New antigens might be exposed through the trauma, leading to the development of autoimmune phenomena. This hypothesis is supported by other studies,1 3 4 which tend to indicate that ankylosing spondylitis is a reactive arthritis following infection with various gram-negative organisms. Cross reactivity between infecting organisms and self components could be involved. The reason why some individuals develop Reiter’s syndrome and others ankylosing spondylitis remains a mystery. It will be informative to seek differences in the genetic map of HLA-B27 positive patients which give rise to either disease.

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References

Mepacrine induced hepatitis

Sir. When mepacrine was introduced in 1930 as an antimalarial it was frequently noted to cause yellow discoloration of the skin.1 Rarely it caused jaundice and fatal hepatitis, introducing the possibility of serious confusion with the common skin discoloration.2 3 Hepatitis due to mepacrine therapy has not been reported during therapy of connective tissue disorders. In view of this we describe such a case.

A 37-year-old woman presented with an 18-month history of malaise, mouth ulcers, and arthralgias. From the age of 18 she had a persistent telangiectatic facial rash, similar to that of systemic lupus erythematosus, and from the age of 25 she had recurrent migraine and frequent episodes of bronchitis with asthma. Skin tests to common allergens were negative, but there was a strong family history of atopic disease. Full blood count and complement levels were normal, the erythrocyte sedimentation rate was 4 mm/1st h, and rheumatoid factor and antinuclear antibody tests were negative. Parotid secretion studies and labial salivary gland biopsy were normal, and skin biopsy did not show immunoglobulin deposition. She was considered to have an undifferentiated connective tissue disorder and received trials of hydroxychloroquine and chloroquine without benefit. After she complained of nausea and blurred vision the chloroquine was stopped. Liver function tests were normal, and mepacrine was substituted at a dose of 100 mg daily, increasing after two weeks to 300 mg daily. The patient was warned of the possibility of skin yellowing. Six weeks later she reported that her skin and eyes had abruptly turned yellow accompanied by feelings of lethargy, loss of appetite, itching and tender cervical lymphadenopathy. She was instructed to stop the mepacrine, but four weeks later her urine contained urobilinogen, her γ-glutamyltransferase was 264 IU/l (normal (n)<65 IU/l), alanine transaminase 210 IU/l (n<45 IU/l), aspartate transaminase 107 IU/l (n<41 IU/l), and alkaline phosphatase 160 IU/l (n<105 IU/l). However, the bilirubin (5 µmol/l) was normal, indicating that she was not jaundiced. An absolute eosinophil count of 680/mm³ (0–68×10⁹/l) was noted. Serological tests for hepatitis A and B and cytomegalovirus were negative. Further investigations were considered unnecessary as the liver function tests gradually improved and after two months were normal. The skin and sclera remained yellow for two months after mepacrine was stopped.

In this patient the systemic symptoms, scleral yellowing, and urinary urobilinogen suggested hepatitis. The liver function tests supported this diagnosis, but the normal bilirubin indicated that the yellow discoloration was due to mepacrine. Mepacrine hepatitis associated with therapeutic doses is an idiosyncratic, unpredictable reaction similar to that caused by halothane. In addition to eosinophilia and lymphadenopathy, fever, rashes, and arthralgias may occur, features commonly found in the connective tissue diseases. Liver histology is similar to viral hepatitis2 or acute massive necrosis may result.3 The precise pharmacokinetics of mepacrine are not known but, like its fellow 4-aminoquinolines, chloroquine, it has an unusually large volume of distribution being widely distributed and bound in liver, lungs, spleen, adrenal, skin, and leucocytes.4 The long half life of mepacrine presents a particular hazard in cases of sensitivity.

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Combination therapy in rheumatoid arthritis

Sr., The case report by Sheldon and Wood is additional evidence of the need to run a full-scale trial of combination chemotherapy in rheumatoid arthritis (RA). The safety of such regimens is well established in Hodgkin’s disease and other lymphoproliferative disorders, and it remains ‘difficult to accept that, while haematologists obtain ten year “cures” in malignant B-lymphoproliferative disease, only a minority of patients with classical RA . . . a non-malignant B-lymphoproliferative disease—will experience any remission on a single drug chemotherapy. The potential for provoking a cure in RA has enormous implications. However, the selection for chemotherapy trials of only those patients with long-established disease, who have failed on ‘conventional’ therapy, will produce in all likelihood an equivocal answer. Such patients will already have suffered severe and irreversible joint destruction, and we should be aiming to produce the cure long before this stage. By analogy, in lymphoma the later the treatment is given the less effective it is.

The evidence is pretty clear that patients with seropositive erosive RA who are DR-4 positive are going to do badly. I believe we should be doing our trials on this group of patients within six months to a year of presentation, and I am sure that the well informed patient would let us.

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References

Recurrent rheumatic fever in adults

Sr., The case report of Murray et al. and our own recent experience suggest that rheumatic fever in adults may be more common than has generally been assumed. In our institution we have seen two such patients in a five-month period. Both patients were Hispanic males, ages 42 and 44, and had past histories of rheumatic fever in childhood. One patient presented with a four-week history of severe polyarthritis, fever, evidence of acute carditis, and an antistreptolysin O (ASO) titre of 250 Todd units. The other patient had a rapidly spreading arthritis over three days, fever, a leucocytosis of 20-3/nl and an ASO titre of 625 Todd units. Both had raised erythrocyte sedimentation rates; but tests for antinuclear antibodies, rheumatoid factor, and multiple blood and throat cultures were negative. These two patients fulfilled the revised Jones criteria for rheumatic fever, and each showed a prompt response to non-steroidal anti-inflammatory drugs within two days.

We were impressed by the sudden onset and severity of the polyarthritis in each of our patients. This clinical pattern of arthritis in adults with rheumatic fever has been well described, as has the rarity of chorea, subcutaneous nodules, and erythema marginatum. 3 This differs from the childhood presentation, where the arthritis may be fleeting and the cutaneous manifestations are somewhat more common.

We agree with Murray et al. that the incidence of recurrent rheumatic fever apparently decreases with age. Although a review of the recent literature shows a number of cases of rheumatic fever in adults, the vast majority of patients were in their second or third decade of life. Very few patients in their forties and fifties, as observed by Murray and by us, have been reported. However, there are reasons why rheumatic fever in the adult may go unrecognized. The severe polyarthritis of adult rheumatic fever may present exactly like more common rheumatic disorders, such as rheumatoid arthritis or systemic lupus erythematosus. Physicians may not appreciate the importance of a rheumatic fever history or determine an ASO titre. Throat cultures, when obtained, are often negative in adults. Finally, manifestations are often self-limiting, and a prompt response to self-administered aspirin or other non-steroidal anti-inflammatory drugs may be sufficient so that medical attention is not sought.

These considerations suggest that the true incidence of rheumatic fever in adults over 40 may be underestimated. As in many other situations it may be that a heightened index of suspicion will lead to more frequent recognition and diagnosis of this disease.

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References