Conference report

Theoretical medicine: the pathogenesis of osteoarthritis

At this symposium held in London on 9-11 September 1987 55 invited participants discussed propositions about the pathogenesis of OA which had been circulated before the meeting. These propositions were succinct statements, outlining a concept, and can be roughly classified into three groups: (a) Largely mechanical, in most of which load leads to fatigue failure of the collagen net. Complexity is introduced by 'glued' junctions between fibres and special circumstances to account for load being excessive. (b) Largely biological, but triggered mechanically, in which the mechanical considerations are very much as in (a), but they affect the cells which release or influence agents (e.g., enzymes) that undo the collagen net. (c) Biological, in which restraints on growth fail and the collagen net is undone.

Views were exchanged on the nature of the early and late disease, subtypes, the influence of pain threshold on the course and rate of progression (Cooke, Kingston; Hutton, Bristol; Sokoloff, New York; Ficat, Paris; Weiss, Miami; Radin, Morgantown). The bias of clinical experience puts the emphasis on late stages of the condition relative to the entire biological process, which creates a gap between clinical and laboratory approaches. Although the gap was recognised, the bridge has yet to be built.

There were three proponents of purely mechanical propositions: O'Connor (Oxford) presented an analysis of load distribution, which indicated high stress levels at the periphery of the loaded cartilage and which would lead to the disruption at the cartilage/bone interface; Cullis-Hill (Sydney) argued for the importance of the viscosity of synovial fluid in maintaining joint stability and the consequence to the joint of its reduction; Tepic (Davos) reported a computer model in which sealing of the interface between contacting articular surfaces establishes a column of water supporting the opposing bones; he considered some of the problems in maintaining the seal and of the causes and consequences of its loss.

A structure for the collagen network was pro-

posed by Broom (Auckland): focal interfibrillar adhesions produce 'pockets' capable of trapping proteoglycan aggregate. The orientation of the fibres at different levels of the cartilage is important to the function of the model. The nature of the 'adhesion', or 'glue', was discussed; type IX collagen had been studied by Eyre (Seattle) and is a strong candidate; aggregated proteoglycan was put forward (Heinegard, Lund; Brown, London) as a less favoured possibility. A calcium ion bridge (Brown, London) was not thought likely. A mechanism for loosening the net was developed in discussion (Thonar, Kimura, Kuettner, Chicago; Howell, Miami; Ghosh, Sydney) in which chondrocytes would affect control of matrix expansion by release of non-collagenolytic proteases which would locally outstrip protease inhibition. This activity would cleave the putative adhesive molecule and so allow local expansion to occur. A reformation of new links would incorporate new matrix elements; the predominance of protease inhibition would be re-established. As this mechanism would involve limited proteolysis it can only apply to sites and adhesive molecules which are sensitive and accessible. The operation of this process at a distance from the chondrocytes was posited (Hardingham, London) to be controlled either by simple diffusion of regulators and matrix components or by cell processes pushed out into the territorial matrix.

There were occasional references to genetic factors (Stanescu, Paris; Kuettner, Chicago), immunological processes, and hormones (endocrine or paracrine) as determinants of normal and abnormal chondrocyte behaviour. The extension into the cartilage of the tide mark was discussed (Bullough, New York; Oegema, Minneapolis) as implying that the cartilage continued to grow in the adult; a rate of 50 μm a year would be negligible in terms of growth but might influence geometry. The growth process requires expansion of the collagen net: the revival of this in the adult was proposed as a prime step in osteoarthritis (Byers/Brown, London).

Improved non-invasive imaging techniques and

marker molecules will advance longitudinal studies in animal models whether naturally occurring, mechanically induced, or chemically induced. The significance of the differences from human disease, and the equal lack of understanding of their pathogenesis provoked inconclusive discussion; nevertheless, the early softening permits study of collagen-matrix alteration, and those that are reversible offer the possibility of studying repair. Chemically induced models have been less exploited. Active exploration for additional agents is in progress: intra-articular iodoacetic acid was reported by Brandt (Indianapolis) to induce osteophytic formation by the entire cartilage. This led to a discussion of the biological import of osteophyte

formation and the recognition that to some it meant repair and to others growth. Such distinctions have quite profound implications for the conceptualisation of the osteoarthritis process. Some promising new models were also talked of: osteotomy of the proximal femur, blunt impact to the patella, and muscle resection. These non-invasive alterations in joint mechanics offer advantages in the study of facets of the disease.

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