looking at the mechanisms for immune dysregulation in many of the connective tissue disorders, since the inflammatory processes involved in such chronic diseases as RA, SLE nephritis, WG, or scleroderma may have as much to do with loss of intrinsic modulating control mechanisms as with unabated production of autoantibodies of various specificities.

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REFERENCES

THERAPEUTIC IMPASSE IN OSTEOARTHRITIS

OSTEOARTHRITIS embodies a spectrum of disorders in which alterations in the chondrocyte and/or its microenvironment culminate in often irreparable cartilage destruction and compensatory bone remodelling. Primary (idiopathic) and secondary forms of disease are recognized, at times clinical, roentgenographic and pathologic features enabling distinct subsetting. Aberrant physiologic and pathologic changes have been largely attributed to a homeostatic imbalance created by accelerated catabolism and ineffectual matrix repair. Although predisposing factors vary from genetic connective tissue abnormalities and endocrine, metabolic and mechanical dysfunctions to aging and preceding inflammatory destructive disease, there are 'common pathway' mechanisms in the complex sequence of pathophysiologic events which can be therapeutically targeted.

Pathologic changes in cartilage appear in part to be induced by select cytokine, growth factor, connective tissue matrix constituent and biomechanical perturbances in chondrocyte metalloproteinase and oxygen metabolite expression. Immune and focal synovial tissue inflammatory responses to sequestered or structurally modified components of extracellular matrix
occurred in conjunction with quantitative and qualitative changes in collagen, proteoglycan and adhesive glycoprotein synthesis. Attrition is further afforded by abnormal forces creating mechanical wear.

In spite of considerable effort in the past three decades, we still know little of the ‘relative importance’ of the basic pathophysiologic mechanisms presumed involved in disease induction and perpetuation. Problems are compounded because the physiology of normal cartilage metabolism is itself complex and poorly understood due to the potential influence of multiple factors originating both systemically and in an autocrine/paracrine manner within the local joint milieu. Cartilage structure and metabolism are to a large measure governed by the integrity of extracellular matrix. Essential nutrients are principally derived from synovial fluid, the diffusion of molecules governed by their size, charge and the pressure gradient established by cyclic joint loading. Water imbibition by polyanionic aggrecan species of proteoglycan provides viscoelasticity. A dominant type II collagen network contributes to structure, shape, strength and support. Adhesive glycoproteins and smaller molecular weight species of proteoglycan appear to function as growth factor ‘reservoirs’ and perhaps allow sequestration of molecules which modulate expression of proteinase activity. Clearly, preservation of the collagen scaffolding is critical for avoidance of irreversible pathologic change. One can thus appreciate the importance of therapeutic strategies that focus in a ‘preventive’ manner on early events in the pathophysiologic cascade.

Current pharmacologic options are limited and those in common use have not been shown to modify the basic disease process in humans. The interpretation of human and experimental animal studies which have addressed the potential efficacy of NSAIDs and heparinoid and other forms of ‘chondroprotective agents’ is limited. Results have shown variability and the validity of some experimental designs could be questioned. There is uncertainty associated with the extrapolation of data obtained from in vitro ‘bench studies’ or the induction of lesions in animals having no direct counterpart in humans. Far too often, promising agents developed to offset a given pathophysiologic event have been discarded because of lack of specificity, bioavailability or failure to attain effective therapeutic concentrations. It is important to recognize that reaction to a given agonist or antagonist often follows a concentration dependent response pattern and the desired effect achieved only within a relatively narrow dose range. Compromise in the integrity of the highly charged extracellular matrix of cartilage and its dense collagen network can clearly influence bioavailability and outcome.

What is the relative importance of cartilage matrix degrading proteinases produced by synovial tissue and chondrocytes? Should this be accomplished by inhibiting enzyme synthesis or by suppressing activity? Technical problems have restricted much of the current work in this area and results of limited clinical and animal studies have in general not been encouraging. Rational approaches can only be dictated by increasing our knowledge of the biochemical and molecular biology of metalloproteinases and mechanisms which govern their transcription and activation. This would allow the exciting potential for development of therapies to precisely target a given regulatory site, enabling precise control of gene expression of enzyme or inhibitor. Beyond transcriptional mechanisms, the recognized heightened stability of metalloproteinase mRNA raises considerations for blockage using antisense oligonucleotides or specific therapies to enhance messenger decay.

The relevance of biophysical forces (hydrostatic pressure, fluid flow, streaming potentials, cell deformation) in directly modulating chondrocyte metabolism or its sensitivity to a given physiologic or pathologic stimulus has virtually been ignored. How is a given factor conducted across the intricate extracellular matrix? What is the relative importance of signal recognition systems such as connective tissue RGD ligand interaction with cell membrane integrins or hyaluronic acid with the membrane CD44 proteoglycan...
superfamily? Can altered joint biomechanics in OA disturb such signalling pathways? What are the consequences of signal disruption? How might this affect a given pharmacologic response? Is preferential joint involvement dictated by aberrant biomechanical forces?

Do environmental toxins induce or contribute to the abnormal cartilage metabolism in OA? It is conceivable that loss of matrix integrity would render chondrocytes more susceptible not only to noxious agents but to anti-inflammatory, immunomodulatory and perhaps other forms of medication. Do chondrocytes in compromised OA cartilage have a greater susceptibility to infection which in turn may contribute to disease perpetuation? Further epidemiologic and laboratory studies addressing these issues are indicated.

Progress in our understanding and management of OA has also been hampered by the attitude of a significant number of physicians (including rheumatologists and orthopaedic surgeons) who view this disorder in a nihilistic manner 'It's just wear and tear—just take these pills'. Few, other than physicians and scientists directly working in the field, have clamoured for increased public awareness and appropriate research funding. We need to mobilize the very large patient base as our advocates. The recent availability of organizations and journals dedicated to OA should provide considerable help.

Advances have also been slow in coming because investigative approaches are often stereotyped and lacking in ingenuity. Novel thinking is often ignored because it lacks compatibility with current trends or philosophy. One need only ask ‘how do we influence the non-orthopaedic care of the OA patient?’. How does our treatment differ today from that which preceded the age of scientific enlightenment? We often lack insight into the ‘why’ or ‘what’ we actually are doing pharmacologically in this disorder. There continues to be disagreement over fundamental issues such as rational strategies for use of anti-inflammatory vs analgesic medications. Why do we ignore the large volume of accumulated experimental information supporting the virtues or ill effects of a given drug?

There is much to be done. Cohesive, uniform concepts of disease pathogenesis remain to be formulated. Better measures must be developed to identify early disease and to monitor stages in the established disease process. Opportunities must be provided to address fundamental questions and pursue innovative directions. Rational therapeutic strategies for development of effective analgesic and potential disease-modifying drugs will only evolve by expanding our knowledge base through cross-disciplinary research in cartilage biochemistry, cell and molecular biology and biomechanics.

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**PHARMACOGENETICS: WHAT ROLE IN RHEUMATOLOGY?**

Drug metabolism polymorphisms may be divided into two distinct areas: genetic polymorphisms as determined by direct genotyping of extracted DNA and metabolic polymorphisms as determined by phenotyping with probe compounds. Which of these two methods is most appropriate for clinical investigations is still under debate by geneticists, and the humble rheumatologist may be forgiven for any misuse of pharmacogenetic terminology [1]. Early definitions of a biological ‘polymorphism’ coined by population geneticists were based on phenotypic observations since genotypic studies (by breeding experiments) were difficult to perform. With the advent of molecular biology, the direct measurement of genotype has become possible and geneticists have adopted the genotype as reference. However, it remains that it is the phenotypic expression of the genotype that determines the clinical consequences of a polymorphism [2]. Essentially the two methods should complement one another and hence, associations between phenotypically-determined pharmacogenetic polymorphisms and disease become difficult to interpret without the back-up evidence of genotyping. Until recently, studies of pharmacogenetic polymorphisms in rheumatology, have centred on phenotypic studies comparing the frequency of a given phenotype in health and disease with the inherent consequence of conflicting results.

There may or may not be an association between drug acetylation polymorphisms and RA [3, 4] and idiopathic SLE [5, 6]. A clearer association exists between acetylator phenotype and adverse drug reactions [7] or drug-induced lupus [8]. More recently, the polymorphic form of the enzyme N-acetyltransferase (p-NAT, NAT-2) has been gene sequenced [9] and will allow a clearer picture of any association (or lack thereof) between acetylation and rheumatic disease.

The problem of defining a genetic polymorphism on phenotypic data alone can be highlighted by the metabolism of S-carboxymethyl-L-cysteine (SCMC). This compound has been used as a pharmacogenetic probe of sulphoxidation status [10]. A number of reports have appeared in the literature showing an association between poor sulphoxidation of this mucolytic agent and development of RA and toxicity to D-penicillamine and sodium aurothiomalate [11–14]. The danger here is that contrary to a previous investigation [10], sulphoxidation of this compound has not been proven to be genetically determined and the weight of current opinion supports a non-genetic control over the metabolism of SCMC [15, 16]. The metabolite previously thought to be a sulphoxide of the probe compound has now been shown to be S-carboxymethylthio-L-cysteine, a mixed disulphide [17, 18]. It appears that patients with RA may exhibit a defect in sulphur