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RHEUMATIC DISEASES

Leader

Oestrogens, joint disease, and cartilage

Serum concentrations of the female sex hormone oestrogen are believed to be the major factor affecting disease expression in some of the commonest disorders in developed countries, including cardiovascular disease and osteoporosis. The prevalence of many common joint diseases is markedly different between the sexes. In rheumatology hormone related research was initially directed towards systemic lupus erythematosus with its marked female predominance. In this disease oestrogens are now believed to promote disease progression and increase autoantibody formation. Clinical observations of increased risk of relapse during pregnancy and oral contraceptive use,¹ with findings of abnormal oestrogen metabolism, have confirmed these impressions.² The detrimental effects of oestrogens have also been shown in a number of studies using experimental models with NZB/W mice.³ The predominant effect of oestrogen in these models seems to be to increase the number and activity of autoantibodies.

The story with rheumatoid arthritis, which shares some similarities with systemic lupus erythematosus, seems completely different, however. There has been considerable attention in the past decade directed towards reproductive and hormonal factors in the pathogenesis of rheumatoid arthritis.⁴ The findings are primarily that pregnancy and exogenous oestrogens have disease ameliorating or protective effects. Most of the experimental work so far has concluded that oestrogens are immunosuppressive, though the exact mechanism is unclear. The models of rheumatoid arthritis that have been studied include adjuvant arthritis (induced with cell wall fragments of *Mycobacterium tuberculosis*) and collagen induced arthritis.⁵ Both these models are primarily T cell dependent inflammatory models, and both proliferation and delayed hypersensitivity reactions have been shown to be suppressed by administration of oestrogens given in physiological and pharmacological doses. In the model of collagen induced arthritis, however, not all strains of mice are susceptible to the effects of oestrogen, and non-MHC genetic strains do not respond in a similar manner. The suppressive effects of oestrogens on T cell immune reactions have also been noted extensively *in vitro*.⁶

Thus oestrogens seem to have opposing effects on the immune system, being immunostimulatory for B cells and immunosuppressive for T cells. Holmdahl suggested that the effects of oestrogens on autoimmune diseases will depend, therefore, on the relative importance of these different kinds of immune reactions in their pathogenesis.⁷ It is interesting that experimental granulomatous reactions induced by cotton pellets can be suppressed by neonatal thymectomy.⁸ The granulomatous inflammation produced

is similar to the pannus in rheumatoid arthritis and is T cell dependent.^{9 10} It is tempting to speculate that if pannus is similarly T cell dependent, oestrogens by exerting immunosuppressive effect on these cells might cause local control of pannus growth.

A possible modifying effect of oestrogens in osteoarthritis has been suggested by the detection of oestrogen receptors in the articular cartilage of the dog, rabbit, and baboon.^{11–13} Animal models of osteoarthritis were tested with oestrogens in the 1960s with conflicting results. Silberberg using male mice with a genetic predisposition to osteoarthritis found that oestrogen treatment caused a decreased incidence and severity of lesions, though conversely female mice undergoing oophorectomy had a reduction of their disease.¹⁴ Rosner *et al* used experimentally induced disease (partial meniscectomy) in rabbits as a model of osteoarthritis.¹⁵ They found that oestradiol suppressed proteoglycan synthesis in both normal and osteoarthritic cartilage. The proteoglycan concentration was not altered, however, suggesting suppression of proteoglycan catabolism. In further studies they found that oestradiol administration led to a worsening of osteoarthritic lesions, but that tamoxifen, an oestrogen blocker, was associated with an improvement in the disease.¹⁵ More recent work has shown that supraphysiological doses of oestrogen markedly increase cartilage degradation in an *in vivo* model using cotton wrapped rat femoral head cartilage. These effects were suppressed by the addition of tamoxifen. The proteoglycan loss was much greater in the presence of cotton, which produces a surrounding granulomatous reaction, suggesting enhancement by the inflammatory process.¹⁶

In vitro culture work has shown that oestrogens suppress chondrocyte proliferation. Depression of sulphate metabolism in both normal rat hyaline costal cartilage and in rabbit epiphyseal cartilage has also been found. Recently, inhibition of [³⁵S]proteoglycan synthesis by pharmacological doses of oestradiol (10^{-5} mol/l) in explant cultures of rat chondrosarcoma has been shown.¹⁷ Similar doses inhibited cell division in the log growth phase. Oestrogens, however, had no demonstrable effect in physiological doses (10^{-9} – 10^{-8} mol/l) either on [³⁵S]proteoglycan synthesis or on articular cartilage growth. A further *in vitro* study using rat femoral head cartilages in culture medium has also shown the degradative effects of oestrogens on proteoglycan, an effect that is greatly enhanced by the presence of fibroblasts (Chander *et al*, International Congress on Inflammation, Spain, 1990). Oestradiol seems to stimulate these cells, leading to secretion of proteases and possibly cytokines.

Overall, the results suggest that oestrogens affect the

regulation of proteoglycan metabolism. Thus they may have a role in the pathogenesis of osteoarthritis, in particular the generalised form, which has a female predominance and a number of clinical and epidemiological clues linking it with oestrogens.¹⁸ The mechanism of this effect on cartilage and the supraphysiological doses needed in most models suggest that the effect is indirect, however.

Transforming growth factor β is one of a family of regulatory polypeptides and acts on a variety of connective tissues. Increased mRNA levels of type I procollagen and transforming growth factor β have been found in cultured human osteoblast-like cells treated with oestradiol, and it might control the transcriptional activity of the transforming growth factor β gene. Moreover, transforming growth factor β has been found to be related closely to the cartilage inducing factor A, which induces the formation of type II collagen and cartilage proteoglycans from undifferentiated mesenchymal cells in vitro.¹⁸

Oestrogens might also exert their effects by way of the ubiquitous cytokines. Workers have recently found that oestradiol and testosterone can stimulate the release of interleukin 1 induced interleukin 6 from human articular chondrocytes.¹⁹ These hormones failed to have any direct effect on interleukin 6 production, however, but in synergy with interleukin 1 there was a five- to eightfold increase in chondrocyte secretion of interleukin 6. It has been shown by these workers that the interleukin 6 released will stimulate acute phase protein synthesis and hybridoma cell proliferation. These findings indicate the pivotal role of the gonadal hormones in regulating chondrocyte function.

Oestrogen may also provoke the release of cytokines from non-cartilage sites. It has been shown to induce the release of interleukin 1 from macrophages,²⁰ which in turn could activate local fibroblasts to produce interleukin 6, prostaglandin E₂, and proteases, leading to cartilage damage.

Thus, apparently, oestrogens play a complex part in rheumatic diseases, having different and contrasting effects on separate stages of the disease process. These vary from effects on the immune response or delayed hypersensitivity, to effects on cartilage itself, either directly or by means of diverse roles in inflammation, and may play an integral part in the regulation of the response to injury. The relation with cartilage metabolism is probably indirect by way of second messengers and interaction with the omnipresent family of cytokines. In this way genetic, inflammatory, and hormonal factors may combine to bring about changes in cartilage that trigger the pathological changes we call osteoarthritis. Oestrogens should not, however, be taken in isolation as they have complex interactions with other hormones, including testosterone and progesterone, as well as their binding proteins, which may regulate the immunological or inflammatory response.

Clinical implications of these findings are also slowly emerging. In patients with systemic lupus erythematosus the use of exogenous oestrogens is best avoided, and some limited success has been obtained with the therapeutic use of androgenic and antioestrogenic substances.²¹ In rheumatoid arthritis the oral contraceptive pill is now generally believed to have mild but long term disease modifying effects, though clinical trials have yet to prove the benefit, and the place of postmenopausal oestrogens is still unclear.^{4, 22} In osteoarthritis preliminary studies have shown that postmenopausal use of oestrogens is not associated with

increased rates of disease.²³ As the increasing use of long term exogenous oestrogens in middle aged women is becoming routine, however, further long term studies would be advisable.

In conclusion, oestrogens can be seen to have both immunosuppressive and immunostimulatory properties, and can influence the inflammatory response and chondrocyte function, either directly or more likely through complex interactions with cytokines and growth factors. The effects of oestrogens on joint disease will therefore depend on the relative importance and predominance of distinct disease processes in the pathogenesis of each separate clinical entity. The further study and elucidation of the exact role of oestrogens on chondrocytes, inflammatory processes, and cytokines will continue to improve our understanding of the mechanisms of joint destruction.

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