CHONDROLYSIS IN ARTHRITIS

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Articular cartilage is composed of cells surrounded by a matrix of protein—chondroitin sulphate complex. It is nourished by diffusion from the synovial fluid. It is probable that synovial fluid is a dialysate of plasma, to which another mucopolysaccharide—protein complex containing hyaluronic acid—has been added by synovial cells.

Synovial fluid does not contain fibrinogen (Ropes and Bauer 1953) unless the permeability of adjacent vessels is increased by trauma or inflammation. After these events fibrin clots may be found but they do not persist. What is the mechanism by which fibrin is removed from joint surfaces? Our own studies have shown that whenever there is fibrinogen there is plasminogen in synovial fluid; Astrup (personal communication) has demonstrated the presence of plasminogen activator in synovial tissue, and I have found that cartilage per se will also activate plasminogen (Fig. 1). Conditions such as trauma and inflammation that release thromboplastin, leading to the clotting of fibrinogen, may also be expected to ensure the digestion of the fibrin clot so formed. The exceptions to this generalisation are mentioned later.

Synovial fluid normally contains inhibitor to plasmin but nevertheless the fibrin is digested. Plasmin, formed by the activation of plasminogen by tissue activator, adsorbs on to fibrin and digests it; no free plasmin remains as it is then inactivated by inhibitor in the surrounding fluid. There may well be several inhibitors of plasmin in synovial fluid, and the rate of fibrinolysis is determined by the relative amounts of inhibitor and plasmin.
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SUPPURATIVE ARTHRITIS

Let us consider what happens in suppurative arthritis caused by staphylococcus pyogenes or a haemolytic streptococcus. Infections by these organisms usually produce rapid and extensive chondrolysis, more so than in other types of infection. Suppuration per se will increase local proteolytic activity—pus cells release proteases, increased capillary permeability and local tissue destruction may eventually raise the plasmin level—but these factors alone are not sufficient to account for the speed with which cartilage matrix is destroyed in streptococcal or staphylococcal infections. Both these organisms produce kinases which activate plasminogen, and plasmin will digest the protein moiety of the mucoprotein of cartilage (Lack and Rogers 1958) (Fig. 2).

Phemister (1924) reported an experiment which led him to the conclusion that chondrolysis in pyogenic arthritis was caused by the digestive action of proteolytic ferments derived very largely from polymorphonuclear leucocytes. He showed that when equal sized pieces of cartilage were placed respectively in saline, tuberculous pus, staphylococcal suspension and staphylococcal pus, only the last digested the cartilage completely within forty hours. Had he put cartilage into a suspension of disrupted leucocytes alone, he would not have observed this rapid destruction. It is evident from experiments carried out in this department that leucoprotease is not itself an important agent in chondrolysis. Keefer, Holmes and Myers (1935) found that leucocytic autolysates from staphylococcal pus digested cartilage and coagulated blood serum. "Digestion of the cartilage was not observed in seven samples of synovial fluid from gonococcal arthritis or in three samples from tuberculous arthritis. In the two cases of staphylococcal arthritis, in which there were large numbers of polymorphonuclear leucocytes, digestion was apparent." The fact that their leucocytic autolysates digested

Fig. 2
Equal sized portions of bovine articular cartilage were incubated in buffered solutions of bovine plasmin and trypsin and are shown here in comparison with cartilage in buffered saline alone.
fibrin suggests the presence of staphylokinase or plasmin, but nothing was known of the 
plasmin system when they made their experiments. Further evidence that they were dealing 
with the action of plasmin is provided in their other paper (Holmes, Keefer and Myers 1935),
in which they reported that some synovial fluids became proteolytic and chondrolytic after 
removal of antitryptic substances with chloroform.

Thomas and others (Thomas 1956; Spicer and Bryant 1957; Spicer and Bryant 1958; 
McCluskey and Thomas 1958; Bryant. Leder and Stetten 1958) have shown that when rabbits 
are injected intravenously with crude papain the ear cartilages of the living animals soften 
in a few hours, but that they return to normal in three or four days. The proteolytic attack 
of the papain has been shown to be on the cartilage matrix; as the cartilage cells have not 
been affected, it must be presumed that these cells in the rabbit are capable of restoring the 
matrix in two days. Restoration of matrix presumably depends on the number and metabolic 
activity of the cartilage cells, which may be related to the age of the subject. It would be 
difficult to achieve such a high concentration of active plasmin in cartilage by intravenous 
injection because there is such excess of plasmin inhibitor in rabbits and in man. But the 
papain experiments may provide useful models.

Pathogenic streptococci and staphylococci produce toxins that kill cartilage cells. It 
is probable, therefore, that in continuing infections by these organisms not only is matrix 
removed but regeneration is impaired or prevented in proportion to their toxic action on 
cartilage cells.

The chondrolytic activity in arthritis caused by other pyogenic organisms such as the 
gonococcus and meningococcus is considered to be less severe because they do not produce 
activators of plasminogen, and such activity as occurs is caused by tissue activation. 
Disrupted leucocytes will activate plasminogen, but more slowly than bacterial kinases.

**TUBERCULOUS ARTHRITIS**

In tuberculous arthritis there is no direct attack on cartilage. Instead there is the sequence 
of fibrin deposition, fibroblastic outgrowth with pannus formation over the surface of cartilage, 
and subchondral granulation tissue undermining the cartilage below. “The hyaline articular 
cartilages display no vital reaction on their own account. Even though they may be detached 
or slowly eroded by granulation tissue, the joint cartilages persist for a long time in a tuberculous 
joint. They are not attacked by proteolytic enzymes, as is the case in a suppurative arthritis.” 
(Collins 1949). Tuberculous tissue has a high content of plasmin inhibitor. Tuberculosis of 
the synovium inhibits the normal fibrinolytic mechanism so that fibrin accumulates and 
persists on joint surfaces. Fibroblasts may subsequently grow into this fibrin, leading to 
pannus formation or to fibrous ankylosis. Cartilage degeneration occurs as a result of the 
interference with nutrition and not as a consequence of toxic or proteolytic attack.

When a tuberculous joint is secondarily infected with a staphylococcus there may be 
bony union instead of fibrous ankylosis because the staphylococcus is able to remove 
intervening cartilage in the way described. Bony ankylosis may occur in tuberculous arthritis 
but is much slower.

**RHEUMATOID ARTHRITIS**

Pannus formation is even more conspicuous in rheumatoid arthritis, and, if one accepts 
the view that fibroblastic proliferation over cartilage surfaces follows fibrin deposition, one is 
thrown back to the question: Is there any reason for supposing that persistence of fibrin 
characterises the rheumatoid state? As the physiological clearing mechanism for removing 
fibrin appears to be plasmin, is there any evidence that plasmin activity is retarded in 
rheumatoid arthritis? Thomas and Dingle (1955) found serum anti-plasmin levels increased 
and serum plasmin levels reduced in rheumatoid arthritis. A study of plasmin inhibitor and
activator in synovial membrane and fluid from patients with rheumatoid arthritis is about to be started in this hospital. An abnormally high inhibitor level in tissue fluids may help to explain the failure to remove protein in other situations in this disease.

DEGENERATIVE ARTHRITIS

Cartilage matrix is lost in degenerative arthritis. It is possible that in a large proportion of instances this is a failure of replacement of ordinary wear and tear. Repeated trauma might release sufficient activator from synovial tissue or cartilage to bring about a digestion of the cartilage surface by plasmin, but there is no experimental evidence for this.

It has been pointed out that plasmin attacks the protein of cartilage, releasing the chondroitin sulphate. Chrisman et al (1958) reported raised sulphate levels in the synovial fluid in established degenerative arthritis and lowered levels in rheumatoid arthritis. It is interesting that they should also find a profound lowering in both varieties of arthritis after treatment with intra-articular hydrocortisone, as this drug has been reported to have an inhibitory effect on plasmin activity.

SUMMARY

Plasmin, a proteolytic enzyme derived from the blood, may be activated in synovial fluid both by trauma to synovial tissue and cartilage, and by kinases produced by streptococci and staphylococci. Plasmin normally removes fibrin, but, when in excess, attacks the protein of cartilage matrix. Conversely, excess inhibitor favours the persistence of fibrin and subsequent fibrosis. The relationship of excess protease to the chondrolysis of suppurative arthritis and of excess inhibitor to pannus formation and fibrous ankylosis in tuberculous and rheumatoid arthritis are discussed.

This research has been aided by a grant from the Research Fund of the University of London. I wish to acknowledge the gift of bovine plasmin from Messrs Parke Davis and Company, Detroit; and Fraction III of human plasma from E. R. Squibb and Sons, by courtesy of the American National Red Cross.

REFERENCES