Both Ryan *et al* and Bruno *et al* rightly suggest that it is timely to screen more widely for these asymptomatic "healthy" people who will need further investigation and possibly treatment. In the general population the prevalence seems to be around 1 in 1400. Screening for hepatitis C virus could well be more cost effective than current mass (non-targeted) screening for high serum cholesterol concentrations since the papers in this issue show that a positive test result indicates problems both for the person and for the community. Furthermore, prevention of the spread of hepatitis C virus infection must at present rely on effective screening programmes.

What should be done about a positive test result for hepatitis C virus? Counselling is essential, and Ryan *et al* have shown it to be effective on a limited scale. More studies of asymptomatic people will be needed to determine the precise risk of progression to chronic liver disease and the effects of treatment, when appropriate. At present the only results we have are of treatment of patients with hepatitis C. Up to half go on to have some form of chronic hepatitis and if untreated, up to a fifth of them may progress to cirrhosis.¹¹ Patients with community acquired hepatitis C may have a lower risk of cirrhosis; meta-analysis suggests that the disease progresses in one fifth of such patients and that two thirds of those develop chronic hepatitis.¹² Furthermore, Irving *et al* suggest that a substantial proportion of donors with repeatedly positive results on hepatitis C virus testing should have liver biopsies to assess any liver pathology.

What treatment is available for patients who are found to be positive for the hepatitis C virus? Interferon alfa at low to moderate doses for 6-12 months is the only effective treatment. This will return the transaminase activities to normal in 80% of patients¹³ and induce complete (25%) or temporary (50%) remission, at least during treatment.¹⁴ Interferon alfa is currently licensed for use in patients with hepatitis C virus and abnormal transaminase activities in a few European countries but not yet in Britain. Trials are needed of interferon alfa in the "healthy" asymptomatic people who are positive for hepatitis C virus and have histologically abnormal

liver tissue. But when this treatment is stopped, relapse rates are high in patients with chronic hepatitis C. In addition, repeated liver biopsy (necessary to assess the hepatic response to treatment) may not be acceptable to people who feel well. Measurement of the serum hepatitis C virus RNA excludes viraemia but tells us nothing about the liver.

The issues highlighted by the papers in this issue have clear implications for the nation's health and preventive medicine. A nationwide policy is needed—with the appropriate resources—for identifying, following up, and treating asymptomatic people with hepatitis C virus infection to prevent cirrhosis in those people and the spread of hepatitis C in the population. Many of the crucial questions about treating this disease remain unanswered.

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- 1 Alter HJ, Purcell RH, Holland PV, Feinstone SM, Morrow AG, Moristugu Y. Clinical and serological analysis of transfusion-associated hepatitis. *Lancet* 1975;ii:838-41.
- 2 Hoofnagle JH. Treatment. In: *Viral Hepatitis (Scientific Basis and Clinical Management)*. Zuckerman A, Thomas HC, eds. Edinburgh: Churchill Livingstone, 1994:303-12.
- 3 Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood borne non-A non-B viral hepatitis genome. *Science* 1989;244:359-62.
- 4 Kuo G, Choo Q-L, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, *et al*. An assay for circulating antibodies to a major etiologic virus of human non-A non-B hepatitis. *Science* 1989;244:362-4.
- 5 Farci P, Alter HJ, Wong D, Miller RH, Shih JW, Jett B, *et al*. A long-term study of hepatitis C virus replication in non-A non-B hepatitis. *N Engl J Med* 1991;325:98-104.
- 6 Ryan KE, MacLennan S, Barbara JAJ, Hewitt PE. Follow up of blood donors positive for antibodies to hepatitis C virus. *BMJ* 1994;308:696-7.
- 7 Bruno S, Rossi S, Letizia Petroni M, Villa E, Zuin M, Podda M. Normal aminotransferase concentrations in patients with antibodies to hepatitis C virus. *BMJ* 1994;308:697.
- 8 Irving WL, Neal KR, Underwood JCE, Simmonds PN, James V, Trent Regional HCV Study Group. Chronic hepatitis in UK blood donors infected with hepatitis C virus. *BMJ* 1994;308:695-6.
- 9 Alberti A. Recurrent HCV hepatitis after liver transplantation. *Lancet* 1993;341:378-9.
- 10 Kiyosawa K, Akahane Y, Nagata A, Furuta S. Hepatocellular carcinoma after non-A non-B post-transfusion hepatitis. *Am J Gastroenterol* 1984;79:777-81.
- 11 Thomas HC. Chronic hepatitis C. In: Kane MA, ed. *The role of interferons in chronic viral hepatitis*. Consultant series (In press.)
- 12 Alberti A, Realdi G. Parenterally acquired non-A non-B (type C) hepatitis. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J, eds. *Oxford textbook of clinical hepatology*. Oxford, New York, Tokyo: Oxford University Press, 1991:605-17.
- 13 Jacyna MR, Brooks MG, Loke RHT, Main J, Murray-Lyon IM, Thomas HC. Randomised controlled trial of interferon-alfa (lymphoblastoid interferon) in chronic non-A non-B hepatitis. *BMJ* 1989;298:80-2.
- 14 Colombo M, Rumi MG, Marcellini R, Ibba M, Parravicini ML, Donato MF, *et al*. Randomised controlled trial of recombinant interferon-alfa in patients with chronic hepatitis C. *Hepatology* 1991;14:73A.

Reactive arthritis

Large, multicentre prospective trials are needed to establish the best treatment

Reactive arthritis is an aseptic arthritis that develops after an infection elsewhere in the body. The triad of arthritis, urethritis, and conjunctivitis—Reiter's syndrome—is one distinct variety of reactive arthritis.

Many micro-organisms may induce reactive arthritis, and new agents are continuously being added to the list, suggesting a pathogenic mechanism that is not antigen specific. The condition is associated most commonly with urogenital or enteric infections with *Chlamydia trachomatis*, *Yersinia enterocolitica*, salmonella, shigella, and campylobacter.^{1,2} Less common or more recently identified agents include *Clostridium difficile*, *Vibrio parahaemolyticus*, *Borrelia burgdorferi*, *Chl pneumoniae*, and ureaplasma. A type of reactive arthritis not associated with HLA-B27 may occur after infections with β haemolytic streptococci and neisseria. In about one quarter of all cases the triggering organism remains unknown.¹

Between 60% and 90% of patients with postvenereal or postenteric reactive arthritis are positive for HLA-B27.^{1,2} The arthritis usually develops within four weeks of the primary infection; it is typically oligoarticular and asymmetric. Painful

joints and muscle and tendon insertions are common. Extra-articular manifestations occur in 10-50% of cases and include mucocutaneous symptoms, ocular inflammation, urethritis, nephritis, and carditis.^{1,2} The average duration of the arthritis is four to five months, but two thirds of patients have mild joint or tendon symptoms for more than a year, and 15-30% develop chronic arthritis or sacroiliitis.¹ The presence of HLA-B27 predicts prolonged and more severe disease.

Recent research has increased our understanding of the relation between host and microbial factors. High and persistent plasma concentrations of antibodies, mainly IgA, directed against lipopolysaccharides and also outer membrane proteins, have been found in serum from patients with reactive arthritis triggered by yersinia and salmonella, indicating chronic stimulation by bacterial antigens of lymphatic tissue associated with the gut.³⁻⁵ Recently, arthritic patients with persistently raised IgA antibodies to yersinia were found to harbour the bacteria in lymph nodes and intestinal biopsy specimens.⁴

Both lipopolysaccharide antigens from salmonella, shigella,

and yersinia and outer membrane proteins have been found in synovial tissue from patients with reactive arthritis, indicating an inflammatory process that might be driven by continuous antigen stimulation.^{3,5} Chlamydial inclusion bodies and chlamydial DNA have also been found in synovial specimens.⁶ In laboratory experiments synovial mononuclear cells from patients proliferate when challenged with bacteria associated with reactive arthritis, the maximum response being to the triggering organism. This might act as the initiator of the synovial inflammation.⁷ Whether viable bacteria are present in the joint as well is of interest when antimicrobial treatment of reactive arthritis is considered. So far, cultures from synovial fluid have yielded negative results—with a few exceptions, all chlamydia.¹

The relation between HLA-B27 and bacteria in the pathogenesis of reactive arthritis remains unclear. The molecular mimicry theory implies immunological cross reactivity between HLA-B27 and microbial antigens. Alternatively, HLA-B27 might act as a receptor for bacterial proteins, resulting in a "foreign" complex subjected to immune attack.¹

The treatment of reactive arthritis is with non-steroidal anti-inflammatory drugs, intra-articular injections of steroid, and physical treatments. The place of antibiotics is still controversial.⁸ In retrospective studies no difference in preventing the arthritis was found between patients who were given antibiotics and those who were not, suggesting that the events causing reactive arthritis take place early during the infection. On the other hand, relapses of postvenereal arthritis in patients with Reiter's syndrome were reduced when the urethritis was treated with antibiotics.⁹

Short term treatment with antibiotics had no beneficial effect on postenteric reactive arthritis in a prospective study,¹⁰ whereas in arthritis triggered by yersinia treatment for four to six weeks resulted in clinical improvement accompanied by disappearance of yersinia antigen in intestinal biopsy specimens and of serum IgA antibodies to yersinia.⁴ In a placebo controlled study three months' treatment with lymecycline shortened the duration of arthritis. The anti-inflammatory effect of lymecycline may have contributed to the favourable outcome, but this was restricted to patients with postvenereal disease.¹¹ In another study a three month

course of ciprofloxacin in postenteric reactive arthritis had no convincing effect.¹²

Overall there is still no evidence that short term treatment of enteric infections with antibiotics prevents reactive arthritis, but treatment of chlamydial infections does probably reduce the risks of postvenereal arthritis. Short term treatment with antibiotics does not seem to have any beneficial effect in established reactive arthritis, whereas some tendency to improvement has been seen with treatment lasting months—at least after chlamydia infection.

Prospective studies with well defined patients and controls are still needed before any firm recommendations for antibiotic treatment can be given. Such studies should take into consideration the triggering microbe, the duration of the arthritis before treatment, and the presence of HLA-B27. Appropriate antibiotics, doses, and the optimal duration of treatment have to be established. Ideally, the synovial fluid should be examined for microbial antigens and the serum antibody concentrations should be monitored during treatment. Such studies will probably have to be multi centre.

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- 1 Lahesmaa-Rantala R, Toivanen A. Clinical spectrum of reactive arthritis. In: Toivanen A, Toivanen P, eds. *Reactive arthritis*. Boca Raton, FL: CRC Press, 1988:1-13.
- 2 Keat A. Reiter's syndrome and reactive arthritis in perspective. *N Engl J Med* 1983;309:1606-15.
- 3 Granfors K. Do bacterial antigens cause reactive arthritis? *Rheum Dis Clin North Am* 1992;18:37-48.
- 4 Hoogkamp-Korstanje JAA, de Koning J, Heesemann J, Festen JJM, Houtman PM, van Oyen PLM. Influence of antibiotics on IgA and IgG response and persistence of Yersinia enterocolitica in patients with yersinia-associated spondylarthropathy. *Infection* 1992;20:53-7.
- 5 Mäki-Ikola O, Granfors K. Salmonella-triggered reactive arthritis. *Lancet* 1992;339:1096-8.
- 6 Taylor-Robinson D, Gilroy CB, Thomas BJ, Keat ACS. Detection of Chlamydia trachomatis DNA in joints of reactive arthritis patients by polymerase chain reaction. *Lancet* 1992;340:81-2.
- 7 Hermann E. T cells in reactive arthritis. *APMIS* 1993;101:177-86.
- 8 Leirisalo-Repo M. Are antibiotics of any use in reactive arthritis? *APMIS* 1993;101:575-81.
- 9 Bardin T, Enel C, Cornelis F, Salaki C, Jorgensen C, Ward R, et al. Antibiotic treatment of venereal disease and Reiter's syndrome in a Greenland population. *Arthritis Rheum* 1992;35:190-4.
- 10 Fryden A, Bengtsson A, Foberg U, Svenungsson B, Castor B, Kämel A, et al. Early antibiotic treatment of reactive arthritis associated with enteric infections: clinical and serological study. *BMJ* 1990;301:1299-302.
- 11 Laubio A, Leirisalo-Repo M, Lähdevirta J, Saikku P, Repo H. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to chlamydia arthritis. *Arthritis Rheum* 1991;34:6-14.
- 12 Toivanen A, Yli-Kerttula T, Luukkainen R, Merilähti-Palo R, Granfors K, Seppälä J. Effect of antimicrobial treatment on chronic reactive arthritis. *Clin Exp Rheumatol* 1993;11:301-7.

Alzheimer's disease

An association with apolipoprotein E4 may help unlock the puzzle

Alzheimer's disease accounts for around half of all cases of senile dementia. Its prevalence increases steeply with age, from less than 1% at age 65 to 15% in the ninth decade.¹ Until last year advances in understanding the genetics of the disease had been confined to a rare variant known as familial Alzheimer's disease, which is of unusually early onset and segregates in an autosomal dominant fashion. Between 15% and 20% of familial Alzheimer's disease is caused by mutations in the amyloid precursor protein gene on chromosome 21²—a small fragment of this protein, known as β amyloid is one of the main constituents of senile plaques. A second gene, which probably accounts for most familial Alzheimer's disease, has been mapped to the long arm of chromosome 14 but has not yet been identified.³

Familial Alzheimer's disease accounts for less than 1% of all cases of Alzheimer's disease. The genetics of the common variety are more complex. A large body of evidence indicates

that this variety is familial, but unlike familial Alzheimer's disease it does not show a mendelian pattern of segregation, and less than half of all patients with the disease have a family history. Not surprisingly, the risk to relatives of patients depends on age: the cumulative risk of dementia in first degree relatives rises to 40% or more by the age of 85-90.⁴ Moreover, recent evidence of greater concordance in monozygotic than dizygotic twin pairs suggests that genetic factors contribute substantially to this increased risk.^{5,6} Attempts to identify the gene or genes responsible have been complicated by the fact that—as with other common disorders—the mode of transmission is obscure. Probably most cases are caused by the action of several different genes together with environmental factors, though the results of some analyses are consistent with a major gene with age dependent penetrance.⁷

Despite the difficulties recent work has shown a strong and apparently robust association of Alzheimer's disease with the