MATTERS ARISING

Sympathetic nervous system in chronic joint pain

Sir: We read with interest the recent review by Dr Kidd and colleagues on the role of the sympathetic nervous system in chronic joint pain and inflammation.¹ The authors suggest, on the one hand, a continued influence of the sympathetic nervous system on the inflammatory synovium while, on the other hand, they postulate that nerve fibres are destroyed in the synovial membrane in chronic rheumatoid arthritis. Based on a study of synovial membrane obtained from patients with rheumatoid arthritis undergoing arthroplasty the authors argue that a reduction in immunostaining for the neuronal marker PGP 9-5, in addition to reduced neuropeptide immunoreactivity as previously described,² favours destruction of nerve fibres over neuronal depletion. In a similar study, Gronblad *et al* examined nerve fibres and neuropeptide immunoreactivity in rheumatoid synovium collected at synovectomy and arthroplasty.³ In this study seven of nine patients showed reduced immunoreactivity for neuropeptides but well marked stromal immunoreactivity for nerve fibres.

Further evidence for increased release of neuropeptide and subsequent depletion of neuronal stores is provided by the following observations. In a recent case report⁴ we studied synovial membrane and fluid in a patient with psoriatic arthritis of the knee, in whom sparing of the contralateral side occurred owing to previous hemiplegia. We noted reduced immunoreactivity for synovial membrane substance P in the clinically inflamed joint, in addition to raised levels of substance P in the synovial fluid, while in the contralateral non-inflamed joint there was marked immunoreactivity for synovial membrane substance P but undetectable synovial fluid levels. Immunoreactivity of nerve fibres was demonstrated equally in both specimens. These observations suggest that substance P is released from nerve fibres into the synovial fluid in the inflamed joint. Finally, synovial fluid substance P levels have been measured in a number of different arthropathies.⁵ In all groups with arthritis higher levels were reported in synovial fluid than in plasma.

The role of neuropeptide in the inflammatory synovium is not clear. Interestingly, neuropeptides have been shown to activate rheumatoid synoviocytes⁶

and to cause production of inflammatory cytokines by human monocytes.⁷ We agree with the authors that the role of these substances within the rheumatoid joint leads to a promotion of the inflammatory response. The evidence herein suggests, however, that depletion of neuropeptide in inflammatory synovium is more probably due to increased release into the synovial fluid rather than destruction of nerve fibres as suggested.

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AUTHORS' REPLY We are grateful for the opportunity to respond to the letter from Drs Veale and Fitzgerald. Histochemical studies performed by us¹ and by da Silva *et al*² using PGP 9-5 as a marker for the overall innervation clearly show a loss of both sensory and autonomic fibres in the more superficial or densely inflamed layers of rheumatoid synovium. In contrast, PGP 9-5-immunoreactive fibres are seen in the deeper or less inflamed tissues. The immunostaining for specific neuropeptides in these fibres is weaker and more varicose than in normal controls, suggesting that neuropeptides are being released into the surrounding tissues. Subsequent animal studies³ have confirmed these observations and suggest that the innervation is lost from the superficial layers early in the inflammatory process.

Neuropeptides may well have a key role in regulating vascular and other events within synovium. As a consequence tissue con-

centrations are critically important, but to date levels have only been reported from assays of synovial fluid.⁴ We have shown the presence of functional degradative enzymes, particularly neutral endopeptidases and angiotensin converting enzyme, both on cell membranes and free within the synovial fluid.⁵ This raises concern about sources of error in the synovial fluid assays due to the presence of immunoreactive, but functionally inactive, peptide fragments. Published reports have not so far identified substance P-like immunoreactivity in synovial fluid as intact bioactive substance P (for example, by high performance liquid chromatography).

Immunohistological data suggest that neuropeptide levels within inflamed synovium are not uniform, with some innervated areas having higher concentrations, whereas in other denervated areas the concentrations might be much lower. Our recent article suggested that sympathetic activity potentiates neuropeptide release from those apparently damaged but still viable fibres found in the deeper or less inflamed areas of synovium.⁶ There are undoubtedly a number of different neurogenic influences on inflammatory responses within joints⁷ and there is plenty of room in this field for controversy, particularly when isolated measurements of individual molecules in synovial fluid are used as the basis for subsequent hypotheses. The search goes on.

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