Review Article

The aetiology of osteoarthritis

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> *There are so many things to complain of in this household that it*
> *would never have occurred to me to complain of rheumatism.*
>
> Saki *(The Quest)*

Osteoarthritis, which is almost universal in people over 55,[1] causes symptoms in only some.[2] The disease is defined on radiological grounds by loss of joint space, sub-chondral sclerosis, cyst formation and the presence of osteophytes and yet these changes do not relate well to the presence of symptoms,[3,4] inflammation in the joint or isotope uptake.[5] Indeed, this lack of association between symptoms and X-ray changes has thrown some doubt over the whole concept of osteoarthritis as a major health problem.[6] Furthermore, there is no agreement over its name – osteoarthrosis, osteoarthritis and degenerative joint disease are all terms in current use,[7] yet none of them is a completely accurate description and, in the words of Bick when writing on the subject of the rheumatic disorders in 1948, 'The relative advantages of one terminology as against another is insignificant as compared to the advantages of mutual agreement on any one.'[8]

Is osteoarthritis a disease at all? One author has suggested it is akin to cardiac failure,[9] i.e. a response to a variety of insults to the bone and cartilage of the joint. Nevertheless it is still regarded as the major cause of rheumatic complaints in the population and a considerable amount of morbidity, loss of work and health care arises from it.[10,11] Set against this background of confusion and the heterogeneity of the disease, the aetiology remains obscure.

The disease

What is clear is that osteoarthritis is a different entity to 'normal' age change in the articular cartilage.[12,13] On the one hand there is the yellowing, fibrillated, effete

tissue less resistant to biomechanical insults,[14] with reduced cellular activity and related to lack of use rather than overuse.[15–17] On the other hand there is osteoarthritic cartilage which is a metabolically active tissue[18,19] with an inflammatory component[20] and is seen in areas of high cyclical loading and which is an age-accelerated disorder.[21]

The condition is commonly described as being primary or secondary, but there is a spectrum of joint involvement and severity and in many cases the aetiological factors are too numerous and complex to make this simple division[22] and the use of the term secondary implies an understanding of the subsequent arthritic process which we do not possess.

At one end of the spectrum is the condition of primary generalized osteoarthritis as described by Kellgren & Moore.[23] It typically occurs in females presenting in their middle years, tends to be symmetrical and polyarticular, affecting the main weight bearing joints and axial skeleton and also the first metatarso-phalangeal joint, the distal and proximal interphalangeal joints of the fingers and the carpo-metacarpal joint of the thumb. The interphalangeal joint involvement gives rise to the clinical appearance of Heberden's (distal interphalangeal)[24] and Bouchard's (proximal interphalangeal)[25] nodes. Some authors, however, do not regard these as a specific feature of generalized osteoarthritis[26] as they can be seen in isolation, and the condition of inflammatory osteoarthritis of the fingers also appears to be a separate clinical subset.[27,28]

It has been pointed out that there is nothing generalized about generalized osteoarthritis[29] which tends to be remarkably joint-specific and although there is no bimodal distribution of patients in the whole spectrum,[30] primary generalized osteoarthritis can be regarded as a meaningful concept.[31]

The aetiology

The search for the aetiology of osteoarthritis has been conducted from the biochemical,[32] biomechanical[33] and genetic[34] standpoint and a reasonable hypothesis is that there is a variable genetic tendency towards articular cartilage failure[35] which is then brought to light by various biomechanical and age factors in later life and, if the normal repair process is overwhelmed, osteoarthritis ensues.

The articular cartilage, bone, synovium, capsule and ligaments of a joint are subject to joint forces throughout life and we know that: (1) the articular cartilage becomes less able to cope with the forces with increasing age; (2) the joint forces may become excessive for a variety of reasons and (3) the articular cartilage may also be abnormal for a number of reasons.

From these basic facts we can construct a simple diagram (Figure 1) where the area outside the tetrahedron represents the joint forces overwhelming the articular cartilage giving rise to breakdown and osteoarthritis. The lines are straight on the illustration for reasons of simplicity and ignorance, but in reality are likely to be hyperbolic.

Clinically this combined influence is well demonstrated by the observations of Docherty et al.[22] who reviewed a group of patients many years after unilateral meniscectomy of the knee and noted that osteoarthritic change in the knee occurred only in those patients who developed other signs of generalized osteoarthritis. The converse is also true: there have been a number of case reports of patients with joints defunctioned by flexor tendon injury,[36] median nerve palsy or poliomyelitis[37,38] which, thus spared from joint forces, have remained unaffected by
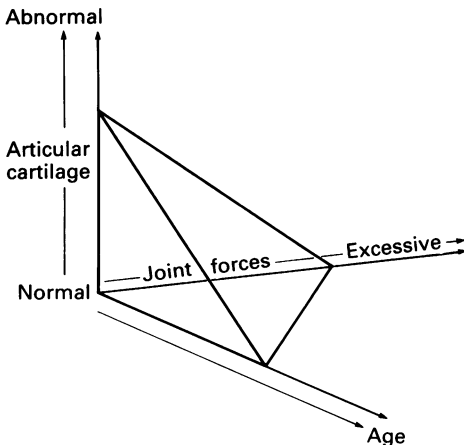

Figure 1   Diagrammatic representation of the influences producing osteoarthritis.

osteoarthritic change when generalized osteoarthritis occurred widely elsewhere.

Age

'OA stands for OsteoArthritis and Old Age' so runs the student mnemonic. The influence of age was recognized by Nichols in 1909[39] and many authors since, though the exact reasons are still unknown.[40] Its effect is twofold: firstly joints undergo a normal ageing process which predisposes them to osteoarthritis and, secondly, there are other age-related disorders, such as diabetic neuropathy, which have an aetiological bearing in their own right.

The effect of age on a joint is a measurable change in gross anatomy as well as a biochemical change in the articular cartilage and these are quite distinct from the changes of osteoarthritis.[12,13]

The joints themselves are subject to a process of continuous remodelling throughout life[41] which changes their fine geometry and renders them more congruous; this not only causes increased loading of previously unloaded areas, but may also cause increased forces in the joint under fully loaded conditions.[42] It is also possible that an abnormality in this remodelling process itself might be at fault in osteoarthritis.[43]

The biochemical changes in the articular cartilage are a decrease in water content and chondroitin sulphate chain length, an increase in keratan sulphate and hyaluronic acid content, link protein undergoes fragmentation, the cartilage takes on a yellow appearance and fibrillation occurs.[40,44] The cell density and collagen content do not alter after maturity.[45] Paradoxically, most of these effects are quite the reverse of those seen in osteoarthritic cartilage, but nevertheless the overall effect of ageing is to reduce the cartilage's ability to withstand fatigue failure.[14]

Work in dogs has revealed that atrophic articular cartilage induced by immobilization reverses when normal ambulation is allowed, but with treadmill exercise generating greater compressive forces this reversal does not take place.[46] This observation combined with that of the remodelling and change in geometry of joints helps provide an explanation for the change from the ageing articular cartilage to the osteoarthritic.

Joint forces

The relationship between osteoarthritis and repetitive joint trauma is well established,[34,47–49] though not inevitable.[50] Joint forces may be abnormal for a variety of reasons:

Anatomical

In order for normal joint forces to act, the joint needs to be congruous (or more accurately, slightly incongruous[15,42,51,52]) and any gross malalignment or abnormality of geometry will give rise to abnormal forces. This is seen in dysplastic hip joints and the frequency of osteoarthritis of the hip has been thought to be due to such a genetic anatomical abnormality.[53] This, incidentally, may be the reason why many cases of osteoarthritis of the hip are atypical of the generalized pattern, a fact which has been frequently reported.[31,54,55] Heberden's nodes are not seen in all cases of hip OA,[56] although an associated radiological subset can be found,[57] and as the hip is a readily accessible joint for study because it is regularly operated on for total hip replacement, research in this area may not always be relevant to the generalized disorder.

Gross traumatic destruction of the joint or malalignment due to malunion of a fracture above a joint, presumably gives rise to the osteoarthritis principally because of anatomical alignment with abnormal joint forces acting.

Another important anatomical abnormality which gives rise to increasing articular cartilage stress is increasing subchondral bone stiffness. This is thought to be due to bony sclerosis arising from microfractures occurring throughout life as part of a normal 'wear and tear' process, thus suggesting the bone is the site of the primary pathology, rather than the articular cartilage.[58,59,60]

Physiological

Hypermobility of joints predisposes to the formation of osteoarthritis,[61-63] although it is not inevitable,[64] but there is no evidence that it plays a major part in the development of generalized osteoarthritis.

The joint must be adequately supplied with a proprioceptive and nociceptive mechanism for normal activity and the prevention of abnormal joint forces[65,66] and osteoarthritis.[67] In the absence of adequate sensation a Charcot joint may ensue, typically a feature of tabes dorsalis.[68] It has often been noticed that in polyarticular osteoarthritics the joints often remain asymptomatic[2,4] and it is possible that an important primary abnormality in patients with generalized osteoarthritis is a sensory disturbance.[21] Certainly there is a measurable loss of proprioceptive function with increasing age, even in the absence of an obvious neurological cause, although this is only apparent with new sensitive techniques,[69] and was not previously recordable.[70]

Loss of motor power, on the other hand, as in poliomyelitis,[37,38] has a sparing effect on the joint, preventing osteoarthritic change even though the joint may continue to move passively and be unstable.

Articular cartilage

Articular cartilage is made up of a hydrophilic proteoglycan matrix enmeshed in collagen fibres both of which are produced by the chondrocytes within the cartilage substance. Water accounts for 70% of the total weight of cartilage and collagen makes up 50% of the dry weight. The large molecular weight proteoglycans hold the water like a sponge and their expansion is resisted by the tensile strength of the collagen,[71] which is arranged in an ingenious pattern to maintain its bracing properties when deformed under load.[72] A primary abnormality in any of these three components could give rise to articular cartilage breakdown.

A great deal is known about the pathogenesis of OA, partly from the study of established human lesions and partly from experimental work in animal models.[73] The former obviously suffers from the *post hoc propter hoc* problem, as the study usually involves the advanced lesion, but material is freely available and the results more relevant. The main advantage of animal work is the ability to study the early disease.

In osteoarthritis the earliest finding is increased water content with initial swelling of the cartilage, there is then a decrease in proteoglycan content, and of this there is a higher proportion of chondroitin-4-sulphate compared with chondroitin-6-sulphate.[40] There is an increase in synthesis of proteins and proteoglycan by the cells in response[74] but there is also increase in enzyme, protease,[75] activity possibly relating to lack of inhibitor function.[76] With progression of these abnormalities the cartilage softens, the surface fibrillates and the articular cartilage breaks down.

Although these changes are well described, the primary failure can still be occurring either in the collagen,[9,71,77] proteoglycan[78] or chondrocyte[32] or a combination of all three, as a response to joint forces. Certainly an abnormality of cartilage alone can give rise to osteoarthritis as is demonstrated by diseases in which the biochemical abnormality is known, e.g. chondrocalcinosis where there is calcification of the cartilage, and ochronosis, laying down of homogentisic acid.

Final common pathway

Once there is articular cartilage breakdown, for whatever cause, a number of reactions ensue, eventually giving rise to the typical patten of OA, this set of steps commonly being referred to as the final common pathway. The use of this term, however, may lead to some confusion as it is used variously by different authors, in some cases more than one pathway is described, and, in view of the positive feedback cycles involved, a more accurate description might be the

final common roundabout (Figure 2). Either way the process is not yet fully understood.

Figure 2 illustrates some of the described processes. Joint forces act on articular cartilage causing release and activation of enzymes and subsequent feedback to articular cartilage destruction. This leads to a chondrocyte repair response and the cartilage fragments give rise to a synovial reaction.[12] Hydroxy-apatite crystals have been found in some cases of OA and are thought to arise as a result of the cartilage breakdown and then exacerbate the inflammation and destruction.[79,20,80] The presence of chondrocalcinosis in association with generalized OA also gives rise to increased joint destruction.[81] Although not thought to be a primary event, the immune system is activated by the exposure of collagen[82] and lymphocyte-mediated collagenase[83] is produced and, like the crystals, continues the vicious cycle.

There are a number of arthropathies associated with endocrine disturbances[84] but the role of hormones in the aetiology and pathogenesis of GOA in the human is not known. The fact that women are more commonly affected with GOA and its presentation is typically peri-menopausal, has suggested that female sex hormones may be important[85,86] and, indeed, there is a definite association in mice and rabbits.[87-91] However, no such link has been found in the human. The only hormone abnormality that has been found in osteoarthritics is a raised level of growth hormone which is associated with an increased bone mass and the observation that OA and osteoporosis are on opposite ends of a spectrum. The significance of this is not clear.[92] It is likely that the main role of sex hormones in GOA is in modification of the disease process, although a primary sex-linked genetic influence was originally postulated by Stecher.[26]

The familial nature of GOA is widely recognized[86,34] and suggests a polygenic inheritance. It can be seen from Figure 2 that genetic factors can act at a number of different sites on the aetiological pathway. Unlike ankylosing spondylitis there is no HLA marker for GOA,[93] nor is there an association with blood groups.[94] There are a number of fascinating inherited osteoarthritic disorders[95,96] although their study has revealed little that has helped with our understanding of the inheritance of generalized osteoarthritis. Epidemiology, though fraught with classification difficulties,[97] reveals that OA is widespread throughout the human race and although there are racial varia-
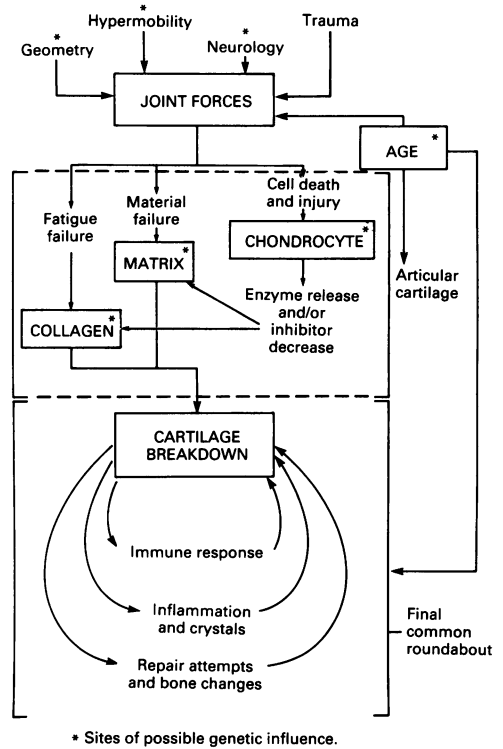

* Sites of possible genetic influence.

Figure 2 Some of the described processes giving rise to typical osteoarthritis.

tions, many may be environmental in origin.[98-100] Although there is still no evidence that GOA results from a generalized defect of bone or cartilage[34] it is thought that a primary genetic abnormality of cartilage may be at fault[101,102] and the use of new DNA recombinant techniques for examining collagen genes might reveal an abnormality here in due course.

Osteoarthritis is as old as joints, older than the human race and has not changed in millions of years,[103] distinctions it shares with DNA. Might this be a clue?

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