Nodal generalised osteoarthritis is an autoimmune disease

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Nature of osteoarthritis
Osteoarthritis (OA), the commonest abnormality to affect synovial joints, has accompanied man throughout his evolutionary history, and a similar process occurs in other animals that fuse epiphyses in the adult.

The recognition that OA is a process rather than a disease, reflecting the response of articular tissues to extrinsic or intrinsic insult, or both. The radiographic remodelling and favourable outcome seen in many patients with OA, and the prevalence of asymptomatic disease, suggest that OA is a repair process.

Like any repair process, OA may succeed or fail when responding to a variety of triggering or perpetuating insults (fig 1). The pathogenesis and variability of OA are poorly understood, but multiple factors, including genetic, constitutional, and environmental, are likely to play a part.

Marked variability in the nature and chronicity of the insult(s), and host differences in effective repair response, result in the confusing heterogeneity of radiographic and clinical manifestations.

The 'subset' of nodal generalised OA (NGOA)
In an attempt to understand OA better and to identify factors initiating and influencing compensation (no symptoms, good outcome) or decompensation (symptoms, functional impairment, 'joint failure'), OA has been increasingly divided into clinically determined subsets. Such categorisation has been by distribution of joint disease (generalised, pauciarticular, mono-articular), predominance of certain radiographic features ('atrophic', 'hypertrophic'), associated crystal deposition (pyrophosphate arthropathy, apatite associated destructive arthritis); and presumed aetiological factors— for example, epiphyseal dysplasia, Kashin-Beck disease. Such subclassification, especially for common forms of OA, has proved problematic because of overlap, temporal transition from one subset to another, and difficulties in radiographic interpretation and clinical identification.

Nodal generalised OA, the best recognised subset, is characterised by paucity of hands OA (principally interphalangeal and first carpometacarpal joints), female preponderance, early symptomatic inflammatory component, and Heberden (with or without Bouchard) node formation, or both, of all OA subsets, familial tendency is particularly recognised. Erosive OA is a less common generalised subset sharing many features of NGOA but differing in having marked subchondral erosive change, a more florid and prolonged inflammatory component, and a tendency to intra-articular osseous fusion. Minor subchondral erosions in NGOA, however, are not uncommon and whether erosive OA is a discrete subset or merely the more severe end of the NGOA spectrum has been questioned. Many elderly subjects have patchy hand interphalangeal OA or nodes: this may relate to obvious prior trauma, but is often asymptomatic and apparently sporadic. Although there is no sharp division between such hand OA and NGOA, the latter is classically symptomatic in middle age, presenting as a stuttering-onset 'mono-arthritis multiplex', is unrelated to obvious trauma, and affects most if not all rays. At sites other than the hand, such as the hip, the tendency to bilateral disease and to diffuse (concentric/central) rather than focal (supero-lateral) cartilage loss further supports the separation of NGOA as an inflammatory subset of OA.

Genetic associations
Surprisingly, despite marked familial predis-
position, few studies have searched for genetic markers in NGOA.13 Until recently only four studies had examined the frequencies of HLA antigens, with conflicting results: Lawrence et al reporting increased frequency of HLA-A1B8,28 Brodsky et al an increase in HLA-B8,29 and two studies finding no associations.30 31 A recent large study by Patr...
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NGOA has not been specifically considered, several observations offer tantalising clues. An increased prevalence of autoimmune thyroid disease was reported in a controlled study of patients with pyrophosphate arthropathy, most of whom were women, many with NGOA5747: the lack of an association between hypothyroidism and chondrocalcinosis46 suggests that this might have arisen through association with NGOA. The reported association between Sjögren’s syndrome and erosive OA49 is also of interest, particularly if erosive OA is a severe rather than separate form of generalised OA5. Similarly, the increased frequency of rheumatoid factors in NGOA1450 may reflect an autoimmune diathesis. Controlled studies determining frequencies of organ specific antibodies, rheumatoid factors, and autoimmune disease in NGOA would thus seem warranted.

Immunohistochemical evidence
The increasingly recognised inflammatory component in OA,5152 and immunohistological studies of OA synovium and cartilage5256 lend further support to the involvement of immune mechanisms in pathogenesis. It is possible of course that the flaking of immunoglobulin (particularly IgA), complement, and immune complexes in OA cartilage,225256 and the identification of lymphoid and mononuclear populations in OA synovium (identical with, though less widespread than those found in rheumatoid arthritis525355), reflect merely non-specific reaction to tissue damage rather than inflammation driven primarily by immunological events. Nevertheless, it is of interest that such cartilage and synovial abnormalities (at the hip) are more common and pronounced in ‘primary’ polyarticular NGOA rather than ‘secondary’ pauciarticular OA,2252 again supporting the possibility of a systemic (primary) rather than just local (secondary) inflammatory reaction.

Although cartilage might enjoy the status of immunological privilege by virtue of its anatomic structure, autoimmunity to cartilage might theoretically develop if sequestered antigens were exposed or became autogenic by intersection with exogenous or intrinsic factors. Anticollagen antibodies and cell mediated immune responses to collagen have indeed been shown in patients with OA, but also in patients with acute joint trauma and inflammatory joint disease.5758 Whether or not such immune responses play a part in perpetuation of joint disease, their lack of specificity favours a secondary rather than primary role in causation. If autoimmunity plays a part in NGOA it is most likely to exert its initial inflammatory effects on non-cartilaginous articular tissues. From a clinical standpoint the synovium/capsule (or even bone) would seem a likely target.

Single shot insult
As in all arthropathies the distribution of joint disease in NGOA remains unexplained. Hypotheses to explain preferential distribution include differing mechanical forces at different sites5960 and effects on joint design resulting from varying rates of evolutionary change.61 The bilateral, ‘symmetrical’ distribution of NGOA is also unexplained. Although the role of neurogenic factors in the symmetry of inflammatory joint diseases has been discussed,62 an alternative hypothesis for autoimmune based disease relates to the selectivity of pathways undertaken by circulating lymphocytes, which limits the distribution of immune mediated disease.63 The symmetry and distribution of disease might thus primarily reflect predetermined ‘homing’ of lymphocytes rather than targeting determined by local events—for example, mechanical insult and usage.59

A generally good prognosis has recently been confirmed by a controlled study of patients with established NGOA which showed that compensated OA has little symptomatic or functional impact on the aging hand.64 If symptomatic NGOA is an autoimmune condition it would thus seem to be a selective ‘single shot’ disease affecting target joints of genetically predisposed subjects at a time conditioned by age, hormonal and other constitutional factors. There is increasing evidence that many autoimmune diseases are triggered by external (predominantly infective) agents,6566 and an unidentified external trigger for NGOA may exist. Whatever its nature, this immune mediated joint insult triggers a hypertrophic repair process which, despite marked cartilage loss, then usually compensates in terms of symptoms and function. Once the inflammatory phase has settled the patient is left with architecturally abnormal joints, which we recognise as ‘OA’ (fig 2).

Inclusion of NGOA within the autoimmune umbrella may further stimulate interest in what has previously been regarded by some as an unexciting ‘degenerative’ condition. From currently available information it would seem that further studies of genetic, constitutional, and immunological factors are warranted if we are to improve our understanding of NGOA, and hence the inherent repair process of synovial joints.

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![Figure 2 Outline of nodal generalised osteoarthritis (NGOA) as an autoimmune disease.](http://ard.bmj.com/Downloaded from http://ard.bmj.com/)
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