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, Kämmel 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

$\epsilon 4$ allele of apolipoprotein E.⁸⁻¹¹ The frequency of the $\epsilon 4$ allele is around 0.50 in affected individuals from families where several other members also have late onset disease. It is around 0.40 in patients unselected for the presence of a family history, including those in whom the diagnosis has been confirmed at necropsy. In control populations the frequency is around 0.12. The odds ratio is 6.4 for those carrying one or more $\epsilon 4$ alleles. The risk of Alzheimer's disease apparently increases and the mean age at onset decreases in direct relation to the number of $\epsilon 4$ alleles—showing that the $\epsilon 4$ allele acts in a partly additive fashion. Nevertheless, some 40% of people with Alzheimer's do not possess an $\epsilon 4$ allele so it is neither necessary nor sufficient to cause the disease and other aetiological factors and probably other genes must play a part. If we assume a polygenic and multifactorial mode of transmission¹² then apolipoprotein $\epsilon 4$ accounts for about 17% of the variance in the liability to develop the disorder in the general population.

A more practical issue, with ethical implications, is whether apolipoprotein E genotyping can be used for predictive or diagnostic purposes. In multiply affected families more than 90% of members who are homozygotes for $\epsilon 4$ seem to develop the disorder by the age of 80.¹⁰ Calculations of the true risk in the general population are, however, complicated by the fact that too few octogenarians have yet been studied. The only published study of a consecutive series of patients reported a risk to 80-90 year olds with the $\epsilon 4/\epsilon 4$ genotype of 84%, but that series included only 37 patients aged over 80. Moreover, it is not possible to conclude from this case-control study (as some have done¹³) that the risk to $\epsilon 4/\epsilon 4$ homozygotes in the general population of 80-90 year olds is as high as 84%. If we adopt a bayesian approach and assume a population prevalence of Alzheimer's disease of 15% in 85 year olds and a frequency of $\epsilon 4/\epsilon 4$ homozygotes of 0.03 in the general population and 0.13 in Alzheimer's disease, then we can calculate that the probability of someone with the $\epsilon 4/\epsilon 4$ genotype having Alzheimer's disease at age 85 is 43%.¹¹

The predictive value of testing for $\epsilon 4$ would be even lower when younger populations were tested—because fewer people will reach the age of risk. For example, if we assume that 35 year olds have a 2% chance of developing Alzheimer's disease in their lifetime then only 6.4% of $\epsilon 4/\epsilon 4$ homozygotes of that age will develop the disease.¹⁴ These calculations are further complicated by the fact that fewer $\epsilon 4/\epsilon 4$ homozygotes are likely to survive long enough to develop Alzheimer's disease because of their risk of cardiovascular disease.

The allele may also be a risk factor for multi-infarct dementia—which is not surprising, given that those with this allele are at increased risk of atherosclerosis. This second association might increase the predictive value of apolipo-

protein E genotyping as a test for dementia, but on current data the risk of dementia at age 85 would still be only about 65%, assuming that being an $\epsilon 4$ homozygote confers a similar level of risk of multi-infarct dementia. Testing is unlikely to be of value in the differential diagnosis of senile dementia since multi-infarct dementia and Alzheimer's disease between them account for over 90% of cases.

The really important issue is how apolipoprotein E contributes to the pathogenesis of Alzheimer's disease. Possibly $\epsilon 4$ acts as a neutral marker for another gene with which it is in linkage disequilibrium and which predisposes to Alzheimer's disease; but, the presence of apolipoprotein E in both senile plaques and neurofibrillary tangles, together with a possible contribution to the response to neuronal injury, points to it playing a direct part in pathogenesis.¹³ Possibly apolipoprotein E4 might increase the rate at which deposits of amyloid accumulate; or it might reduce the stability of microtubules, leading to the accumulation of neurofibrillary tangles. Whatever the mechanism, its elucidation will ultimately offer a real hope for effective treatment.

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- 1 Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A. A population based study of senile dementia in 85 year olds. *N Engl J Med* 1993;328:153-8.
- 2 Goate A, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991;349:704-6.
- 3 Clark RF, Goate AM. Molecular genetics of Alzheimer's disease. *Arch Neurol* 1993;50:1164-72.
- 4 McGuffin P, Owen M, O'Donovan M, Thapar A, Gottesman II. *Seminars in psychiatric genetics*. London: Gaskell Press, 1994.
- 5 Breitner JCS, Gatz M, Betgem ALM, Christian JC, Mortimer JA, McClearn GE. Use of twin cohorts for research in Alzheimer's disease. *Neurology* 1991;43:261-7.
- 6 Bergner ALM. Estimation of concordance rate in demented twin pairs as a function of age of onset and age of sample. *Psychiatric Genetics* 1993;3:139.
- 7 Farrer LA, Myers RH, Connor L, Cupples LA, Growdon JH. Segregation analysis reveals evidence of a major gene for Alzheimer's disease. *Am J Hum Genet* 1991;48:1026-33.
- 8 Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance MA, Enghild J, Salvesen GS, et al. Apolipoprotein E: high avidity binding to beta-amyloid and increased frequency of type 4 allele in late onset familial Alzheimer's disease. *Proc Natl Acad Sci USA* 1993;90:1977-81.
- 9 Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH. Association of apolipoprotein ϵ allele with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467-72.
- 10 Corder B, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GN. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921-3.
- 11 Poirer J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthiers S. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet* 1993;342:697-99.
- 12 Edwards J. The meaning of the associations between blood groups and disease. *Ann Hum Genet* 1965;29:77-83.
- 13 Scott J. Apolipoprotein E and Alzheimer's disease. *Lancet* 1993;342:696.
- 14 Ben-Schlomo Y, Lewis G, McKeigue P. Apolipoprotein E- ϵ allele and Alzheimer's disease. *Lancet* 1993;342:1310.

Towards the safer use of traditional remedies

Greater awareness of toxicity is needed

About 80% of the world's population does not have access to Western medicine and therefore depends on traditional medical practices. When people from less developed countries emigrate they continue to seek medical advice from traditional practitioners working in their own communities, even in countries where all citizens have free access to good quality Western medicine. Though the main reasons for this are probably cultural and linguistic, the role of mistrust and fear should not be underestimated.

Large amounts of traditional medicines are imported into Britain, legally and illegally, and use of such medicines is frequently not admitted on occasions when serious illness forces patients to consult Western medical practitioners. These medicines carry with them a risk of adverse reactions; the risk needs to be quantified and as far as possible minimised.

The safer use of traditional remedies was the subject of a one day meeting held last month at the Royal Botanic