thereby lowering the local pressure at junction sites and contributing to the survival of both fluid and boundary films, therefore enhancing the effectiveness of the lubricant. Thus, it is apparent that cartilage elasticity plays a pivotal role, both allowing passage of fluid in and out of the cartilage and decrease in friction by altering the surface peculiarities under load. Stiffening of articular cartilage by exposing it to formaldehyde greatly increases its coefficient of friction (56). Since matrix proteoglycan has been shown to be responsible for the elastic properties of

cartilage, and as we shall see later, definite abnormalities of this material have been found in early osteoarthritic cartilage, it is apparent that the matrix proteoglycan plays a very important role in the pathogenesis of osteoarthritis.

In summary, the available information indicates that the low coefficient of friction in mammalian joints is due to a combination of lubricating mechanisms, boundary lubrication at low loads and boosted lubrication with formation of squeeze films and possibly flattening out of surface irregularities at increased loads.

## III. DEFINITION

Osteoarthritis or degenerative joint disease is a non-inflammatory disorder of movable joints characterized clinically by pain and dysfunction and pathologically by attrition and lysis of cartilage, subchondral bone sclerosis, remodeling of bone ends with marginal osteophyte formation and juxta-articular bone cysts. In England, the name osteoarthrosis is preferred, emphasizing the non-inflammatory aspects of the disease; nevertheless, mild to moderate synovitis may sometimes be an associated finding.

## IV. CLASSIFICATION

Osteoarthritis may be classified as primary or idiopathic when no specific etiological factors can be determined or secondary when any such factors are apparent. Primary osteoarthritis may prove to be a heterogeneous collection of different entities and some secondary causes may well be merely localizing factors suggesting that these terms should be used with caution.

CLASSIFICATION OF OSTEOARTHRITIS

PRIMARY OR IDIOPATHIC OSTEOARTHRITIS

a. Heberden's and Bouchard's nodes
b. Primary generalized osteoarthritis (Kellgren's syndrome)
c. Inflammatory erosive osteoarthritis

SECONDARY OSTEOARTHRITIS

a. Trauma
b. Metabolic
c. Neuropathic
d. Other joint disorders
e. Chondrocalcinosis

## V. EPIDEMIOLOGY

Evidence of osteoarthritis has been found in the dinosaur (57) and in ancient skeletal remains (58) as well as in fish, birds (59) and all mammalian species. The 1960-1962 United States Health Examination Survey showed radiological evidence of osteoarthritis in the hands or feet of over 40 million Americans, about 37% of the target population (60). It should be pointed out that there is very poor correlation between radiological findings and clinical symptoms in this disease, nevertheless, symptoms were reported in 5 million persons or 12.5% of the individuals with radiological changes (61). That these figures are not excessive is suggested by similar findings in epidemiological studies in England showing that 80% of the population over the age of 55 have radiological evidence of osteoarthritis (62).

In all epidemiological studies, the prevalence of osteoarthritis rises markedly with advancing age, but it is worth noting that in one survey, radiological evidence of disease was present in 10% between the ages of 15 and 24 (63). Clinically, however, overt disease is rare in young subjects and when present is more prevalent in males than females, whereas over the age of 45 moderate and severe osteoarthritis is seen to a

greater extent in females. Although the collected data show a uniformly high prevalence across geographic and ethnic barriers, there are fascinating exceptions such as the low incidence of osteoarthritis of the hip in Chinese (64).

The next table shows an epidemiological comparison between rheumatoid arthritis and osteoarthritis taken from Engel and Burch (65). Even though osteoarthritis tends to be a mild disease, because of the large number of people involved, disabling disease occurs in a larger population group than rheumatoid arthritis. It should also be pointed out that although osteoarthritic patients constitute a majority of first visits to an arthritis clinic, most affected patients are easily controlled with simple therapeutic measures so that they only make 5% of the revisits to the clinic.

EPIDEMIOLOGICAL COMPARISON BETWEEN

OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

| | Osteoarthritis | Rheumatoid Arthritis |
|---|---|---|
| Affected Population | | |
| Total Number | 40.5 million | 3.5 million |
| Severe Disease | 9.3 million | 1.0 million |
| % Disabled | 57% | 27% |
| % of general Arthritis Clinic Population | 57% | 27% |
| % of Revisits | 5% | 82% |

## VI. ETIOLOGIC FACTORS

*a. AGE.* The high incidence of osteoarthritis with advancing age tends to support the wear and tear theory, that is, the accretion of a series of cumulative insults to the articular tissues. There is very little evidence regarding the intrinsic effects of aging cartilage. The biochemical changes seen in aged costal cartilage for instance, are much less marked in artic-

ular cartilage (66-68) so that the possible decrease in the capacity of aging cartilage to resist mechanical stress is still a controversial point.

*b. TRAUMA.* Abnormal physical stresses play an important role in the development of osteoarthritis. In animals, for example, osteoarthritis of the hind limbs is seen in older draft horses who perform hard work primarily with their hind limbs, young thoroughbreds, whose forelimbs are subjected to great concussive forces in racing, develop a similar form of osteoarthritis at the sites of weight bearing stress in the forelimbs (69). Other illustrative examples include the spurring of the lumbar spine and degeneration of hock joints resulting from the erect gait of the famed Lipizzaner horses of Vienna and the degeneration of the left hind hip in racing greyhounds who run counterclockwise using the left hind leg to pivot. In man, the prevalence of osteoarthritis is also increased in certain joints that are subjected to excessive use, and the list of such associations is both long and fascinating as seen in the next table (70-82).

OSTEOARTHRITIS ASSOCIATED WITH SPECIFIC OCCUPATIONS

| Joints Involved | Occupation |
|---|---|
| Elbows and knees | Miners |
| Ankles, feet and knees | Soccer players |
| Knees | Football players |
| Hands | Boxers |
| Ankles and feet | Ballet dancers |
| Shoulders and elbows | Baseball pitchers |
| Patella | Cyclists |
| Fingers | Cricket bowlers |
| Ankles and knees | Lacrosse players |
| Spines, knees and elbows | Wrestlers |
| Fingers | Cotton pickers |
| Shoulders and elbows | Pneumatic drill operators |
| Hips | Farmers |

Normal use of a well aligned joint rarely induces cartilage breakdown, unusual stresses resulting from alterations in congruity of articulating surfaces may lead to osteoarthritis. Abnormal physical stresses are probably responsible for the development of osteoarthritis in congenital or acquired hip dysplasias such as subluxations, slipped epiphyses, Legg-Perthe's disease or aseptic necrosis.

*c. HEREDITY.* The influence of genetic mechanisms upon the development of osteoarthritis has been a tantalizing problem for many years. Incontrovertible evidence of genetic influences is provided by the osteoarthritis that complicates some local or systemic genetically determined diseases such as familial chondrodysplasia (83,84) the nail-patella syndrome (85) and alkaptonuria (86,87). With regard to idiopathic osteoarthritis, Kellgren (88) has demonstrated familial aggregation with a probable recessive and polygenic transmission. One study by Stecher (89) suggested that the development of Heberden's nodes was transmitted as an autosomal dominant trait in the females and recessive in males. The statistical basis of this report have been questioned (88-90) and the data at hand can be compatible with other modes of transmission.

In mice, the importance of genetic factors has been established (91). The inheritance appeared to be polygenic and the overall behavior was found to be a recessive type. There was no evidence of major sex linkage. Surprisingly, obesity did not appear to be a major deleterious factor in the development of the lesions.

*d. OBESITY.* Obesity, as a contributory factor to osteoarthritis, has been generally accepted without question because it would seem self evident that it poses a mechanical burden on the joints undergoing abrasion. Several recent studies have dealt with this and they suggest that this is a more complicated problem than previously recognized. It has been recently recognized that weight bearing is a minor part of the physical stress brought to bear on cartilage. Muscle pull clearly generates much more physical stress than weight-bearing, it has been calculated that forces of up to 4 times and 5.8 times body weight are encountered in the knee (92) and hip joints (93) respectively when walking. Sokoloff (94) has suggested values of up to 10 times body weight in the knee joint during deep knee bending on the basis of several different methods of estimation. Much of the load across the joint is attributable to muscle contraction and not to weight bearing, therefore the upper limb joints must be subjected to forces of the same magnitude per unit area as the lower limb counterparts. This would explain in part the involvement of the distal interphalangeal joints in females, recent evidence suggests that feminine grasp subjects these joints to higher stresses than are experienced by men (95) where the power grip seems to distribute the loads uniformly throughout the small joints of the hand. The relationship between obesity and osteo-

arthritis is by no means clear, it has caused considerable debate and much divided opinion. Although from population surveys there appears to be a clear association between obesity and severe osteoarthritis of the weight bearing joints, hips and knees (96,97), nonweight-bearing joints such as the distal interphalangeal and acromio-clavicular joints are also severely involved in the obese (98). On the other hand, radiological surveys have revealed no excess of osteoarthritis in the knees and hips (99) or in the hands and feet (100) of obese subjects. In females under the age of 64, obesity was found to favor osteoarthritis of the hands but not the feet (101), Heberden nodes have been found to be correlated with the presence of obesity (96). As mentioned above, Sokoloff found no correlation between osteoarthritis score and body weight of mice. He was also able to separate the genetic susceptibility to obesity and osteoarthritis in breeding experiments (91). Therefore, it is probable that the influence of obesity on osteoarthritis is real but the pathogenic mechanism involved is not just that of the increased load of weight bearing but more subtle metabolic influences may be playing a role.

Other metabolic influences also seem to modulate the development of degenerative joint disease. An increased incidence of osteoarthritis has been reported in patients with diabetes mellitus in the absence of any neuropathic involvement (102,103). In acromegaly, osteoarthritis is prominent and it is seen in unusual joints such as wrists and elbows. In this disease, the articular cartilage is not only thickened but active proliferation of cartilage cells is seen (104).

Administration of large doses of cortisone acetate in rabbits results in a marked reduction in the rate of protein and polysaccharide synthesis in articular cartilage (105). Such factors may be at least partially responsible for the development of Charcot-like joint changes following repeated intra-articular injections (106,107) or oral corticosteroid therapy (108).

Interest in the possible influence of nutritional factors have been focused by the recognition of osteoarthritis in Kashin-Beck disease (109). This is a disorder of growing children and is endemic in certain areas of Siberia, Mongolia and North Korea. The disorder has been attributed to ingestion of grain contaminated with the fungus *Fusaria sporotrichiella* (110) but others considered the disease due to a mineral defect of grain growth in endemic areas (111). It is manifested by fusiform swelling of the joints, and in addition to growth defects, those children suffering from it develop florid osteoarthritis later in life.

## VII. PATHOLOGY

*a. HISTOLOGY.* One of the problems which has made difficult the elucidation of the pathogenetic mechanisms in osteoarthritis is the difficulty in unravelling the precise sequence of early histologic events in this disorder. This difficulty may stem from the fact that several of the early changes of osteoarthritis have been described as occurring simultaneously, so that even the most detailed analysis has failed to contribute to the clarification of the pathogenic mechanisms at play. The earliest changes of osteoarthritis are loss of the surface layers of the cartilage, diffuse increase in the number of cells, appearing as hypertrophy and hyperplasia of chondrocytes in clusters and a moderate decrease in metachromatic staining indicative of depletion of the matrix of proteoglycan. At this point, the interface between cartilage and bone which is normally a continuous calcified line is violated by the ingrowth of blood vessels from the underlying bone. This abnormality is highly characteristic of the disorder and is considered to be a cause of osteophyte formation. As the disease progresses, there is a tendency toward vertical cleft formation beginning at the cartilaginous surface. The clefts first descend through the gliding layer, altering the normal tangential arrangement of the dense collagen bundles, and with advancing disease, become progressively deeper until they are found to extend to the calcified zone producing a pattern commonly spoken of as fibrillation. Staining of the matrix with a special dye discloses a progressive loss of color, indicating further depletion of the proteoglycans. The chondrocytes increase in number and tend to lie in clumps or clones, a finding characteristic for the disease and virtually pathognomonic. Later on, the cartilaginous tissue is further eroded and disappears completely from local areas of the surface leaving denuded sclerotic and eburnated bone. Subchondral cyst formation and the development of patches of new cartilage over eroded areas and over marginal osteophytes complete the picture. The early biochemical alterations consisting of the loss of metachromatic staining suggested a progressive depletion of the ground substance (112). These findings were subsequently confirmed by direct biochemical analysis (113,114) and it has now been well established that the proteoglycan of osteoarthritic cartilage is diminished and that the decrease is directly proportional to the severity of the disease (115).

The collagen content of osteoarthritic cartilage is assessed quantitatively and has never been found to vary from that of normal tissues (116). Nevertheless, a recent study by Nimni (117) suggests a variation in the quality of the collagen. This work

has shown that osteoarthritic chondrocytes synthesize not only the type II collagen chains that are characteristic of articular cartilage but also substantial amounts of type I collagen. This observation suggests that despite growth maintenance of the collagen content in osteoarthritic cartilage, the pattern of chondrocyte renewal of its collagen is one of synthesis of fibers more closely resembling those found in skin and bone than those in normal articular cartilage.

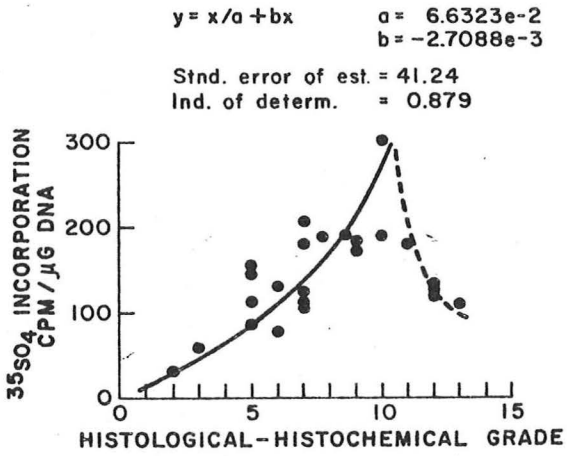


Figure 4 - Rate of incorporation of $^{35}SO_4$ into human osteoarthritic cartilage.

Studies of the metabolic alterations accompanying the biochemical abnormalities have given us a further insight on the mechanisms involved in cartilage degeneration. Collins and McElligott (118) clearly showed that osteoarthritic articular cartilage had an increased rate of $^{35}SO_4$ incorporation, and since then numerous studies have supported the concept that synthetic activity is considerably increased (115-118). Recent studies by Mankin (Fig. 3) have shown that the rate of synthesis of proteoglycan in osteoarthritic cartilage is directly proportional to the severity of the process for mild or moderate disease, but as the disease worsens, a point is reached where the rate of synthesis appears to fall off markedly, suggesting that the capacity of the cell to respond has been exceeded and reparative mechanism has failed (115).

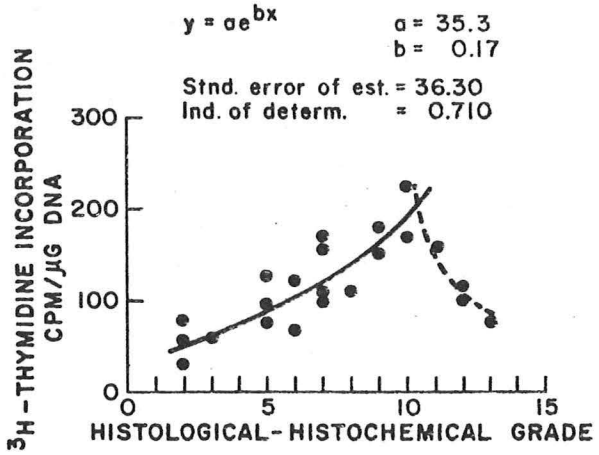


Figure 5 - Rate of incorporation of $^{3}H$-thymidine into human osteoarthritic cartilage

The evidence provided by histology that the chondrocyte in osteoarthritic cartilage seems to become activated and undergo mitotic division has also received biochemical confirmation. The proliferation of cells is believed to be the means by which the tissue becomes hypercellular, and the localized collection of clumps of cells frequently seen probably represents multiple division of a single clone of cells. When DNA synthesis and osteoarthritic cartilage was studied quantitatively by incorporation of tritiated thymidine by Mankin (115), the rate of synthesis of new cells was found to be directly proportional to the severity of the disease for mild to moderate osteoarthritis, but with advancing severity thymidine incorporation diminished rapidly indicating a cessation of cell replication. This data again suggests a failure of the reparative mechanism with increasing disease activity.

The physical chemical characteristics of the matrix proteoglycan osteoarthritic cartilage has also been shown recently to be abnormal (119). Using very elegant microultracentrifugal methods to analyze the size of the proteoglycan molecule in normal and osteoarthritic cartilage, Howell and collaborators showed that the proteoglycan obtained from osteoarthritic lesions had a strikingly lower sedimentation value as compared to normal areas of the same cartilage.

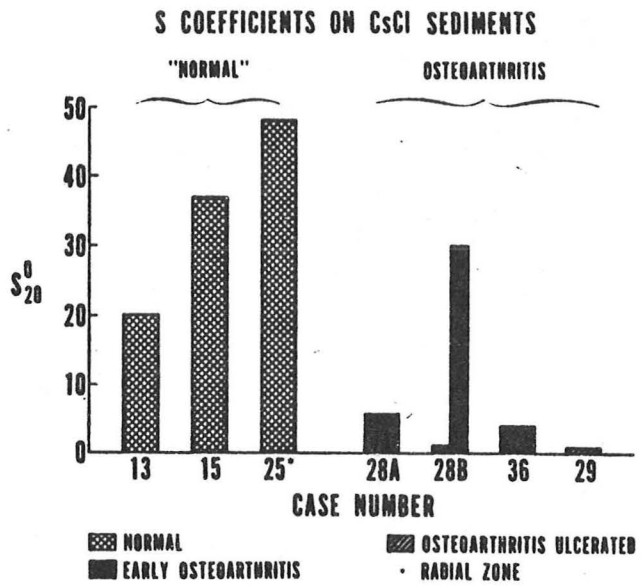


Figure 6 - Sedimentation coefficients of proteoglycan obtained from normal and osteoarthritic cartilage.

These findings, as well as previous findings by Bollet suggested that degradative enzymes may play a role in the loss of matrix seen in osteoarthritic lesions. The same group went on to show (34,35) that there is a highly significant elevation of acid and neutral proteins in diseased cartilage. The findings also suggest that these enzymes originate in the lysosome of the chondrocyte.

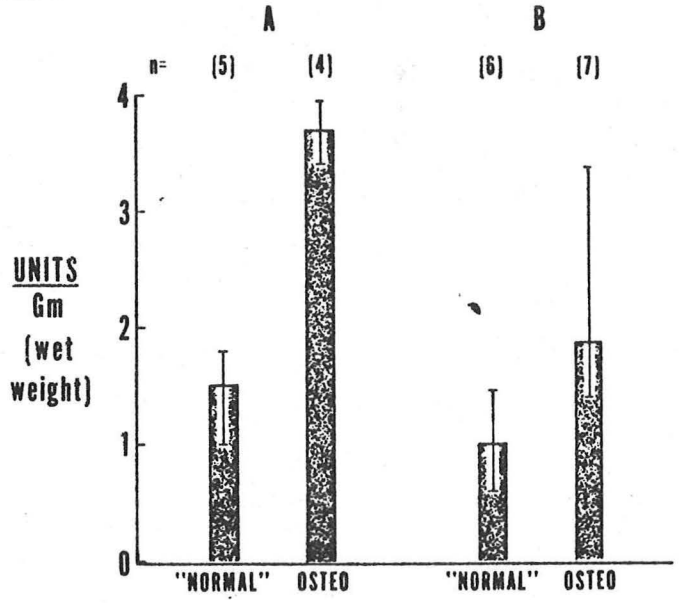


Figure 7 - Cathepsin D activity in normal and osteoarthritic cartilage.

## VIII. PATHOGENESIS

In view of the many metabolic abnormalities demonstrated in osteoarthritic cartilage, it seems likely that a variety of metabolic factors are involved in the pathogenesis of osteoarthritic cartilage breakdown. Bollet (120) postulated that, regardless of specific plausible multiple etiologies of primary osteoarthritis, there is a final common pathway of cartilage degradation. By this view, the final common pathway leads to cartilage cellular injury whether from physical, nutritional or toxicologic sources, there ensues surface abrasion, entry of synovial fluid enzymes or release of chondrocyte lysosomal enzymes with destruction of cartilage matrix. The documented loss or alteration of proteoglycans in several studies have provided some general support for the above theory. We have seen previously that a loss of proteoglycan may lead to loss of elasticity and self lubricating properties of the articular surface, therefore accounting for the erosive changes that are the hallmark of this disease. The finding of accelerated cartilage repair in osteoarthritic cartilage of early to moderate severity as opposed to advanced severity, and the concurrent maintenance of total proteoglycan content in early disease are strongly suggestive of a response to accelerated breakdown of such cartilage.

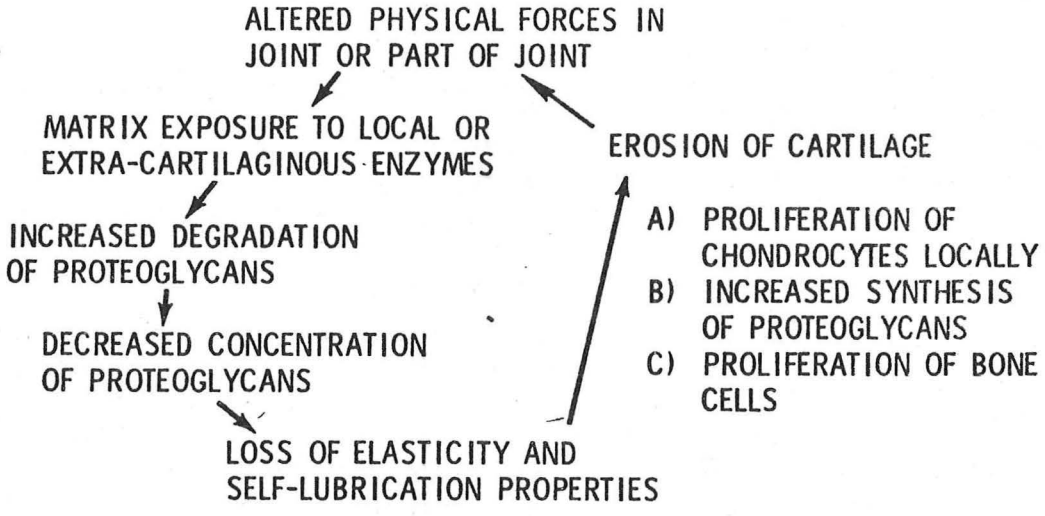


Figure 8 - Pathogenesis of osteoarthritis.

Figure 8 shows the process in the form of a vicious circle. In our present state of knowledge it is difficult to indicate at what point the process of proteoglycan degradation and chondrocyte breakdown start. Of the several theories advanced, two or three deserve some mention. Some authors feel that the abnormal physical stress exerted on the cartilage leads to release of lysosomal degradative enzymes mainly by the chondrocyte with subsequent degradation of proteoglycans. Another theory supports a view that primary damage to the collagen fiber might lead to proteoglycan loss by leakage or as a consequence of cellular injury. The loss of proteoglycan might then lead to the overstressing, loss of elasticity and development of the osteoarthritic lesion. Which, then, comes first - proteoglycan depletion or collagen fracture? Since there is no reason to suppose that idiopathic osteoarthritis is a single disease entity, these are not mutually exclusive alternatives. As mentioned previously, histological studies provide no convincing grounds for deciding which abnormality is primary. Finally, a recent theory proposed by Radin deserves some comment. He feels that in view of the very low coefficient of friction of the articular surfaces, it is very unlikely that shearing stresses may lead to cartilage damage. In his studies using bovine joints, he found no significant wear of the articular cartilage despite prolonged oscillation under high constant loading (21). However, repeated impact loading caused rapid cartilage wear with an early and marked rise in coefficient friction and exposure of subchondral bone. Radin suggested that it is unlikely that cartilage, being only 1 to 7 mm. thick, could be a major energy absorber and that the main force of impact is normally absorbed by subchondral bone and soft tissues. He demonstrated microfractures in the subchondral bones of joints subjected to repeated impulse loading and he postulated that healing of this microfracture leads to bone remodelling, with resulting stiffening and reduced ability to absorb stresses thereby exposing the articular cartilage to greater insult.

## IX. CLINICAL MANIFESTATIONS

Symptoms of osteoarthritis are local in character and related to involved joints. Involvement of a number of joints suggest a systemic form of arthritis, in these cases symptoms may be widespread. It should be pointed out that there is a disparity in the relationship between symptoms and structural disease changes since over 80% of all persons over 40 years old show degenerative changes in weight bearing joints by roentgenographic examination; only a small group complained of

symptoms related to the disease. Cobb, Merchant and Rubin (122) reported that there was no association between morning stiffness and x-ray evidence of osteoarthritis, and only about 30% of persons with radiologic evidence of degenerative joint disease complained of pain at the relevant sites.

The main symptom of degenerative joint disease is pain, which at first occurs on use and is relieved by rest. As the disease progresses, pain may occur with minimal motion or at rest. In advanced cases, pain may awaken the patient during sleep due to loss of normal joint splinting which limits painful motion during the waking hours. Since articular cartilage has no nerves, pain and osteoarthritis cannot be the direct result of cartilage degeneration. Nerve endings are present primarily in the capsule, ligaments and about vessels in the synovial membrane, secondary alterations in these structures presumably produce the pain. Recently, the possibility of a prostaglandin-mediated pain mechanism has been raised by the observation that prostaglandins may sensitize the tissues to pain (123,124), and this would provide a rationale for the successful use of prostaglandin synthetase-blocking anti-inflammatory and analgesic drugs such as aspirin and Indomethacin.

SYMPTOMS AND SIGNS OF OSTEOARTHRITIS

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Pain on motion: Pain at rest in severe disease

Localized stiffness of short duration.

Associated muscle spasm may be present.

Limitation of motion in progressive disease.

Joints commonly involved:
- Distal interphalangeal
- First carpo-metacarpal
- Knees
- Hips
- Spine (cervical and lumbar)

Symptoms uncommon before age 40.

No systemic manifestations.

---

Morning stiffness and after inactivity during the day is a common complaint. Such stiffness, however, is relatively short in duration and rarely persists for more than 15 to 30 minutes. Limitation of motion develops as the disease progresses, due to joint surface incongruity, muscle spasm and contracture, capsular contracture and mechanical block due to osteophytes or loose bodies. In weight bearing joints, abrupt giving way may occur. Objectively, joints may show localized tenderness, especially if synovitis is present. Pain on passive motion may be a prominent finding even though local tenderness may be absent. Crepitus, a feeling of crackling or grating as the joint is moved, may result from cartilage and joint surface irregularity. Enlargement of the joint may occur due to synovial reaction, increase in synovial fluid or proliferative changes in cartilage or bone. The most common is the latter case, where the joint will have a hard, bony consistency to palpation. Late stages of disease are associated with gross deformities and subluxation due to cartilage loss, collapse of subchondral bone and cysts and gross bony overgrowth.

Although these symptoms and signs are common to osteoarthritis in various locations, the clinical picture and course varies somewhat with the specific joint involved. The most commonly involved joints in primary osteoarthritis are the distal interphalangeal joints of both hands, the first metatarsophalangeal joints of the feet (hallux valgus), the proximal interphalangeal joints of the fingers, the metacarpophalangeal and carpometacarpal joints at the base of the thumbs, the spine, the knees and hips. Although the earliest symptoms seem to be in the bunion joints of patients in their late thirties and early forties, pain in the anatomic snuff box of the wrist alerts the physician to degeneration of the 1st carpo-metacarpal and scaphotrapezoid joints. Stiffness of the fingers and developing Heberden's nodes are features of the late forties and early fifties, particularly in women.

SYNOVIAL FLUID IN OSTEOARTHRITIS

| | Appearance | Viscosity | Mucin Clot | WBC |
|---|---|---|---|---|
| Normal | Clear | High | Good | 100 |
| Osteoarthritis | Clear | High | Good | 700±700 |
| Rheumatoid Arthritis | Cloudy | Poor | Poor | 15000±10000 |

Routine laboratory examinations fail to disclose specific abnormalities attributable to osteoarthritis. In uncomplicated osteoarthritis, the joint fluid should be relatively normal, it should be clear and yellow and newsprint can be read through it. Few, if any, cells should be contained in the fluid although microscopic examination may disclose cartilaginous fibrils. Viscosity is usually normal, a drop of fluid expressed from the syringe produces a long string in its fall. The ropy clot produced when joint fluid is added to 5% acetic acid is comparable to that found in normal synovial fluid.

RADIOLOGIC FINDINGS IN OSTEOARTHRITIS

| |
|---|
| Narrowing of joint space |
| Subchondral bony sclerosis |
| Marginal osteophyte formation |
| Bone cysts |
| Gross deformity in advanced cases |

The main roentgenologic findings consist of narrowing of the joint space due to destruction and loss of articular cartilage, subchondral bony sclerosis (eburnation) due to new bone formation, marginal osteophyte formation due to proliferation of cartilage and bone, bone cysts and gross deformity with subluxation and loose bodies in advanced cases. It should be stressed that x-ray evidence of degenerative disease may be extensive but yet bear little relationship to the patient's symptoms. This is particularly important in osteoarthritis of the spine where the large osteophytes arising from the vertebral bodies that are very commonly seen in most affected individuals are clinically silent. On the other hand, severe symptomatology may develop with relatively minor spur formation localized in a critical area. If a patient presents with symptoms compatible with radicular compromise, oblique views of the lumbar spine should be routinely performed if degenerative changes involving intervertebral foramina and apophyseal joints are to be accurately delineated.

## X. PRIMARY IDIOPATHIC OSTEOARTHRITIS

*a. HEBERDEN'S NODES.* One of the most common manifestations of primary degenerative joint disease is the Heberden's nodes (125). This is a cartilaginous and bony enlargement of the distal interphalangeal joint of the finger, often associated with flexion and lateral or medial deviation of the distal phalanx. Similar nodes may be seen in the proximal interphalangeal joints and are often called Bouchard's nodes. There are two types of nodes, the traumatic and the primary nodes. The primary nodes begin most often after age 45, women are affected much more frequently than men. We have already discussed the possible hereditary transmission, the nodes appear to have a genetic origin, but the exact mode of transmission remains open to question since several genetic patterns fit the data presently available. As mentioned previously, physical stress may be an important factor in the development of Heberden's nodes. Heberden's nodes do not develop in the feet and this may be due to the fact that the extensor and flexor tendons do not insert in the distal phalanx. It is also known that joint changes are much more severe on the right hand in right handed people (126). Paralysis of a limb usually preserves it from further arthritic change (127).

Clinically, Heberden's nodes may develop gradually with little or no pain and progress essentially unnoticed for months or years. In other cases they appear rather rapidly with redness, swelling, tenderness and aching particularly after use. Individuals afflicted by then may complain of paresthesias and clumsiness on use. The swelling may be soft and fluctuant or may be quite hard. At times, the original swelling is complicated by the appearance of small, gelatinous cysts. These appear generally on the dorsal aspect of the distal interphalangeal joints or just proximal to it. They often are attached to tendon sheets and resemble ganglions. They may recede spontaneously or persist indefinitely. Occasionally the acute cyst may ulcerate and viscous clear fluid which has been reported to be an almost pure solution of hyaluronic acid may drain from this cyst.

*b. PRIMARY GENERALIZED OSTEOARTHRITIS (KELLGREN'S SYNDROME).* This is a generalized form of osteoarthritis described by Kellgren and Moore in 1952 (128). This syndrome is seen predominantly in middle aged women. The joints involved are primarily distal and proximal interphalangeal joints and 1st carpometacarpal joints of the hands. These patients were also affected with severe osteoarthritis in other joints including the knees, hips, metatarsophalangeal joints and the spine.

Chronic articular symptoms were frequently preceded by an acute inflammatory phase. The erythrosedimentation rate could be normal or slightly elevated. The tests for rheumatoid factor were usually negative. Although the overall pattern of radiologic involvement was similar to that usually seen in localized osteoarthritis, certain differences were noted. Articular facets, neural arch and spinous process of the vertebral column were often enormously enlarged and led to the radiologic picture characterized as "kissing spines". Examination of knee x-rays revealed marked narrowing of the joint space with rounded osteophytes and the absence of a more usual sharply pointed osteophyte. Radiologic changes in the advanced cases were striking and greatly in excess of the clinical findings.

*c. INFLAMMATORY EROSIVE OSTEOARTHRITIS.* In 1961, Crain (129) described a group of patients with arthritis localized to the distal and proximal interphalangeal joints of both hands. The syndrome was characterized by degenerative changes with intermittent inflammatory episodes leading eventually to deformities and ankylosis. X-ray changes showed marked narrowing of joint spaces, osteophyte formation and destruction of epiphyseal bone and subluxation of digits. The patients were predominantly women of middle age. There was a strong hereditary and familial pattern. Erythrosedimentation rate and rheumatoid factor tests were characteristically normal. Peter et al, described a series of 6 women with joint findings similar to those described by Crain. Interphalangeal arthritis was similar in many respects to idiopathic Heberden's nodes but differed from them in certain clinical and radiologic aspects. Acute flares often occurred for many years but the patients were relatively asymptomatic after ten years. The acute inflammation and synovial swelling were often sufficiently severe to suggest a diagnosis of rheumatoid arthritis. Bony ankylosis, rare in classical osteoarthritis was seen. Radiologic changes also included cartilage loss, osteophyte formation and subchondral sclerosis. In addition, juxta articular bone erosions were prominent. There were no x-ray changes of primary generalized osteoarthritis. Study of synovium revealed an intense proliferative synovitis often indistinguishable from rheumatoid arthritis. Peter et al, suggested that this syndrome represented a unique disease distinct from both rheumatoid arthritis and classical osteoarthritis. They suggested the name erosive osteoarthritis because of the prominent cartilage destruction and bony erosions.

Ehrlich (131) reported a similar group of 170 patients with inflammatory osteoarthritis. He noticed that in 15% of these patients the development of rheumatoid arthritis, particularly involving the dorsal aspect of both wrists, ensued. Although the findings described in the above reports support the existence of this variant form of primary osteoarthritis, it is

difficult to rule out the co-existence of mild seronegative rheumatoid arthritis and diffuse degenerative changes in some of the patients with the so called erosive osteoarthritis. This could well account for the inflammatory nature of some of the cases described.

## XI. SECONDARY OSTEOARTHRITIS

Secondary osteoarthritis includes the cases which occur in response to some clearly recognizable underlying local or systemic factor.

SECONDARY OSTEOARTHRITIS

| | |
|---|---|
| A. TRAUMA | Acute<br>Chronic |
| B. METABOLIC | Alkaptonuria<br>Hemochromatosis<br>Gout<br>Wilson's disease<br>Hemophilia<br>Corticosteroid overuse |
| C. NEUROPATHIC | Tabes dorsalis<br>Diabetes mellitus<br>Syringomyelia<br>Meningomyelocele<br>Peripheral nerve section |
| D. SECONDARY TO OTHER JOINT DISORDERS | Aseptic necrosis<br>Congenital abnormalities<br>Infection<br>Rheumatoid Arthritis<br>Old fracture |
| E. CHONDROCALCINOSIS | |

*a. TRAUMA.* Degenerative joint disease may follow acute injury. The anatomic changes which develop are similar to those seen in the primary form of the disease. Injury of this nature, which involves the distal interphalangeal joints of the hands may lead to development of traumatic Heberden's nodes (132).

Acute trauma to any of the interphalangeal joints of the hands may lead to the commonly "baseball fingers". We have already seen the increased prevalence of osteoarthritis in association with chronic trauma related to certain occupations.

*b. METABOLIC.* Generalized osteoarthritis may be associated with metabolic disease such as alkaptonuria (133). In this inheritable metabolic disease associated with an absence of homogentisic acid oxidase, there is binding of homogentisic acid to connective tissue components. Tissue deposition of brown-black pigment (ochronosis) occurs and is seen primarily in cartilage, skin and sclera. Degenerative joint disease of the spine is frequently seen. Calcifications of numerous intervertebral discs are a characteristic finding. Arthritis of peripheral joints such as hips, knees and shoulders is seen less frequently and develops later.

An arthropathy associated with hemochromatosis was first described by Schumacher in 1964. The most frequent appearance is that of osteoarthritis which has been reported in 20 to 50% of patients with hemochromatosis. Hands, knees, and hips are most frequently involved although most of the joints can be affected. Acute inflammation has occasionally been described but this may be associated with chondrocalcinosis and pseudogout also associated with hemochromatosis.

Articular alterations in Wilson's disease were first described in 1957 (135). Articular involvement ranges from premature osteoarthritis with marked symptoms to asymptomatic radiographic findings. Early age of onset and prominent involvement of wrists and metacarpophalangeal joints suggest a difference from the usual osteoarthritis. No correlation has been found between total disease severity, spasticity, tremors, osteopenia, liver or renal disease and the arthropathy.

In hemophilia, with repeated hemarthrosis, there is gradual failure of the joint to return to fully normal form and function. The chronic changes are characterized by thickening of the periarticular soft tissues, crepitation, atrophy of muscle which accentuates the bony enlargement of the joint,and various deformities the most common of which are flexion contracture of the elbows and knees. The hemophilic joint disease is characterized by irregular narrowing or obliteration of the joint space and later by marginal spurring and sclerosis of bone which often contains one or more area of cystic translucency.

We already have mentioned the development of localized osteoarthritis following repeated use of intraarticular injections of adrenal corticosteroids (106-108).

*c. NEUROPATHIC.* Although neuropathic joint disease was first described with tabes dorsalis, similar lesions may be seen in other diseases associated with neuropathy including diabetes mellitus, syringomyelia, meningomyelocele and peripheral nerve section. The distribution of affected joints depends on the area of neurologic abnormality. The degenerative changes which develop are similar qualitatively to those seen in ordinary osteoarthritis but of a different degree, with exuberant overgrowth of bone and cartilage presenting a characteristic radiologic picture. Frequently, clinical symptoms are minimal and disproportionate to the extensive pathologic changes observed.

*d. SECONDARY TO OTHER JOINT DISEASES.* Secondary osteoarthritis may follow local joint disorders of other cause, such as old fractures, aseptic necrosis or acute or chronic infection. Localized osteoarthritis of the hip may follow childhood disorders such as congenital dysplasia of the hip, slipped capital epiphyses and Legg-Perthe's disease.

*e. CHONDROCALCINOSIS.* This disease entity is characterized by calcium pyrophosphate crystal deposition in articular cartilage. On x-ray examination, the calcium seen in the articular joint space is in the form of flecks or plates. About 30% of these patients develop acute, crystal-induced pseudogout but the majority of the cases have a progressive, chronic arthritis involving the larger joints that is indistinguishable from osteoarthritis (136). At present it is not possible to say whether the crystal deposition is the primary event or a consequence of the degenerative changes. However, recent work by Howell (137) has shown that the dividing chondrocyte and the chondrocytes obtained from osteoarthritic cartilage demonstrated a substantial output of pyrophosphate as compared to normal controls. This work suggests that the chondrocyte is the source of the pyrophosphate in osteoarthritic cartilage and this may constitute one of the factors that leads to the high incidence of osteoarthritis and chondrocalcinosis.

## XII. TREATMENT

Acetylsalicylic acid is the foundation of drug therapy in osteoarthritis. Adequate use of the drug is the key to success

for symptomatic relief. Although many patients will have tried aspirin before formal medical consultation, inquiry usually reveals that the drug is being used on an "as needed" basis or in regular doses too small to be effective. Usually, 640 mg. 4 times a day constitutes an adequate dose. The patient should be observed and the dose can be increased gradually if needed for adequate relief. There is some evidence that salicylates not only have a nonspecific analgesic effect on this disease but they may prevent cartilage degeneration and further progression of the disease. In a study in patients with recurrent lateral dislocations of the patella, a group was given 3 grams of aspirin daily for 6 to 8 weeks after each dislocation and the control group did not receive any aspirin. In the aspirin treated group, only 3 of 16 patellas obtained surgically revealed chondromalacia. In the control group, 21 of 23 knees showed chondromalacia. On the basis of these observations, routine use of aspirin as prophylaxis against chondromalacia for patellar dislocation was recommended (138).

In severe disease not controlled by moderate doses of aspirin, nonsteroidal anti-inflammatory agents have been found to be useful. Again, agents such as Indomethacin have an effect that goes further than mere analgesic and anti-inflammatory effect. Since Indomethacin is a very powerful inhibitor of prostaglandin synthesis, it is possible that decrease in prostaglandin produced by synovial membrane may result in a concommitant increase in proteoglycan synthesis and chondrocyte division, therefore stimulating cartilage repair so that the reparative process would maintain pace with or exceed degradative changes (139).

Another agent that stimulates cartilage to maintain pace with degradative changes is an experimental compound called Rumalon, an extract derived from bovine costal cartilage and bone marrow. This agent has been found to be able to stimulate chondrocytes and polysaccharide synthesis. Short term clinical studies using this agent in the treatment of osteoarthritis have been carried out (140,141). In one study differences between control and treated group appeared after 48 weeks of treatment and consisted mostly of a decrease in pain. Radiologic studies reveal no differences in the rate of joint deterioration between treatment and control groups. In another study radiologic findings after 6 months favored the Rumalon treatment group. In a group of patients with bilateral knee osteoarthritis in whom the effects of Rumalon given intramuscularly were compared with the effects of placebo, 64% of Rumalon treated patients showed favorable results as compared with 29% of placebo patients. Side

reactions of Rumalon treatment have thus far been mild. Further studies will have to be done to confirm the value of this agent for the treatment of osteoarthritis.

Systemic adrenal corticosteroids or ACTH are of no benefit in osteoarthritis and are not recommended because of potential serious side effects. On the other hand, local intraarticular administration of depo-corticosteroids is frequently of benefit and involves minimal hazards. In most cases, relief is only temporary but it is measured in weeks or months. In nearly 1000 patients with osteoarthritis of the knee who had received such injections on an "as needed" basis, over a period of 9 years, nearly 60% no longer required injections having benefitted sufficiently to respond to more conservative measures (142). Intraarticular corticosteroid administration is most effective when used in treating an acute flare or swelling precipitated by trauma or joint overuse. Injections should be judiciously used, in most cases they should be given at a minimum of 4 to 6 month intervals. Corticosteroid injections in nonweight-bearing joints such as distal interphalangeal joints of the hands provide little risk and may be particularly helpful. The acute Heberden nodes usually respond very well to a single intraarticular injection.

Experimental studies are presently underway using intraarticular injections of agents that may decrease the coefficient of friction of affected joints. Silicone oil has been used in two studies (143,144), functional and symptomatic improvements have been described but no appropriate control studies exist. Although clinical complications have not been noted, formation of encapsulated siliconomas and silicone emboli are potential hazards. In addition, Radin has shown that silicone oil seals the cartilage so that the weeping effect is lost and the friction coefficient is not decreased substantially below the decrease obtained with buffer alone (145.

In preliminary reports, acupuncture had been reported to be effective in osteoarthritis, however a recently published double-blind, controlled study (146) indicates that there was no difference in the reduction of pain after treatment between control and experimental groups.

Rest, physical therapy, and surgery will not be considered in detail in this presentation.

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