amples cited in the report include computed tomographic scanning, some screening procedures, elective induction of labour, and coronary care units; we might add plasmapheresis, various ultrasonic and electrical devices for treating soft tissue injuries and non-union of fractures, and a whole range of supplementary foods for patients undergoing surgery.

How do regional and district health authorities decide whether to agree to a request from hospital staff for the purchase of new equipment or the introduction of a new treatment? When equipment is very expensive regions consult their advisory committees—but a new treatment or laboratory investigation may be introduced simply on the decision of an individual clinician. The report explains several ways in which a “cuckoo may turn up in an unsuspecting district’s nest.” A piece of laboratory or radiological equipment may be replaced by a model of the next generation—capable of advanced tests or of working much more quickly. A consultant may be appointed bringing with him a special interest and the appropriate skills (transplantation surgery is one example). Local public opinion may be mobilised to raise money to buy a new machine (but not the revenue costs to run it). Prototype equipment may be introduced with the support of research funds—but the NHS may later be asked to take over the running costs.

All too often the new technique or treatment becomes

fashionable before it has been properly evaluated—a process which usually requires painstaking, lengthy clinical trials. Nor are there usually good data on the numbers of patients likely to benefit from the innovation. The introduction of these new techniques should, the report argues, depend less on capricious initiatives and enthusiasms and should be preceded by a clinical as well as technical evaluation. The conclusion reached in the report is that the Secretary of State should set up an advisory group on expensive medical techniques which would ensure that these were properly evaluated. The group’s reports would provide health authorities with the objective, independent advice that they need before deciding whether and how quickly to provide money for a technological innovation.

Certainly some sort of independent assessment would be helpful for clinicians as well as administrators when faced with the claims made for an innovation by the enthusiasts who have developed it. Slowly and painfully over the past 20 years most doctors have learnt that proper clinical trials are the only way of assessing new drugs and putting them into their true perspective. The same critical process needs to be applied to new operations, new treatments of every kind, and new diagnostic techniques.

¹ Council for Science and Society. *Extensive medical techniques. Report of a working party*. London: Council for Science and Society, 1983.

Regular Review

The nature and causes of osteoarthritis

D L GARDNER

The term osteoarthritis describes the condition which may succeed damage to the avascular, aneural hyaline cartilage of synovial joints. Some authors continue to use the alternative older term osteoarthritis, implying inflammation rather than degeneration.^{1 2} Any of man’s 190 or so synovial joints may be affected; frequently several joints are diseased but occasionally the disorder is generalised osteoarthritis.³

Characteristically the freely moving diarthrodial joints have a synovial lining and contain a little viscous synovial fluid. The opposed bones that constitute a synovial joint, the hyaline cartilage that covers each articulating surface, and the synovial fluid have a common developmental origin. A diarthrodial joint moves normally only when the actions of the skeletal muscles that act across the joint are physiological, when the relevant ligaments and tendons are intact, and the menisci and labra normal and whole. Any discussions of the origins and nature of failure of hyaline articular cartilage in osteoarthritis must therefore take into account the possible parts played by abnormalities of bone, synovial fluid, tendon, ligament, accessory structures, and skeletal muscle.

Osteoarthritis is a common cause of disability and suffering in man. In one survey the prevalence of severe joint disease was 19% in men and 22% in women.⁴ Five or more joint

groups were affected in 0.5% and 1.8% of men and women respectively. Osteoarthritis is seen in all surviving mammals, but an analogous failure of load bearing cartilage may even have occurred in prehistoric dinosaurs and early man.⁵ The prevalence of osteoarthritis in domestic animals, including horses and dogs, has led to investigations by veterinary scientists and comparative anatomists,⁶ and weakness of the legs and diseases of the joints in pigs have also attracted interest.⁷

Cartilage is a unique gel reinforced with fibre; it contains few cells and a large proportion of extracellular matrix material.⁸ Wide variations in its structure are seen both between individuals and between different parts of the cartilage of a single joint. The composition of cartilage changes considerably during growth. The matrix, which forms 90–99% of adult hyaline cartilage, is 65–75% water, with the cells occupying only 1–10% of the total volume. Half of the total cartilage protein is type II collagen, and, of the remainder, about one eighth is the core protein of the giant proteoglycan molecules that are normally aggregated with hyaluronic acid. The principal function of the proteoglycans is to retain water. The extent to which these molecules expand and hold water is determined by a meshwork of type II collagen. All the

constituents of normal cartilage are synthesised and secreted by chondrocytes.

Given these structural aspects, it may be proposed that the failure of cartilage as a biological material and the development of osteoarthritis is determined partly by heritable and partly by environmental agents. The underlying mechanisms may include impairment or loss of chondrocyte function; death or injury to chondrocytes; defective chondrocyte replication or growth; inadequate or abnormal synthesis, secretion, maturation, or aggregation of proteoglycans; inadequate or abnormal synthesis, secretion, maturation, or cross linking of type II collagen; defective aggregation of collagen and proteoglycans; and the provocative action of physical agents, or of chemical agents, such as proteolytic enzymes that degrade cartilage matrix.

Two categories of osteoarthritis may be recognised. Firstly, in a substantial but diminishing group of people the hyaline cartilage fails with no recognisable hereditary defect, no metabolic or endocrine abnormality, and no history of injury, infection, or other disorder. In these people osteoarthritis may be said to be "idiopathic" (primary). Secondly, disease of the cartilage may be shown to have been caused by injury, infection, nutritional or metabolic disorder, endocrine dysfunction, or other insult. For example, fractures affecting articular surfaces, suppurative and tuberculous arthritis, rickets, gout, acromegaly, and rheumatoid arthritis may be complicated by secondary osteoarthritis. The structure and function of cartilage may be affected by congenital deformity of the whole joint or skeleton, and this deformity or that associated with metabolic disease may be heritable. The genetic locomotor diseases,⁹ the lysosomal storage diseases,¹⁰ and the inherited disorders of collagen and those of amino acid metabolism may all promote failure of the cartilage. In one clinical and radiological study of 976 arthrotic hips in 654 patients (mean age 42) the damage was thought to result from congenital dislocation in as many as 419, epiphyseal necrosis of the femoral head in 194, trauma in 79, and chondrodystrophy¹¹ in nine. These figures contrast with the general experience in which one quarter of cases of osteoarthritis cannot be attributed to known, previous disease.

The elbows of coal miners, the toes of ballet dancers, and the knees of footballers are thought to be particularly susceptible to osteoarthritis.^{12 13} The evidence is, however, conflicting. Whereas the footballers of Leeds appear not to be prone to osteoarthritis of the knee,¹² those of Vejle are subject to disease of the hip.¹³ Parachutists sustain many minor and some major orthopaedic injuries but do not develop accelerated osteoarthritis.

Age and osteoarthritis

Early anatomical studies showed that osteoarthritis is recognised with increasing frequency in older persons,¹⁴ an observation confirmed epidemiologically.⁴ By the age of 60 the knee, acromioclavicular, elbow, first metatarsophalangeal, hip, sternoclavicular, and shoulder joints are affected in decreasing order of frequency. Clinically arthritis of the hip and of the joints of the cervical spine becomes more important, and the Heberden node of the distal interphalangeal joint causes early cosmetic anxiety and later painful disability. Older people, in the sixth to eighth decades of life, do not, however, complain of more pain and disability than younger individuals.

Much attention has been directed to the relation between

aging and osteoarthritis. The view has been strongly expressed that aging of cartilage and osteoarthritis are unrelated,⁵ but the argument is difficult to assess because the anatomical changes and secondary clinical signs of osteoarthritis become more prevalent with advancing age. Nevertheless, important evidence has emerged that suggests that load bearing cartilage surfaces, such as those of the femoral head, undergo at least two patterns of gross degenerative change,^{15 16} and these changes may be unrelated.

The first of these disorders becomes more common with age. It comprises granularity, superficial fraying, fissuring, flaking, and, finally, loss of cartilage with subsequent ossification. Occasionally this loss of cartilage leads to exposure of bone principally around the edge of the cartilage and at the periphery of the load bearing surface. Although related to age, these changes in the cartilage are not thought to be progressive and hence not to be the precursors of clinical osteoarthritis.

The second microscopic pattern of cartilage abnormality is recognised only in later life. It has been regarded as a disease process, not an age change. This much less common pattern comprises circumscribed zones of granularity that progress to complete loss of cartilage and, finally, to the anatomical lesions of osteoarthritis. On the femoral head these changes affect different areas from those described in the first pattern of cartilage loss. The areas affected include the anterosuperior parts of the cartilage, outside those displaying the non-progressive cartilage changes.

The relation between osteoarthritis and age is more easily examined in animals than man, particularly in mammals such as inbred mice, with brief life spans. Degenerative changes in the cartilage develop with age in many male and some female dwarf mice. Study of ICR mice shows a high incidence of degeneration in the cartilage of the temporomandibular joint in adult early life. The changes progress to fibrillation and osteosclerosis, which suggests that in this strain of mouse aging chondrocytes synthesise matrix materials increasingly incapable of withstanding normal mechanical stresses.

Anatomy

The gross lesions of osteoarthritis have been described in extreme detail.⁵ Osteoarthritis culminates in complete loss of cartilage with exposure of bone and eburnation, remodelling of bone, and the development of bone osteophytes and cysts. The synovium then absorbs fragments of cartilage and bone (figure). The characteristic change under the light microscope is fibrillation of the superficial layers of cartilage. Fibrillation related only to age and fibrillation as a hallmark of osteoarthritis are not histologically distinguishable. Fibrillation¹⁷ is assumed to be the result of a sequence of molecular disorders of the cartilage matrix. These disorders probably stem from alterations in the function of the chondrocytes. As the chemical structure of the matrix changes a stage is reached at which the electron microscope can detect morphological abnormalities; in time these abnormalities become sufficiently severe to be visible with the light microscope.

Light microscopical examination of the human patellofemoral articulation from patients with age related change of cartilage structure show a range of abnormalities from "minimal fibrillation" to "full thickness cartilage loss."¹⁸ The process is not uniform either in terms of site or in the time sequence of its development. Comparable surveys of the shoulder and hip joints suggest that similar age related fibrillation develops

in the cartilage of all synovial joints and that regions of fibrillation may appear as early as the second decade of life.¹⁹ The ankle joint also shows a central "minimal fibrillation" that extends with age but is not affected by the vertical wear of clinically demonstrable osteoarthritis. The bare area of the lateral tibial plateau shows "overt fibrillation" to a degree

Evolution of idiopathic osteoarthritis.

proportional to an individual's age, and to a greater extent than the part of the plateau covered by the meniscus.

There have been many studies of hyaline cartilage from animals, particularly mice with heritable osteoarthritis but also from other species in which degenerative change of the cartilage has been induced experimentally. Access to fresh material from people with sufficiently early disease of the cartilage to make electron microscope study worth while has proved less easy, Weiss describing the main features.²⁰ Ghadially, Lalonde, and Yong²¹ drew attention to the occasional occurrence of amiantoid ("asbestos like") fibres that are an index of altered cross linking of collagen. The use of special electronmicroscopical techniques such as freeze etching and replication²² has shown some of the minute changes in chondrocyte structure in human osteoarthritis, "coronal" zones containing vesicles have been identified around the cells, and matrix vesicles with foci of apatite crystal formation have been seen. Scanning electronmicroscopical analyses have defined the surface structure of cartilage.²³ Recently advances in low temperature electronmicroscopical techniques have enabled unfixed, hydrated human and animal cartilage samples to be studied,²⁴ and it is now possible to analyse the fine structure of tissue from cases of osteoarthritis in which water and proteoglycan and collagen are present in the sites where they exist during life.

Osteoarthritis as a disorder of cartilage growth

In the search for an explanation for idiopathic osteoarthritis a possible disorder of cartilage growth should be considered. Once it is mature, the metabolism, synthesis, and secretory activity of the chondrocyte continue to be regulated by growth

hormone.²⁵ This influences cartilage cells through somatomedins produced by the liver—though, as somatomedins can act directly on chondrocytes (an action which is used to advantage in a bioassay of plasma somatomedin in chondrocyte culture²⁶), there is no evidence that the abnormal chondrocyte metabolism and growth detectable in human and experimental osteoarthritis are due to altered synthesis, release, or action of somatomedin. Excess growth hormone may promote osteoarthritis, as shown by the development of secondary osteoarthritis in acromegaly,²⁷ but acromegalic joint disease is rare.^{28 29} Insulin stimulates the incorporation of ³⁵S sulphate into cartilage slices and chondrocytes, thus aiding assembly of proteoglycan, yet diabetics do not have a noticeably higher prevalence of osteoarthritis than non-diabetics. Other hormones also influence the metabolism of cartilage but no single abnormality of the endocrine system can explain idiopathic osteoarthritis.

Within cartilage there are systems that control the synthesis and secretion by chondrocytes of matrix macromolecules. When chick embryos are grown in culture in the presence of hyaluronidase some constituents of the matrix are lost.³⁰ During recovery from this treatment, and to some extent during treatment, the rate of formation of proteoglycan precursors and of collagen and of non-collagenous protein is enhanced. Under some circumstances, therefore, chondrocytes can re-establish a normal environment after injury. Repair of defects deliberately caused in whole cartilages in living animals is, however, followed by very limited repair,^{31 32} unless the injury extends to the subchondral bone marrow.

Possibly osteoarthritis is due to a sustained disturbance of the finely adjusted mechanism regulating repair after trivial day to day mechanical injury.^{33 34} This concept is supported by the demonstration that only hyaluronic acid, from among several macromolecular substances extracted from, or analogous to, those in cartilage, reduces chondrocyte metabolism of ³⁵SO₄, probably interacting with proteoglycan at the cell surface.^{35 36} Since hyaluronic acid is an important compound of the normal cartilage matrix,⁸ there is evidently an intrinsic feedback mechanism for regulating the synthesis of the matrix. A disorder of chondrocytes may explain an insidious breakdown of this system in osteoarthritis.

Biochemical changes

There are early changes in the proteoglycans in osteoarthritis: these become smaller, less mature and are synthesised at increased rates, and aggregate less well than normal. A striking abnormality of osteoarthritis in the cartilage is the alteration in its content of water. Normally this is greatest in the surface zones and least in the deep zones.³⁷ In human osteoarthritis the water content of the cartilage is increased,³⁸ a change also found soon after experimentally produced joint disease.³⁹ At first it might seem difficult to reconcile the demonstrable changes in proteoglycan⁴⁰⁻⁴² with the increase in cartilage water. The swelling pressure of the proteoglycans and the extent to which they expand are, however, determined by the integrity of the collagen of the cartilage. It is therefore natural to search for evidence of an alteration in the quality, content, or arrangement of type II collagen in osteoarthritis. Although the scanning electron microscope is a crude tool to search for changes in collagen fibrils or fibre bundles, some evidence suggests that their arrangement in human osteoarthritis and in experimental joint disease in dogs is altered.⁴³ Experimentally, the rate of collagen synthesis is increased.⁴⁴

Another explanation of the molecular failure of cartilage is the occurrence of age related molecular defects or of molecular disorganisation such as amyloid. Amyloid deposits in the articular cartilage of older people are more common than suspected.⁴⁵ These must alter the mechanical properties of cartilage, and not surprisingly amyloid is recognisable in a substantial proportion of the knee and hip cartilages examined after arthroplasty for osteoarthritis.⁴⁶ In the knee joints such deposits are often near the cartilage surfaces, and calcium pyrophosphate crystals may lie among amyloid microfibrils.

Interest in the part played by proteolytic enzymes in the destruction of cartilage in inflammatory joint diseases such as rheumatoid arthritis has prompted a search for comparable mechanisms in the breakdown of cartilage in osteoarthritis. Proteases may be activated by stimuli such as crystal formation; alternatively, protease activity, regulated by inhibitors, may be manifest when inhibitors are removed or suppressed.⁴⁷ Chondrocytes may release proteases that degrade the nearby matrix when synovial tissues are induced to secrete catabolins.⁴⁸

Joint lubrication

Effective articular lubrication⁴⁹ may depend more on the quality and quantity of the protein fraction of synovial fluid than on the unique content of hyaluronic acid.⁵⁰ Recently one of two glycoproteins associated with the lubrication fraction of synovial fluid has been found to be of particular importance and has been given the pseudonym "lubricin."⁵¹ Whether a failure of synthesis or secretion of lubricin may in part explain the onset of the cartilage failure of osteoarthritis is not known. In some circumstances defective lubrication would exacerbate material failure by the imposition, during normal movement, of higher loads than normal. At present, most accept that failure of lubrication is not a sufficient explanation for idiopathic osteoarthritis.

Cartilage may fail because the normal material is subjected to abnormal loads or the defective material to physiological loads.⁵²⁻⁵³ There is ready agreement that major trauma to synovial joints is likely to lead to secondary osteoarthritis. Whether idiopathic osteoarthritis may be attributed to the cumulative effect of repetitive minor trauma on normal but aging cartilage is debated. The response of cartilage to one or more deliberate, superficial lacerations has been extensively studied,⁵⁴ but this is a poor model of the minor everyday injuries. Single or repetitive blunt injuries are closer to the style of trauma encountered in day to day life.⁵⁵ Nevertheless, the investigation of these superficial experimental injuries has shown how death of the chondrocytes at the site of laceration is followed within 24 hours by a burst of mitotic activity, enhanced synthesis of matrix, and increased activity of the catabolic enzyme. These changes persist for a few days only; there is little or no further progress towards healing of the injury by replacement of the lost cartilage; equally, over periods of up to two years there is no suggestion that the unhealed injuries progress to osteoarthritis.

Deep injuries inevitably affect the underlying bone and its vascular supply. The response to such injury, in which the formation of haematomas leads to the synthesis of granulation tissue, new bone formation, and fibrosis, is similar to that seen in other vascular tissues. At the margin of deep injuries the reparative response by residual hyaline cartilage is no more than that seen in superficial injuries. There is no resurfacing of the kind characteristic of the healing of excised skin wounds. The fibrous tissue is gradually changed to a

hyaline chondroid material, becoming fibrocartilaginous; this new tissue persists indefinitely, with a slightly roughened surface depressed below the level of the surrounding intact cartilage, which remains free from osteoarthritis. The extent to which repair occurs is influenced by the size of the defect and by the extent to which the healing limb is mobilised: continuous passive movement over four weeks encourages rapid healing in deeply injured rabbit cartilage with the production of a tissue that resembles hyaline more closely than fibrocartilage.

Can cartilage heal in osteoarthritis?

In the embryo and in cell and organ culture, chondrocytes and their precursors avidly take up ³H-thymidine, synthesise DNA, and divide. In mature articular cartilage, however, mitotic figures are not seen. This raises the possibility that cartilage undergoes repair not by cell division but by a creeping molecular substitution analogous with that of the central nervous system. Nevertheless, the clusters of cells that comprise the "chondrones" of osteoarthritis are clones of newly divided cells. The cartilage in osteoarthritis shows increased synthesis of DNA, probably limited to these cellular islands that are often seen close to the fissures of the fibrillated matrix. The presence of these islands suggests that in response to injury mature cartilage can, after all, effect focal cell regeneration. The groups of chondrocytes that form as chondrophytes at the articular margins in experimental osteoarthritis provide further evidence for this view, but overall they are so limited that they give no confidence that whole fibrillated zones can be reconstituted.

Contribution of bone to osteoarthritis

Cartilage is susceptible to repetitive impulsive loading but resistant to rubbing.⁵⁶ Much of the force of impact sustained on walking downstairs, running, or jumping is transmitted to large, adjacent bone structures which are strong, brittle, and less deformable, and so the thin cartilage lamina is spared the adverse effects of repeated impact. Any change leading to increased stiffness of the bones, however, may increase the susceptibility of articular cartilage to trauma caused by impact. Thus it has been argued that bone may contribute to disease of the hyaline cartilage by stiffening, as a result of numerous microfractures that may occur before any disorder of the cartilage is demonstrable.⁵⁷ If circumferentially unrestrained, cartilage can survive impact stresses of up to 25 N/mm²; a force less than 13 kN is sufficient to fracture a femur.⁵⁵ Expressed in another way, if the contact area in impact loading is greater than 500 mm² then a compressive load sufficient to fracture a femur should not damage cartilage. Equally, it may be argued that the increased rate of osteogenesis in subchondral bone and osteophytes in early osteoarthritis may prejudice cartilage integrity by increasing stiffness of the bone. The bone does, however, have a normal mineral content.

When the knee joints of adult rabbits are subjected to impact loads equivalent to one and a half times their body weight at a rate of 40 cycles a minute 20 to 40 times each day, the bones become more stiff. After only one week there is surface loss of hexosamine, a measure of proteoglycan, and an increase in cells of DNA synthesis as shown by a rise in ³H-thymidine incorporation. The loss of hexosamine becomes more pronounced after 20 days of testing and is accompanied by a

further increase in stiffness, though the collagen content remains unchanged. The evidence supports the concept that microfractures in trabecular bone occur early and are associated with the loss or degradation of those cartilage macromolecules that resist compressive stresses.

It has long been suspected that an alteration of arterial and venous blood flow plays a part in the development of osteoarthritis.^{58 59} Though isotope scanning techniques often show increased flow at sites of osteoarthritis, this is probably an index of the increased metabolic activity of the cartilage and bone cells in active disease and of the associated secondary synovitis rather than a primary disorder. The formation of new bony osteophytes is, however, an early manifestation of experimental osteoarthritis and raised articular blood flow may be one explanation for this.

Inflammation and osteoarthritis

Idiopathic osteoarthritis is widely accepted to result from a primary disorder of cartilage or of cartilage and bone together. Osteoarthritic joints may, however, become inflamed and in primary generalised osteoarthritis a systemic illness with a raised erythrocyte sedimentation rate may occur. When the synovium from cases of established osteoarthritis is examined histologically it often shows evidence of low grade inflammation with a mononuclear cell infiltrate, fibrin, synovial cell hyperplasia, increased vascularity, and synovial villous hypertrophy.⁶⁰ These findings can be confirmed by electron microscopy. Since fragments of cartilage and of bone are often found in inflamed synovia, the inflammation may reasonably be attributed to the release of these particles into the joint cavity and their uptake by the actively phagocytic synovium.⁶¹

An alternative explanation of the synovitis of established osteoarthritis is the presence in the synovial fluid or synovium of crystals.^{62 63} Crystals of monosodium urate dihydrate (in gout) and of calcium pyrophosphate (in chondrocalcinosis) may both cause secondary osteoarthritis and readily excite inflammation. The inflammatory action may be direct, the shape and size of the crystals inviting phagocytosis, or a coating of protein may result in complement being activated and chemical mediators of inflammation being produced—including prostaglandin E_1 . A similar argument has been advanced for the deposition of bone crystals (apatite) in the synovium. In these circumstances the enzymes polymorph elastase or macrophage neutral collagenase might degrade the cartilage matrix.

Living synovium may have a remarkable influence on the integrity of nearby hyaline cartilage.⁶⁴ This is not surprising, for hyaline cartilage is avascular and usually dependent on the blood vessels of the synovium and subchondral bone for its gas exchange and metabolic requirements. In organ culture the synovium (and macrophages and small blood vessels) can release a family of substances, the catabolins, that instruct individual chondrocytes to degrade the cartilage matrix in the microenvironment of the cell.⁶⁵ Proteoglycan is broken down and collagen released. The structural integrity of the cartilage matrix is lost and its mechanical properties presumably impaired. The degradative action of chondrocytes on their own matrix in this system is likely to be the result of action by lysosomal proteases normally held latent within the cell.

Thus endogenous systems in both living synovia and viable chondrocytes might cause disintegration of cartilage in early osteoarthritis. Their operation might be more frequent in people with a heritable tendency to osteoarthritis. These are

acceptable explanations of how the integrity of cartilage might be lost when idiopathic osteoarthritis results from a disorder of the synovium or chondrocyte.

Very many different chemical agents have been injected into joints,⁶⁶ and some have been used to cause secondary osteoarthritis in animals. Such agents include the proteolytic enzyme papain, which degrades proteoglycan, and the polysaccharide caragheenan, which is taken up by the macrophages. For over a century direct and indirect trauma have been used for the same purpose, and in recent years particular attention has been directed to surgical procedures that replicate defects that occur naturally in man and some quadrupeds—for example, rupture of a meniscus⁶⁷ or of a cruciate ligament.⁶⁸ Horses, dogs, rabbits, guinea pigs, and rats are most often employed in these studies, but very little work has been conducted in primates. Most of the papers published on experimental osteoarthritis may be criticised because the mechanical circumstances are different from those under which idiopathic osteoarthritis develops in man. Nevertheless, many advances in our understanding of the biochemical anomalies of cartilage in joint disease have been possible only by the study of animals.

Osteoarthritis is uncommon in hip and knee joints controlled by muscles that have been weakened by anterior poliomyelitis.⁶⁹ This might appear to support the view that prolonged rest or immobility protects against osteoarthritis by removing the mechanical stimuli that lead to degradation of cartilage, but experimental immobilisation of dog and rabbit knee joints results in the loss of fibrillated cartilage from joint surfaces and osteophyte formation, succeeded by eburnation. Depletion of metachromatic matrix is soon followed by increased incorporation of $^{35}\text{SO}_4$, indicating renewed, active matrix synthesis.^{70 71} Some indication of the complex interplay of factors that influence atrophy or repair of cartilage in response to immobility may be gained from the results of studies in dogs. In the immobilised dog leg, the water content of the cartilage is increased, while the thickness, uronic acid content, and net proteoglycan synthesis are all decreased. Both newly synthesised and total tissue proteoglycan have a reduced ability to form aggregates, possibly owing to an abnormality in the hyaluronate binding region of the core proteins.⁷²

Drugs for osteoarthritis

"To develop drugs specifically for osteoarthritis . . . the thinking that has gone into the development of antirheumatic drugs should be discarded."⁷³ The evidence suggests that the early changes in the cartilage matrix are not inflammatory. But pain and secondary inflammation are common late results of the early changes in the cartilage and controlled trials to determine the best regimen of palliative analgesic and anti-inflammatory treatment continue to be published.⁷⁴

Whether treatment can be truly restorative for the damaged cartilage is debatable.⁷⁵ Possibly aspirin protects against the development of cartilage defects which may follow surgery for disorders such as recurrent dislocation of the patella.⁷⁶ Sodium salicylate appears to suppress the augmented synthesis of glycosaminoglycans that follows surgical division of the anterior cruciate ligament in dogs,⁷⁷ although it does not reverse the defective aggregation of the proteoglycan or the defect in proteoglycan—collagen interaction. Its efficacy in one induced abnormality, however, should encourage a search for agents that may restore chondrocyte function to normal at an early stage of osteoarthritis. Care must be

exercised so that analgesia and the suppression of inflammation do not exacerbate disease.⁷⁸

Conclusions

Hypotheses have been constructed to explain the nature and origin of osteoarthritis,⁷⁹ and my views are summarised in the figure. Chemical agents may be discovered that allow the chondrocyte in early osteoarthritis to repopulate the depleted cartilage matrix with new macromolecules. The clinical problem will be to identify potential sufferers before the cartilage has been wholly lost, when no new synthesis can occur. The possibility of grafting whole cartilage or chondrocyte cultures to replace lost tissue has been investigated without profit, and the great successes in arthroplasty for late, established disease have tended to mask the need for early effective medical treatment.

Perhaps more intensive genetic, social, and epidemiological surveys will identify groups particularly prone to idiopathic osteoarthritis. Do they include joggers and water skiers?

Under some circumstances the effects of a new life style, diet, appropriate exercise programme, and drug supplements may encourage young people to embark on regimens that will enable them or their descendants to avoid the insults that culminate in osteoarthritis. For the first time it may be necessary to think, as in atherosclerosis, not only of the individual sufferer but of susceptible populations. Much suffering results from osteoarthritis and much of the hard pressed resources of the Health Service go towards remedial treatment; perhaps new, untried approaches to prophylaxis should be considered more carefully.

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