# Disorders of the Skeletal System: Osteoarthritis

**Uptodate**

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**University of London Audio-Visual Centre, 1976.**

**Directed by Trevor A Scott.**

**Black-and-white**
**Duration: 00:45:09:03**

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**<Dr Ali to camera>**

In this programme we are going to take a new look at osteoarthritis, and one of the difficulties one has when examining the literature on this disease is the fact that the term osteoarthritis has been very loosely used. Moreover, the criteria by which osteoarthritis is defined are again very vague. For example, if we take a term like fibrillation, some people use this synonymously with osteoarthritis and this can lead us into difficulties. Some of the earlier studies, postmortem studies, have been shown to indicate that wherever you've got fibrillation that in itself is osteoarthritis. And it was not surprising to find, therefore, that in all the older post-mortem material, there was fibrillation and people called this osteoarthritis.

The other difficulty is that people associate osteoarthritis simply with wear and tear of the joints; again this is misleading. Some of the studies in Liverpool and in Finland have given other facts; for example, in Liverpool they carried out a detailed study over a 10 year period of soccer players in their football club and examined their joints over a period of time, and again in Finland they examined long distance runners and athletes over a long period of time. In both these studies, they found that in these

subpopulations of the soccer players and the athletes, the incidence of osteoarthritis was much lower than that in the general population. In fact, their joints were much healthier than that in the general population. So thus we come to the conclusion that there are several interacting factors which lead up to osteoarthritis. There are certainly more than two factors acting at one time which produce osteoarthritis, and we shall be looking at these in a moment. Although the factors may differ, sometimes the pathway that is followed in terms of the degeneration in the joint is very similar and it ends up with a very common lesion, which is common in any pathway that is taken.

At a clinical level, osteoarthrosis, which should be the right term for this disease because there's no inflammation and there's no arthritis as such, osteoarthrosis is recognised in patients when they complain of prolonged, persistent pain and when the surgeon finds on examination in the X-rays that the joint space has narrowed. The patient also complains of stiffness in the joints and there's loss of function. And when this is combined with bone sclerosis and cyst formation, marginal lipping and osteophytes, this gives us clues to osteoarthrosis. Now, all these features are closely associated with osteoarthrosis, none of them singly have got any diagnostic value or can predict the disease in its early stages.

Clinically, osteoarthritis is divided into two: primary osteoarthritis implies that it's idiopathic and that there is no antecedent cause. Secondary osteoarthritis implies that there is some antecedent cause, mainly anatomical in the sense that it could be derived from a congenital dislocation of the hip, it could be as a consequence of slipped epiphyses, Perthes disease or other hip dysplasias.

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**<Ali narrates over diagram of knee joint, using indicator>**

There are many hypotheses at the moment on what leads to osteoarthritis and we can't go into details of all these, but we shall examine one or two very briefly. If we examine the joint in a diagrammatic view, as shown in this diagram here, one finds

that the cartilage lines the bones down here, and it's the cartilage which suffers the main degenerative process in this particular disease. Michael Freeman at Imperial College has postulated that the collagen in the cartilage in this area, because it is being impounded by the joint movement, fractures and the fibrils fracture under fatigue just as metal fibres do, and that this fracture leads to the release of proteoglycans and other matrix components from the cartilage and this leads to the degenerative condition. Another hypothesis postulated by Eric Radin states that the subchondral bone that is underneath the cartilage, and lining the bone up here and again down here in this diagram of the knee joint, the subchondral bone is the first to deteriorate and that this sets in motion the changes that occur in cartilage. Equally well, there are hypotheses which link the changes in the synovial fluid and its lubrication properties to the degeneration of cartilage and therefore to osteoarthritis.

**<Ali to camera>**

These all theories are equally valid where the aetiology of these diseases is concerned, but people, by and large, now accept that the main tissue that is first affected in osteoarthritis is cartilage and that the changes seen in either the subchondral bone or in the synovium or in the capsule of the joint are secondary. And therefore, one would like to examine the cartilage in greater detail. Now, cartilage is not a static tissue, it is changing all the time. And it's important to regard this as a living tissue which is generating new cells and is generating new matrix components. It's very easy to compare the changes in cartilage with the changes that one sees in a rubber tyre in a motor car. Now, obviously if the alignment of the wheels in a motor car is abnormal or wrong then you will get a great wear and tear on the rubber tyres of the motor car, but these alignment changes are very similar to some of the anatomical changes one sees in secondary osteoarthritis. For primary osteoarthritis our analogies should be restricted to examining whether there are any changes in the chemical formation of the tyre, that is, whether the rubber components are of the right type or not. For example, if the rubber were too brittle or too elastic, then we know that it would wear away too rapidly. Of course, quality control at a factory level doesn't permit us to use abnormal tyres; we only use the perfect combination, the right chemical mixture for our rubber tyres. Now, cartilage is

changing all the time and if there are enzyme poisons affecting the cartilage, it can then manipulate the circumstances to secrete the corrective factors and thus perpetuate a normal situation. And therefore, in this one respect, cartilage is very different from rubber tyres that it can correct any changes that are abnormal.

We can examine cartilage at a gross macroscopic level, that is, there would be changes in the whole surface and the anatomy of cartilage. These could be either progressive changes or regressive changes, but, more important, one would like to examine what are the changes taking place in the internal milieu of the cartilage itself. There are cellular changes, and we shall we examining these in greater detail at electron microscopic level, and then there are changes in the matrix component and we shall be examining these at a chemical level. But before we come to examining these in detail, it is very important to determine what we mean by normal cartilage and what we mean by osteoarthritic cartilage. And therefore I would like to now let Dr Byers say a few words because he has examined a number of joints and has arrived at much more stricter definitions of normal tissue and osteoarthritic tissue.

**00:10:39:17**

**<Dr Byers to camera>**

Well, as Dr Ali's said, my interest in joints is concerned with the problem really more of defining what is osteoarthritic cartilage than normal. One tends to think, of course, that normal is a self-evident phenomenon, but I want to leave that aside just now and talk really about what is osteoarthritic cartilage. And that's a problem very much in classification and it begins, I think, with the problem of trying to classify patients. Dr Ali suggested that the recognition of the disease in patients was not too difficult, but, at least at its periphery, it has its problems – these concern, largely, recognition of inflammatory joint disease.

The study of osteoarthritic cartilage really nowadays is dependent upon the femoral head.

**<Byers narrates over: slide showing femoral head specimens, diagrammatic slide of femoral head, and then diagrammatic slide of zones in joint>**

Numerous of these are resected in treatment of the disease and they come in great numbers into laboratories and represents the kind of material that we have to look at. And here you see a collection of femoral heads taken at random and the thing that's, to my eyes, striking about them is how different they are. As they say on the fairground, everyone's different. And yet, we reduce this great difference to some simple schematic representation, which we can look at in this next diagram. They all have an area here on the superior part which is exposed bone. That's surrounded by shelving, cartilage – starts at nothing here, increases in thickness until it comes to what is full thickness, represented by this pale zone which surrounds this abnormal area. Outside that, then, there are osteocytes seen here, these vary in extent and size from case to case.

In about 30% of the femoral heads that we get in the laboratory at the Institute of Orthopaedics, there is an appreciable amount of tissue in this anteroposterior region, enough to allow current chemical techniques to be applied to them. And it is this material which is examined for characterisation of osteoarthritis. Why it should only be 30% that have this is open to speculation, but it does means that we're perhaps not looking at representative tissue.

What we've done in our laboratory is to take samples of every specimen which is examined biochemically, that is, we have got a histological sample of a chemical sample, if you like, and we've analysed the destructive surface mechanisms which appear. And the next few illustrations will show these. First, perhaps, it might be best to make the point that we are going to, in the end, show their distribution in these four zones. Let's look and see what the destructive mechanisms at the surface are.

**00:14:57:00**

**<Byers narrates over series of photomicrographs, using indicator stick>**

These are fine fibrillation; you can see it along the surface here, a very fine break up of the surface, and then there's a coarser fibrillation, which the next illustration shows us, here. And then there is a group of changes which we've described as 'other changes'; it's a sort of composite hotchpotch of things that we can look at quickly in the next three illustrations. There is a very fine tangential fraying. The next one shows some deep splits; they are few in number compared with the numerous clefts in the fibrillated cartilage, a few deep clefts, some of them lying right down at the base of the cartilage. And then there is a third category in this group of things we call other changes, that is, matrix resorption by cells, presumably by chondrocytes. You see these resorption cavities with collapse of the matrix. And finally, then, in our categorisation of surface mechanisms is fibrous surface change, what is usually referred to as 'pannus'.

**<Byers narrates over slide of graph showing distribution of destructive mechanisms in 4 zones>**

Now, the distribution of these at the surface in these cartilage samples as seen in the next illustration. Here are the representations of these destructive mechanisms: fine fibrillation, coarse fibrillation, other changes – you remember those 3 different things which we are lumping together as other changes, pannus, that fibrous surface there, and of course there's always unchanged surface. Now this histogram shows the distribution in the four zones.

In the first zone, the zone that shelves down onto the expose bone, the predominant thing is fine fibrillation, 80%. And then there are a few other cases showing odds and bits. In the second zone, there is some fine fibrillation, there is also coarse fibrillation, but these other changes are affecting something like 50% of the cases and there isn't any unchanged surface here. And the third zone: fibrillation is not a predominant, even a prominent finding; other changes are: the fibrous tissue appears in a few cases, but there are many cases with unchanged surface. And then finally in this fourth zone, which is out at the periphery of the articular cartilage, there is virtually no

fibrillation, some other changes, pannus now more common than ever before, and a little bit of unchanged surface.

Well, what does that actually mean?

**<Byers to camera>**

I think that it means, first of all, that there is a good deal of variation in the surface of this material which is being looked at for biochemical examination. But we can make an attempt to get a further interpretation if we look for a brief moment at the results of a post-mortem study of hip joints. And our next illustration is going to show you a diagrammatic representation of the hip joint: the head and the acetabulum.

**<Byers narrates over diagrammatic slide of head and acetabulum of hip joint, using indicator stick>**

Her you see the distribution of articular cartilage changes. These have been demonstrated in a number of post-mortem studies and everybody is agreed to this distribution. In the particular study that I conducted, I merely paid attention to the fate of lesions in particular sites and to something about their histology. The term ‘limited’ which you see here, demonstrated by this shade, which is present here in the head and here in the acetabulum, simply means that those areas affected in this way rarely ever lead on to bone exposure. And that contrasts with what is styled ‘progressive’, only to be seen here in the acetabulum and here in the head. Here, once the lesion starts, it progresses relentlessly to bone exposure and followed by joint deformity of the order which we’ve seen in the specimens at the start of my talk.

**00:20:27:18**

**<Byers narrates over slide showing age prevalence of limited and progressive cartilage alterations of head and acetabulum>**

We can look at the next illustration to see what is the relative age prevalence of these two classes of lesion and you see how very common the limited are. They begin early and they arise to great prevalence and that contrasts with the progressive, which are relatively few – they start later in life and their prevalence corresponds with the clinical prevalence of osteoarthritis, so what we've called progressive lesion equals osteoarthritis.

**<Byers narrates over table comparing limited and progressive lesions and then over a previous graph showing distribution of destructive mechanisms in different zones>**

Now, histologically, the findings in these two kinds of lesions are seen on our next illustration; and you see on the left, these are the mechanisms we found at the surface – the same words as we are using before: fine fibrillation, coarse fibrillation, the fibrous surface layer, that is the pannus, the other changes of fraying and splits and cellular resorption. Now, the thing that's interesting is their distribution between limited and progressive lesions. They all appear in the limited type of lesion except the fine fibrillation. That appears only in the progressive. But coarse fibrillation appears in the progressive too. Now, we can take that information and return to our histogram and get our final bit of interpretation. You see that in zone 1, fine fibrillation, the characteristic change, if you like, of the progressive disorder, that is, of osteoarthritis, is found in zone 1 and to some extent in zone 2. Coarse fibrillation, which seems to mean either a progressive osteoarthritic lesion or the limited non-osteoarthritic lesion, appears also in zone 1 but to very little extent, more prominently in zone 2 and zone 3.

**<Byers to camera>**

It looks then as though the interpretation of this little look at osteoarthritic cartilage in the resected femoral heads means that, by strict criteria, the osteoarthritic cartilage is that bit that lies contiguous to the area of exposed bone. Well, now I think we can turn back to Dr Ali and see what he's going to make out of that.

**<Ali to camera and then over diagrammatic slide of femoral head>**

Now after that description of the cartilage that we find on femoral heads obtained at total hip replacement, we are in a better position to see the electron microscopic and chemical aspects of the tissue. And just for a moment, I would like to re-project the diagram he showed you and mention that the type of tissue we have examined is from zones 1 and 2 in this region and, again, in this region here on both sides of the fovea.

**<Ali narrates over series of electron micrographs of cartilage, using indicator stick>**

The next diagram shows the appearance of this type of cartilage at electron microscopic level. The surface itself, the surface of cartilage, is highly irregular and it would appear grossly irregular at electron microscopic level, but just below the surface in the surface areas of the cartilage, we find that the cells are very flat and they are embedded in thick collagen bundles surrounding them. These cells have got long processes and do not appear to have a lacuna around them. So the first change that we notice is in the collagen of the matrix in this type of osteoarthritic cartilage, and if we examine the collagen in greater detail in the next electron microscopic picture, we find that the collagen bundles, seen in transverse section here and in longitudinal section here and up here, we find that the collagen fibrils are next to one another without much inter-fibrillar space between them, so there is very little proteoglycans, glycoprotein or protein in this area of cartilage in osteoarthritic tissue.

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Now, secondly, we find changes in the cells themselves as shown in the next diagram. We find that the cells are degenerating very rapidly in this kind of tissue. Again, they are surrounded by the highly collagenous matrix, and the cells have pyknotic nuclei and cisternae with empty spaces in the cytoplasm of the cell itself. The subcellular organelles are also affected and have lost their shape, so all in all

this shows to us that the cells are in a very bad state in this type of osteoarthritic tissue from zone 1 and 2.

Next, if examine the matrix in detail in the next diagram, we find that in the deeper zones, deeper layers of cartilage, there is a bit more inter-fibrillar cement in between the collagen fibrils. These collagen fibrils appear to anastomose and form very thick fibrils up to 3000 angstroms in diameter. The proteoglycan granules, which would be quite evident at this stage in normal cartilage, are microscopic indeed and are really pinpoints at this magnification in this picture. Apart from these changes, we also find some electron-dense material, which could be [unclear word] in nature in this osteoarthritic tissue and we are hoping to analyse that in detail later on.

If we now go back to the cells in the next diagram, we find that cells in the deeper zone, and this is more or less a normal cell, a healthy cell, have various organelles inside them – the lysosomes, mitochondria and the Golgi apparatus etc., but in the area surrounding the cell, just outside the lacuna on the side here, we find that it is surrounded by these small membranous particles, the matrix vesicles.

At high power, we can examine the matrix vesicles in greater detail and we find that there are membrane-bound bodies, as seen in this high power view right now. These membranous particles were first found in growth cartilage and they have been shown to initiate the mineralisation of growth cartilage, or epiphyseal cartilage. And their occurrence in articular cartilage, especially osteoarthritic cartilage, implies there is something wrong with the calcification mechanism in this particular tissue. In addition, these matrix vesicles have been shown to contain a lot of alkaline phosphatase in growth cartilage and, again, I'll be taking about the chemistry of osteoarthritic cartilage in a minute and, again, we have found high levels of alkaline phosphatase in this type of tissue.

Now, all these electron microscopic findings have been confirmed by chemical analysis, that is, the change in the proteoglycan level and in, probably, the structure of proteoglycans and also the elevation of some of the degradative enzyme activity derived from the lysosomes. But the important thing to remember is that the

architecture of the tissue itself has changed tremendously and, in addition, we also find changes in calcification or mineralisation of cartilage.

**<Ali to camera and then over diagrammatic slide illustrating water tanks with varying sizes of inlets and outlets>**

Now we shall go on and examine these changes in the chemistry of the tissue in greater detail. And how are these chemical changes brought about? If we take as an analogy, in the next slide, a diagrammatic view of a water tank, we find that to keep it filled up, we have to have the inlet and the outlet the same size. And this is how the tissue also replenishes itself, that is, the synthesis, which would be analogous to your intake, if the synthesis is the same as the outlet, the degradative side, then the balance of matrix components is in equilibrium in cartilage or in any other tissue. But if, for a minute, you imagine that the synthesis has gone down but that the outlet or degradation is the same as before, then you'll get a lowering in the level of the matrix component or as you would in the level of the water tank. But there's an additional fact: supposing the synthesis were quite normal, as before, but that the degradative activity, or the outlet, of the matrix component were greater then you would also reduction in this level.

**00:30:10:16**

And now, is there any situation in cartilage which can bring about this kind of change? And the changes that are brought about in cartilage are by enzymes.

**<Ali to camera>**

These can be activated by hormones or other metabolites and they are dependent on the cellular activity of the tissue, so we can postulate that if there is a change in the level of degradative enzymes then there would be a change in the matrix components of cartilage especially in diseases like osteoarthritis. Now, what gives us the right to say that these enzymes can bring about a change in articular cartilage? The biggest or the best example one can give is that if you have a proteolytic

enzyme like papain and if you can inject this into the joint in an active form, then this would deplete the matrix proteoglycans, and if this is true then we should end up with an osteoarthritic situation. And, indeed, one finds this to be case and if I can go briefly over the next histological slide, […]

**<Ali narrates over photomicrograph of cartilage from rabbit joint>**

[…] which was taken from a rabbit which was injected 5 weeks previously with papain in the joint cavity up here. Now subsequent to the injections, changes took place in the cartilage and later on in the whole joint itself. The very first change that one notices is in the proteoglycan content of the cartilage itself because the cartilage loses its metachromasia and the level of proteoglycan in serum and in urine is elevated. Secondly, the cells in the tissue become necrotic and disappear, and subsequent to that there is fibrillation and roughening of the surface of the articular cartilage. And in the pressure-bearing areas, the cartilage is worn away completely, exposing the subchondral bone. And as you can see from this slide, and some of the slides that Dr Byers showed you, that the histology of this rabbit tissue is not very different from the human osteoarthritic condition that Dr Byers pointed out to you. And, therefore, this single injection of papain reproduces, in all its forms, in the rabbit joint, exactly the situation that you obtain in osteoarthritis in human beings.

Now, we go back to our postulate and would like to examine what are the enzymes present in cartilage, which can bring about these changes.

**<Ali to camera>**

And I shall ignore some of the enzymes derived from the leucocytes, which may be filtering into the joint cavity, and I shall ignore too some of the enzymes derived from the synovial membrane itself which could affect the cartilage. I shall concentrate on the enzymes which are present in cartilage itself and can bring about a change from within. And I shall be examining some the degradative enzymes in osteoarthritic tissue.

**<Ali narrates over slide of graph showing cathepsin D activity in articular cartilage>**

The next slide, again, shows that if you measure the amount of activity in normal cartilage, as shown by these dark circles in this area, and in other types of normal cartilage obtained from fracture of the neck of femur, and plot the level of this activity against the age of the patient, as shown here, then you find that the level stays fairly constant with age, although there is variation at each age group here. But when you examine osteoarthritic tissue, derived from the type of cartilage Dr Byers mentioned, then you get 2 to 3 times the activity of cathepsin D, which is a degradative enzyme present in cartilage. So one can easily see that in osteoarthritic tissue there is an elevation of this degradative enzyme. In addition, there is an elevation of acid phosphatase activity and cathepsin B1 activity, indicating that the whole spectrum of lysosomal enzymes are elevated in osteoarthritic tissue.

**<Ali narrates over slide of graph showing alkaline phosphatase activity in articular cartilage>**

In addition, we have found, as shown in the next diagram, that if we examine alkaline phosphatase activity, again plotted against the age of the patient from which the tissue was derived, we find that there is slightly higher activity in young tissue, that is, from children and infants, but that after puberty the level goes down and remains constant throughout life right up to the age of 100. But if we now examine the osteoarthritic tissue then we find up to 10 times the normal level of alkaline phosphatase activity in osteoarthritic cartilage. And it is therefore clear to us that there is an elevation of the degradative enzymes and some of these calcification enzymes in osteoarthritic cartilage.

**00:35:33:22**

**<Ali to camera>**

Now, the tissue that I have talked about till now has been derived from cartilage obtained after total hip replacement surgery, that is, the tissue was post-osteoarthritic and certainly was not pre-osteoarthritic. I have had some good luck in finding a specimen in which we could detect pre-osteoarthritic or early osteoarthritic changes and we examined these enzymes again in that tissue.

**<Ali narrates over slide of graph showing cathepsin D activity in articular cartilage>**

The next diagram shows some of our results obtained from this type of femoral head. Now, this femoral head was obtained after amputation, hindquarters amputation, and it was from a patient who did not complain or suffer from arthritis, but up in this area here, marked A, I could notice some superficial fibrillation and fraying of the fibres and it looked to me as if this could be in a pre-osteoarthritic or early osteoarthritic state because this is the area which Dr Byers defined as the progressive area which leads up to osteoarthritis. Now, the area B and the rest of the femoral head had just normal cartilage. And I examined the enzyme levels in these two areas and these are displayed here, and the activity is plotted against the incubation time for that particular enzyme. And as you can see, area A had about twice as much cathepsin D activity as the normal area B derived from the same femoral head.

**<Ali narrates over slide of graph showing alkaline phosphatase activity in articular cartilage>**

Now, in the next diagram, we examine alkaline phosphatase, again obtained from the same femoral head and in the same two areas that I mentioned. And this time we find that the alkaline phosphatase activity was 4 to 5 times that in the normal area B. And this indicated to us that in early osteoarthritic condition there may be enzyme changes taking place and, therefore, one could say that some of the changes noticed in osteoarthritis may be due to the enzyme changes that have occurred.

**<Ali briefly to camera and then over slides outlining sequential changes in osteoarthritis>**

And I'm now taking a bold step and postulating some of the sequential changes that can occur and bring about osteoarthritis and these will be displayed in the next two diagrams. Now, this is very much a postulate, but if you start by assuming that there are various initiating factors in this disease and these could be either anatomical, in which sense you would be getting secondary osteoarthritis, or these could be changes in hormones or other metabolites. It is known that hormonal changes in acromegaly can lead up to osteoarthritis and, again, in ochronosis because of the faulty tyrosine metabolism, the production of homogentisic acid and its location in cartilage can lead up to osteoarthritis. Therefore we can say that there may be other metabolites activating which directly affect the cells in some way in the matrix of articular cartilage. And if this is so, and if we can now bring in the data that we've obtained in the sense that there is high degradative enzyme activity in osteoarthritic tissue, we can then see that these enzymes, these degradative enzymes, will act on the matrix components and change the concentration and perhaps the ultrastructure of the proteoglycans molecules. Now, that change can have quite deleterious consequences because it can affect the type of collagen that is formed in the tissue, that is, it can affect the collagen diameter, it can affect the collagen cross-linking. In addition, it can affect the cartilage and change its resilience and weight-bearing properties. It can also induce calcification in cartilage because it has been shown by other workers that the removal of proteoglycans leads on to mineralisation in other cartilages.

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So if we examine the sequence further, then these changes in the matrix components will bring about changes in the collagen and this will lead to fibrillation. And now this fibrillated cartilage is susceptible to very rapid breakdown in cartilage. And if we go on to this next point, the fifth point in this sequential slide, we arrive at the clinical osteoarthrotic condition. So all the changes that have taken place before, we can refer to as pre-osteoarthrotic, and after this clinical osteoarthritic condition,

we can refer to the remaining parts as post-osteoarthrotic. In the clinical osteoarthrotic condition, there is wearing away of cartilage and there is narrowing of joint space and there's complaint of pain, stiffness in the joint and lack of function. That is the clinical picture one sees in osteoarthritis which one is familiar with.

Now, secondary to that change, as I implied with the papain experiments, you could get small bits of cartilage going into the joint cavity and being sequestered by the synovium. These would set in motion secondary changes in the synovium which gets inflamed and you get inflammatory changes. There may also be other changes in the capsule synovial fluid and in the bone, subchondral bone, etc. These, one feels, may be secondary to the osteoarthrotic condition.

In the seventh step, we can postulate that there are attempts at repair and reversal of these changes, so one finds a lot of granulation tissue, fibrous tissue overlying the femoral head and other joint surfaces. And you find proliferation of chondrocytes at this stage because you can see them in nests of cells in clusters and you can even get an increase in the synthesis of proteoglycans at this particular stage.

Now, going to the final point, we find that because of the high degradative enzyme activity and various other changes that have occurred, the cartilage is incapable of regenerating itself or, at least, it tries to regenerate, but because of the loss in architecture of the tissue, because of lack of orientation in the regenerating tissue, it's rapidly worn away and you end up with a chronic disease condition in osteoarthritis.

**<Ali to camera>**

Now this more or less concludes my postulates and the sequence of events that I see as obtaining in an osteoarthritic condition. Now, is there any hope for the future? I think in the first osteoarthritic condition, after a clinical diagnosis has been made, I think total hip replacement surgery and other surgical interventions, such as osteotomy, offer the best possible ways out. We haven't got any therapeutic alternatives at the moment, but this is a very much a [unclear word] hope for the

future that perhaps if we can diagnose osteoarthritis very early, perhaps we can then introduce at a pre-osteoarthritic state, activators, that is, compounds which will elevate the synthesis of matrix components and inhibitors, which would stop the effect of some of these degradative enzymes, introduced at an early stage to prevent the osteoarthrotic condition. But I come back to the main point that, at the moment, we have no way of judging an osteoarthrotic condition in its early stages till we get the full clinical picture. Until we are able to diagnose osteoarthritis at a very early stage, we cannot treat it at the moment.

**<End credits>**