environment of the families in our study may have allowed free expression—in both parents and children—of genetic tendencies to overweight.

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Role of Chlamydia trachomatis and HLA-B27 in sexually acquired reactive arthritis

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Summary and conclusions

Inflammatory arthritis, tendinitis, and fasciitis after non-specific urethritis ("sexually acquired reactive arthritis" (SARA)) was studied prospectively in 531 men with non-specific urethritis, with particular reference to the frequency of isolation of Chlamydia trachomatis and the presence of HLA-B27. Satisfactory cultures were obtained from the urethral swabs from 384 patients; and HLA typing was performed on 482, of whom 30 (6%) were HLA-B27-positive. Arthritis developed in 16 patients, and five of the 14 (36%) with satisfactory cultures were positive for C trachomatis; 135 of the patients without arthritis were also positive for C trachomatis, an identical proportion. Seven of the 15 patients (40%) with arthritis who were HLA-typed were HLA-B27-positive.

Six of the 30 patients with HLA-B27 developed peripheral arthritis in contrast to only nine of the 452 patients lacking the antigen, suggesting a tenfold increased susceptibility. C trachomatis, however, was no more prevalent in cultures from HLA-B27-positive men than from the others. Thus carriage of C trachomatis is unlikely to be influenced by HLA-B27.

C trachomatis may be an important pathogen in some cases of SARA but does not appear to be an exclusive trigger factor for this condition.

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Introduction

Since Sir Benjamin Brodie's observation in 1818[1] of arthritis and inflammatory disorders of the eye after sexually acquired urethritis, increasing epidemiological evidence has suggested that non-specific urethritis and this form of arthritis result from infections. A clinically similar acute arthritis with conjunctivitis and urethritis after gastrointestinal infection was described by Fiessinger and Leroy[2] and by Reiter,[3] and enteric infections with *Shigella*,[4 5] *Salmonella*,[6] and *Yersinia*[7] are now known to cause Reiter's syndrome.

With improved culture techniques,[9] 30-50% of men with non-specific urethritis have *Chlamydia trachomatis* isolated from the urethra[10-12]—even more in selected groups of patients.[13-15] Various strands of evidence have led to the conclusion that *C trachomatis* is at least one of the causative agents of non-specific urethritis.[16-18] It has also been isolated in Reiter's syndrome,[19-22] though the numbers of patients have been too small to establish a causal relationship. Moreover, raised titres of antibodies to Chlamydia have been found,[22 25] and a high proportion of patients with Reiter's syndrome and ankylosing spondylitis affecting peripheral joints have been reported[23 24] to show evidence of lymphocyte sensitisation to chlamydial antigens.

Reiter's syndrome and postenteric reactive arthritis occur especially in individuals possessing the HLA-B27 antigen.[8 26-32] In our study of arthritis and the role of *C trachomatis* in men with new episodes of non-specific urethritis we therefore carried out HLA typing to assess the prevalence of HLA-B27. We refer to arthritis after a proved or putative infection of the genital tract as sexually acquired reactive arthritis (SARA), the

arthritis (referred to as "reactive"[8]) being a sterile inflammation of the synovial membrane, tendons, and fascia. This definition therefore includes sexually acquired Reiter's syndrome.

Patients and methods

We studied 531 heterosexual men attending a clinic for sexually transmitted diseases with new episodes of non-specific urethritis. This was diagnosed if over 10 polymorphs were found in at least three consecutive high-power fields (magnification ×600) on a urethral smear, provided that microscopy, culture, and serology excluded gonorrhoea and syphilis.[33] We excluded patients who had had symptoms of genital infection within the preceding three months; had received any antibiotics within the previous month; had genital warts or herpes; or had contacts who were found to have gonorrhoea, trichomoniasis, or candidiasis. Not all the remaining patients were included, but we tended to select those with arthritis.

Arthritis was usually a self-limiting, inflammatory disease of connective tissue and tended to be asymmetrical, affecting mainly joints of the leg (all patients had knee effusions) and tendon sheaths and attachments. Sheep cell agglutination and latex tests for rheumatoid factor were negative in all cases. We excluded alternative diagnoses, such as gonococcal arthritis, gout, and pyoarthrosis, by appropriate investigations. Only two patients developed ocular inflammation and therefore satisfied the criteria for Reiter's syndrome.

Cultures were taken when we first saw patients before they started treatment, using endourethral swabs (Medical Wire and Equipment Co Ltd).[34] Specimens were normally inoculated into cell cultures (in University College Hospital's virology laboratory) on the same day. *C trachomatis* was isolated by a described method.[35]

For HLA typing we used a modified microlymphocytotoxity assay,[37] with antisera supplied by the National Tissue Typing Reference Laboratory, Bristol, and the tissue immunology unit of the London Hospital. We first tested most patients on a screening plate for the presence or absence of HLA-B27, full confirmatory HLA typing being performed only if the result of this test was positive.

Results

Sixteen of the 531 men studied developed arthritis. Fifteen of these (like most patients in the series) had had a recent, new sexual contact before their joint symptoms started; the interval ranged from 14 days to 8 weeks, with a mean of 30 days (it was unknown in two cases). These symptoms started 0-14 (mean 7·7) days after the onset of dysuria or urethral discharge.

We obtained satisfactory cultures from 384 of the 531 men studied. Of these, 140 (36%) were positive for *C trachomatis*, and five patients in this group developed arthritis (table I). The same proportion of the patients with negative culture results—9 out of 244—also developed arthritis, as did two of the men whose cultures were unsatisfactory. *C trachomatis* was isolated from the same proportion of patients with arthritis as of patients with non-specific urethritis alone (table II).

Six of the 15 patients (40%) with arthritis who were HLA typed had the B27 antigen, in contrast to only 30 out of the 482 (6%) typed in the total series (table III). Six of the 30 HLA-B27-positive patients developed arthritis, but only nine of the 452 B27-negative patients ($P < 0.001$), a relative risk[36] of 12·3.

TABLE I—*Number of patients with non-specific urethritis, with positive and negative cultures for C trachomatis, developing arthritis*

C trachomatis	With arthritis	Without arthritis	Total
Positive	5	135	140
Negative	9	235	244

TABLE II—*Number of patients with non-specific urethritis, with and without arthritis, with positive and negative cultures for C trachomatis*

	C trachomatis		Total
	Positive	Negative	
With arthritis	5	9	14
Without arthritis ..	135	235	370

TABLE III—*Occurrence of arthritis in HLA-B27-positive patients with non-specific urethritis*

	No with HLA-B27	No without HLA-B27	% HLA-B27-positive
Total series (n = 482)*	30	452	6·2
No with arthritis	6	9	40

*Seventy-nine were not HLA-typed.

Of the 20 HLA-B27-positive patients with a satisfactory culture, nine were positive for *C trachomatis*, not significantly different from the incidence in the whole series. Nor was there any significant difference between the culture positive and negative groups in the incidence of arthritis. Of the nine culture positive patients two (22%) had arthritis compared with four (36%) of the 11 who were negative.

Discussion

Circumstantial evidence—new sexual contacts and appropriate time intervals—suggests that the arthritis in our patients was a direct result of non-specific urethritis. Altogether 16 patients out of the 531 studied fulfilled our criteria for the diagnosis of SARA, but only two had Reiter's syndrome. This selective study was not designed to provide epidemiological data on the incidence of the condition in the general population or in hospital-based patients with non-specific urethritis.

The isolation of *C trachomatis* from about 36% of patients with non-specific urethritis is consistent with the results of other studies[10-12] using the same isolation techniques. The same proportion of the patients with arthritis and with non-specific urethritis alone yielded isolates of *C trachomatis*, and similar proportions of the culture positive and negative patients developed arthritis. Although a more sensitive culture system might give somewhat higher proportions, these findings suggest that *C trachomatis* is not an exclusive trigger factor for SARA. Possibly (as in other forms of reactive arthritis) the disease is initiated by several sexually acquired organisms, perhaps sharing a common antigenic determinant. Current serological studies and future investigations of cell-mediated immunity may clarify this point.

The finding of HLA-B27 in 40% of the patients with arthritis as opposed to 6% in the total series is consistent with but substantially lower than the high frequencies of the antigen reported in postenteric reactive arthritis[8 29-32] and Reiter's syndrome.[26-28] HLA-B27 is strongly associated with sacroiliitis, spondylitis, and iritis; but apart from ocular inflammation in two cases, none of these features occurred in our patients. Rheumatologists are likely to see only patients with severe or persisting disease or with extra-articular features and may not be familiar with the limited form of disease that we describe.

Patients with reactive arthritis lacking the HLA-B27 antigen may have a shorter duration of arthritic symptoms, affecting fewer joints, and a lower incidence of sacroiliitis and iritis than their HLA-B27-positive counterparts.[8] The high proportion of HLA-B27-negative patients (9 out of 15) in this study may partly explain why our patients tended to have a short-lived arthritis restricted to the peripheral joints, though our series is too small for analysis. Of the 30 men who were HLA-B27-positive, 6 (20%) developed arthritis, a proportion similar to that of patients with ankylosing spondylitis among individuals carrying this antigen.[38 39]

From this study an HLA-B27-positive man appears to be 10 times more likely to develop SARA than one who lacks the antigen. The two patients (both HLA-B27-positive) whose symptoms have persisted for more than six months will be followed up to see whether spinal or extra-articular manifestations appear. A long-term follow-up study of all our patients would show whether sexually acquired infections are an important cause of more serious and chronic rheumatic syndromes associated with HLA-B27.

The mechanisms by which HLA-B27 increase susceptibility to inflammatory arthritis are not yet clear. Many bacteria bear cell-surface antigens closely related to mammalian tissue antigens, and in mice these cross-reactive antigens may be responsible for the pathogenicity of *Salmonella typhimurium*.[40] Preliminary evidence also suggests cross-reactivity between certain Gram-negative bacterial antigens and HLA-B27,[41] which could lead to autoimmunity. If there is similar cross-reactivity between *C trachomatis* and human tissues this could also provide a basis for autoimmune processes, which may play an important part in the pathogenesis of reactive arthritis.

As all our patients took antibiotics as soon as non-specific urethritis was diagnosed, the risk of arthritis is clearly not eliminated by the standard antibiotic treatment we used. Others[12] have concluded that the course of such arthritis is not influenced by antibiotics; but a controlled trial would be needed to show whether they can prevent it or modify its course.

The importance of our study lies in the clear demonstration of interaction between genetic and environmental factors in an inflammatory rheumatic disease. In spite of our failure to implicate a specific organism as the sole cause of SARA, further studies on such patients with appropriate methods should help to identify the mechanisms whereby a susceptible host responds abnormally to his environment.

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Vitamin D status of Asian infants

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Summary and conclusions

Vitamin D intakes of infants aged 6 and 18 months from the Asian community in Southall, Middlesex, were studied to assess the effectiveness of food fortification as a means of preventing vitamin D deficiency. Infants aged 6 months generally had similar diets to white children of the same age and had reasonable vitamin D intakes owing to consumption of fortified dried milks and cereals, reinforced by health visitors and baby clinics. Children aged 18 months, however, ate largely Asian diets and had much lower vitamin D intakes than the 6-month-old group with a corresponding increase in symptoms of vitamin D deficiency.

Hence new measures for preventing vitamin D deficiency should probably be aimed at children aged over 1 year. The results of this survey suggest that fortifying chapati flour would be the most effective method of doing this.

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Introduction

Clinical and subclinical vitamin D deficiency in Asian immigrants has been widely reported.[1-6] Although rickets and