Clinical Phenotype Is Related to HLA Genotype in the Peripheral Arthropathies of Inflammatory Bowel Disease

TIMOTHY R. ORCHARD,* S. THIYAGARAJA,* KENNETH I. WELSH,† B. PAUL WORDSWORTH,§ J. S. HILL GASTON,‖ and DEREK P. JEWELL*

*Gastroenterology Unit, University of Oxford, Radcliffe Infirmary, Oxford; †Transplant Immunology Laboratory, Nuffield Department of Surgery, Churchill Hospital, Oxford; §Musculoskeletal Research Unit, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford; and ‖Department of Rheumatology, University of Cambridge, Addenbrooke's Hospital, Cambridge, England

Background & Aims: The detection of phenotype-determining genes as opposed to disease susceptibility genes requires precise phenotypic characterization of patients. Peripheral arthropathies in inflammatory bowel disease (IBD) are well recognized and are classified with the HLA-B*27-related spondyloarthropathies by the European Spondyloarthropathy Study Group. However, previous HLA studies in IBD have only shown this association with axial disease rather than peripheral arthropathy. We recently reported a clinical classification that describes 2 types of peripheral arthropathy, distinguished by their natural history and articular distribution. We now report the results of immunogenetic studies in these patients and compare them with other spondyloarthropathies. *Methods:* IBD patients with type 1 (n = 57) and type 2 (n = 45) peripheral arthropathy were identified by case note review and questionnaire. Patients and 603 controls from Oxfordshire were assigned HLA-A, -B, -C, -DR, and -DQ genotypes by sequence-specific primer polymerase chain reaction. Patient results were compared with controls (corrected for multiple comparisons), then with each other in light of existing hypotheses. The results were compared with those of a cohort of 30 patients with postenteric reactive arthritis (ReA) and 16 patients with IBD-associated ankylosing spondylitis (IBD-AS). *Results:* Type 1 arthropathy was associated with HLA-DRB1*0103 (DR103; a rare subtype of DR1) in 33% ($P < 0.0001$; relative risk [RR], 12.1), B*35 in 30% ($P = 0.01$; RR, 2.2), and B*27 in 26% ($P = 0.001$; RR, 4.0). In contrast, type 2 was associated with HLA-B*44 in 62% ($P = 0.01$; RR, 2.1). Similar significant associations to type 1 arthropathy were found in ReA, except that the HLA-B*27 association was significantly stronger and an association was found with DRB1*0101 (DR1) in 43% ($P = 0.001$; RR, 2.2). IBD-AS was associated only with HLA-B*27 and DRB1*0101. *Conclusions:* These data suggest that the clinical classification into type 1 and type 2 arthropathies describes immunogenetically distinct entities and establish that in polygenic disorders, genes may determine clinical phenotype without conferring overall disease susceptibility (in this case, HLA genes). Type 1 arthropathy is clinically and immunogenetically similar to the spondyloarthropathies, but different HLA associations may define phenotypically distinct groups. Type 2 arthropathy has different HLA associations and may have a different etiology. Further studies are now required to confirm these associations and to elucidate the different pathogenetic mechanisms.

Ulcerative colitis (UC) and Crohn's disease are characterized by intestinal, and sometimes extraintestinal, inflammation. There is now good evidence that genetic susceptibility is important in the pathogenesis of these disorders and that several genes are involved.[2–4] Microsatellite screening of the genome has revealed several loci in linkage with these diseases. Some of these loci are common to both UC and Crohn's disease (presumably determining overall susceptibility to inflammatory bowel disease [IBD]), but others appear to be disease specific.[5–7] However, other genes may influence the clinical course of the disease without conferring susceptibility, but detection of these "phenotype-determining genes" depends on precise clinical characterization of patients. In IBD, this has been well illustrated by the conflicting data from previous studies of HLA associations, possibly due to ethnic differences in the populations studied and the failure to study a sufficient number of patients to allow meaningful analysis between phenotype and genotype. A previous study from Oxford did describe specific phenotype-genotype associations in UC, although not in Crohn's disease.[8]

The most striking of these associations was between HLA-DRB1*0103 (a rare subtype of DR1) and extraintestinal manifestations (arthropathy, erythema nodosum, uveitis).[8,9] For patients with arthropathy, 27.2% pos-

Abbreviations used in this paper: PeA, peripheral arthropathy; ReA, reactive arthritis.

0016-5085/00/$10.00

sessed HLA-DRB1*0103 (DR103) compared with 8.6% for UC as a whole and 3.3% for healthy controls.[9]

The peripheral arthropathies (PeAs) of IBD are often classified with the HLA-B*27–related spondyloarthropathies.[1] However, previous association studies have failed to find any significant associations with HLA-B*27.[10] This may be a result of the small numbers of patients studied and the failure to characterize the different forms of arthropathy accurately. We recently reported a clinical classification of PeAs in IBD that describes 2 types, distinguished by their articular distribution, natural history, and disease associations (Table 1).[11] In this classification, type 1 PeA is clinically similar to postenteric reactive arthritis (ReA), which is associated with HLA-B*27 in up to 80% of cases, depending on the initiating organism and severity of the arthropathy,[12–14] and with HLA-B*35 in some studies. This classification may facilitate the demonstration of HLA associations previously masked by allowing the definition of more homogeneous clinical groups. This study was performed to identify the HLA associations of type 1 and type 2 PeA of IBD, with the a priori hypothesis that type 1 is associated with HLA-B*27, -B*35, and -DRB1*0103. In addition, the study aimed to determine whether HLA status influences the clinical course of the arthropathies and to elucidate their relationship to the other spondyloarthropathies.

Materials and Methods

From our population of 976 UC patients and 483 Crohn's disease patients, 59 patients with type 1 PeA were identified, 46 with type 2 PeA, and 16 patients with IBD-associated ankylosing spondylitis (IBD-AS). Blood was obtained from 57 type 1 patients, 45 type 2 patients, and 16 patients with IBD-AS (for which ethical approval had been given). Patients were white subjects from Northern Europe, with less than 5% having Jewish ancestry. DNA was separated from peripheral blood leukocytes by a salting-out technique and was dissolved in sterile water with concentrations of 10–100 ng/μL. HLA-A, -B, -C, -DR, and -DQ genotyping was performed using the phototyping technique described by Bunce et al.[15] on initial cohorts of 30 patients with type 1 and 30 patients with type 2 PeA. Briefly, sequence-specific primers for the HLA alleles were used in polymerase chain reaction with patient DNA and *Taq* polymerase (Bioline, London, England). One hundred forty-four separate reactions per patient allow the determination of HLA class I and II typing as described by Bunce et al.[15] The products were then run on 1% agarose gels with ethidium bromide and viewed under UV light. HLA types were assigned according to the primers that had amplified. This method has been previously validated and is in routine use for histocompatibility testing in the United Kingdom.[15]

Table 1. Classification of Peripheral Arthropathy in IBD

Type 1 (pauciarticular)
An acute, self-limiting arthropathy lasting a median of 5 wk; affects less than 5 joints, normally including a large joint; associated with relapses of IBD and both erythema nodosum and uveitis
Type 2 (polyarticular)
A symmetrical seronegative polyarthropathy that runs a course independent of IBD; tends to cause persistent symptoms with a median duration of 3 yr; is associated with uveitis but not erythema nodosum.

NOTE. Neither form is seropositive, erosive, or deforming.
Modified and reprinted with permission.[11]

The results were analyzed by the Fisher exact test against a panel of 603 normal controls from Oxfordshire, using 2 × 2 contingency tables for alleles of interest (HLA-B*27, -B*35, and -DRB1*0103), with the Bonferroni correction for multiple comparisons for other alleles (correction factor of 33 for the HLA-B locus). Further hypotheses were generated and tested against 92 IBD disease controls (52 UC patients and 40 Crohn's disease patients) and each other. The disease controls were patients randomly selected from the Oxfordshire IBD population who had not suffered from IBD-associated arthropathy.

The remaining patients with arthropathy (27 type 1 and 15 type 2) were typed for HLA-B*27, -B*35, -B*44, -DRB1*0101 (DR1), and -DRB1*0103 (DR103) by the same methods and were analyzed as a cohort to replicate the findings from the first cohort. The results were then combined with the first cohort to undertake analysis by disease type (UC and Crohn's disease).

A further cohort of 30 patients with established postenteric ReA and the 16 patients with IBD-AS also underwent HLA genotyping for HLA-B*27, -B*35, -DRB1*0101, and -DRB1*0103, and the results were compared with the results for IBD arthropathy and healthy controls.

Results

In the first cohort, when compared with controls (with correction for multiple comparisons where appropriate), type 1 arthropathy was significantly associated with possession of HLA-B*27 (27% vs. 7%; $P = 0.001$; relative risk [RR], 4.0), HLA-B*35 (33% vs. 15%; $P = 0.01$; RR, 2.2), and HLA-DRB1*0103 (40% vs. 3%; $P < 0.0001$; RR, 12.1). Type 2 arthropathy was associated with possession of HLA-B*44 (63% vs. 31%, $P = 0.0005$, $P_c = 0.017$; RR, 2.1). These differences were also significant when comparisons were made against the 92 disease controls (B*27, $P = 0.004$; B*35, $P = 0.02$; DRB1*0103, $P < 0.0001$; B*44, $P = 0.0001$) and when the 2 PeA groups were compared (B*27, $P = 0.03$; B*35, $P = 0.02$; DRB1*0103, $P = 0.0001$; and B*44, $P = 0.0001$). These associations were all confirmed in the smaller second cohorts compared with IBD and healthy controls (type 1 arthropathy: B*27, 26% vs. 7%, $P = 0.02$ [RR, 3.9]; B*35, 33% vs. 15%, $P = 0.025$ [RR, 2.2]; DRB1*0103, 30% vs. 3%, $P < 0.0001$ [RR, 8.9]; type 2 arthropathy: B*44, 60%

vs. 31%, $P = 0.02$ [RR = 1.9]). The results of the entire population with IBD-associated PeA are shown in Table 2. When the groups were split and analyzed separately for UC and Crohn's disease, all the associations remained statistically significant, and there were no significant differences between UC and Crohn's disease. Further analysis of type 1 arthropathy was undertaken by clinical phenotype; 17 patients had recurrent (2 or more) episodes of arthropathy, and 40 had a single episode. The prevalence of DRB1*0103 in the former was 11 of 17 (65%) and in the latter was 9 of 40 (23%) ($P = 0.003$). No other positive HLA associations were noted, but the prevalence of HLA-DR15 was decreased in type 1 compared with type 2 (7% vs. 30%; $P = 0.04$).

The results of HLA typing in the cohort of postenteric patients with ReA are shown in Table 3. There was a significant increase in prevalence of HLA-B*27, -B*35, -DRB1*0101, and -DRB1*0103 in this group compared with controls. There is no significant difference between HLA-DRB1*0103 or HLA-B*35 compared with type 1 IBD PeA, but there was a significant increase in HLA-B*27 and -DRB1*0101 over and above that seen in patients with type 1 IBD PeA. An increase in HLA-B*27 was also found in the small group of IBD-AS patients, in which there was also a significant association with HLA-DRB1*0101 but not with HLA-DRB1*0103 or -B*35.

Other HLA-B alleles tested were B*7, B*8, B*13, B*18, B*39, B*41, B*45, B*46, B*47, B*48, B*49, B*50, B*51, B*52, B*53, B*54, B*55, B*56, B*57, B*58, B*60, B*61, B*62, B*63, B*70, B*71, B*72, B*75, B*76, B*77, B*78, and B*82.

Other HLA-DR alleles tested were DRB1*0101, DRB1*15, DRB1*03, DRB1*04, DRB1*07, DRB1*08, DRB1*09, DRB1*10, DRB1*11, DRB1*12, DRB1*13, and DRB1*14.

No positive or negative associations were found with any of the above.

Table 2. HLA Associations of Peripheral Arthropathy in IBD

	Type 1 arthropathy (n = 57)		Type 2 arthropathy (n = 45)		Controls (n = 603)		IBD controls (n = 92)	
HLA type	Number	%	Number	%	Number	%	Number	%
HLA-B*27	15	26[i]	2	4	40	7[a]	5	5[e]
HLA-B*35	19	33[j]	3	7	90	15[b]	13	14[f]
HLA-B*44	7	12	28	62[k]	186	31[d]	10	11[h]
HLA-DRB1* 0103	20	35[l]	0	0	20	3[c]	4	4[g]

Type 1 vs. controls: [a]$P < 0.0001$; RR, 4.0; [b]$P = 0.01$; RR, 2.2; [c]$P < 0.0001$; RR, 12.1.
Type 2 vs. controls: [d]$P = 0.01$; RR, 2.1.
Type 1 vs. IBD controls: [e]$P = 0.0004$; RR, 4.8; [f]$P = 0.008$; RR, 2.4; [g]$P < 0.0001$; RR, 8.1.
Type 2 vs. IBD controls: [h]$P < 0.0001$; RR, 5.7.
Type 1 vs. type 2: [i]$P = 0.003$; RR, 5.9; [j]$P = 0.001$; RR, 5.0; [k]$P < 0.0001$; RR, 5.1; [l]$P < 0.0001$; RR, incalculable.

Table 3. HLA Associations of Type 1 IBD Associated Peripheral Arthropathy and Other Spondyloarthropathies

	IBD type 1PeA (n = 57)		Reactive arthritis (n = 30)		IBD-AS (n = 16)		Controls (n = 603)
HLA type	No.	%	No.	%	No.	%	%
HLA-B*27	15	26	17	57[a]	9	56[b]	7[c,d]
HLA-B*35	19	33	9	30[e]	3	19	15
HLA-DRB1*0101	10	18	13	43[f]	10	63[g]	19[h,i]
HLA-DRB1*0103	20	35	4	13[j]	1	6[k]	3[l]

HLA-B*27: [a]IBD PeA vs. ReA, $P = 0.009$; [b]IBD PeA vs. IBD-AS, $P = 0.03$; [c]ReA vs. controls, $P < 0.0001$; [d]IBD-AS vs. controls, $P < 0.0001$.
HLA-B*35: [e]ReA vs. controls, $P = 0.03$; RR, 2.0.
HLA-DRB1*0101: [f]IBD PeA vs. ReA, $P = 0.02$; [g]IBD PeA vs. IBD-AS, $P = 0.002$; [h]ReA vs. controls, $P = 0.001$; [i]IBD-AS vs. controls, $P < 0.0001$.
HLA-DRB1*0103: [j]IBD PeA vs. ReA, $P = 0.04$; [k]IBD PeA vs. IBD-AS, $P = 0.03$; [l]ReA vs. controls, $P = 0.02$.

Discussion

This study reports significant HLA associations with the arthropathies of IBD that influence the pattern of peripheral joint involvement and that may indicate their relationship to other spondyloarthropathies. The clinical phenotypes of the articular problems in UC and Crohn's disease are the same, and the HLA associations are identical and are not present in IBD patients without joint complications. This implies that genes of the HLA region have an important role in determining the clinical course of the articular disease in IBD, although not in susceptibility to IBD itself. Thus, phenotype-determining genes may have a role in other polygenic disorders, affecting the clinical outcome without conferring disease susceptibility.

Association studies of this sort allow the detection of associations with specific genes that may be pathogenetically important. However, they may simply reflect linkage disequilibrium with the actual pathogenic gene located close by. Subdividing the IBD population may create inadvertant stratification of the population that may lead to errors, and adequate statistical allowance for multiple comparisons is also essential to minimize the chances of detecting spurious associations. This study shows that the 2 types of IBD arthritis have distinct immunogenetic characteristics, irrespective of whether the genes identified are pathogenetically relevant. However, the consistency of the findings and the relationship

to ReA suggest that the identified associations may be of pathogenic importance.

The class I associations of type 1 IBD arthropathy and ReA are very similar. Previous studies of ReA have also shown associations with HLA-B*27[12–14] and the B*35 cross-reactive group of antigens[16]; therefore, classification of type 1 PeA with the spondyloarthropathies seems justified.

This study also shows strong associations between HLA class II and type 1 IBD PeA, especially with HLA DRB1*0103, an uncommon subtype of DR1. DRB1*0103 is also increased in patients with postenteric ReA, but DRB1*0101 was also increased in these patients and in the IBD-AS group. This association was not seen in type 1 IBD PeA.

Idiopathic ankylosing spondylitis has been associated with DR1 in a previous study, but this was largely attributed to linkage disequilibrium with HLA-B*27.[17] Because of the linkage disequilibrium between HLA-B*27 and DRB1*0101, it is difficult to assess the relative importance of the class I and class II associations in the current study. However, in peripheral disease (type 1 IBD PeA and ReA), the DRB1*0103 association was clearly independent of HLA-B*27. This may have important implications for the interpretation of the HLA associations in acute peripheral joint disease of the spondyloarthropathies: HLA-B*27 may primarily be a determinant of axial disease, in which it is the most potent genetic trigger of axial inflammation. However, other class I molecules may be able to initiate disease in the presence of other susceptibility factors such as intestinal inflammation or increased permeability, allowing increased antigen presentation to the intestinal immune system. This would be consistent with the findings of Mielants et al.[18] that pure axial ankylosing spondylitis is not associated with intestinal inflammation, whereas in the spondyloarthropathies, generally 68% of patients were found to have evidence of intestinal inflammation.[19] It would also be consistent with the general observation that the HLA-B*27 association in ankylosing spondylitis is weaker in patients with coexisting IBD than in idiopathic ankylosing spondylitis.

In contrast with axial disease, the acute peripheral arthritis seen in type 1 IBD PeA and ReA may primarily be determined by class II HLA alleles, and the structurally similar HLA-DRB1*0103 and -DRB1*0101 may be the most effective initiators of disease. For the disease to progress, there has to be active intestinal inflammation that is associated with the induction of HLA-DR in the colon[20] and up-regulation of HLA-DR expression in the ileum.[21] This would be consistent with the finding that the majority of proliferative lymphocyte responses to triggering bacteria in the synovium of ReA patients are HLA-DR restricted,[22] and also with the recurrence of joint disease that may occur in IBD when there is an acute relapse of gut disease.[11]

It has previously been shown that up to 40% of patients with ReA develop chronic problems, including axial disease.[23] Nearly all of these patients are HLA-B*27 positive. Longitudinal studies of type 1 IBD PeA are now required to show whether the B*27-positive patients show a predisposition to the development of axial disease.

Type 2 arthropathy is not associated with HLA-B*27 or class II alleles, and its immunogenetic characteristics suggest an etiology distinct from the other seronegative spondyloarthropathies. It has been suggested that HLA-B*44, which is associated with type 2 arthropathy, may form part of an extended haplotype with DR4 in rheumatoid arthritis (particularly in association with Felty's syndrome).[24,25] However, in our patients, the prevalence of DR4 in type 2 arthropathy was only 28%, which is similar to the normal population (35%). This, in conjunction with the nonerosive and seronegative nature of the condition, would suggest that the primary association is with HLA-B*44 and that the pathogenesis is distinct from the seropositive rheumatoid diseases as well as the seronegative spondyloarthropathies.

This study strongly supports the concept of 2 immunogenetically distinct forms of PeA in IBD and that HLA genes are important determinants of these phenotypes. Furthermore, it shows for the first time strong HLA class II associations in both type 1 IBD PeA and other spondyloarthropathies. Further studies are now required to extend these results to other patient populations. For type 1 PeA and ReA, long-term prospective studies will be required to elucidate the role of DR1 subtypes in determining clinical features such as axial involvement and intestinal inflammation.

References

1. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, Cato A, Dijkmaas B, Olivieri I, Paseo G. The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. Arthritis Rheum 1991;34: 1218–1227.
2. Tysk C, Lindberg E, Järnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut 1988;29:990–996.
3. Thompson NP, Driscoll R, Pounder RE, Wakefield AJ. Genetics versus environment in inflammatory bowel disease: results of a British twin study. BMJ 1996;312:95–96.
4. Satsangi J, Grootscholten C, Holt H, Jewell DP. Clinical patterns of familial inflammatory bowel disease. Gut 1996;38:738–741.
5. Hugot JP, Laurent-Puig P, Gower-Rousseau C, Olson JM, Lee JC, Beaugerie L, Naom I, Dupas JL, Van Gossum A, Orholim M, Bariti-Pellic C, Weissenbach J, Mathew CG, Lennard-Jones JE, Cortot A, Colombol JF, Thomas G. Mapping of a susceptibility

locus for Crohn's disease on chromosome 16. Nature 1996;379: 821–823.
6. Ohmen JD, Yang H, Yamomoto KK, Zhao HY, Ma Y, Bentley LG, Huang Z, Gerwehr S, Pressman S, McEltree C, Targon S, Rotter JI, Fischel-Galston N. Susceptibility locus for IBD on chromosome 16 has a role in Crohn's disease but not in ulcerative colitis. Hum Mol Genet 1996;5:1679–1683.
7. Satsangi J, Parkes M, Louis E, Hashimoto L, Kato N, Welsh KL, Bell JI, Jewell DP. Two-stage genome-wide search in inflammatory bowel disease: evidence for susceptibility loci on chromosomes 3, 7 and 12. Nat Genet 1996;14:199–202.
8. Satsangi J, Welsh KI, Bunce M, Julier C, Farrant JM, Bell JI, Jewell DP. Contribution of genes of the major histocompatibility complex to susceptibility and disease phenotype in inflammatory bowel disease. Lancet 1996;347:1212–1217.
9. Roussomoustakaki M, Satsangi J, Welsh KI, Louis E, Fanning G, Targan S, Landers C, Jewell DP. Genetic markers may predict disease behaviour in patients with ulcerative colitis. Gastroenterology 1997;112:1645–1653.
10. Dekker-Saeys B, Meuwissen S, Van den Berg-Loonen E, Haas WD, Agenant D, Tytgat G. Prevalence of peripheral arthritis, sacroiliitis and ankylosing spondylitis in patients suffering from inflammatory bowel disease. Ann Rheum Dis 1978;37:33–35.
11. Orchard T, Wordsworth B, Jewell D. The peripheral arthropathies of inflammatory bowel disease: their articular distribution and natural history. Gut 1998;42:387–391.
12. Thomson G, Chiu B, deRubeis D, Falk J, Inman RD. Immunoepidemiology of post-*Salmonella* reactive arthritis in a cohort of women. Clin Immunol Immunopathol 1992;64:227–232.
13. Sieper J, Braun J, Wu P, Hauer R, Laitko S. The possible role of *Shigella* in sporadic enteric reactive arthritis. Br J Rheumatol 1993;32:582–585.
14. Herrlinger J, Asmussen J. Longterm prognosis in *Yersinia* arthritis: clinical and serological findings. Ann Rheum Dis 1992;51: 1332–1334.
15. Bunce M, O'Neill CM, Barnardo MC, Krauser P, Browning MJ, Morris PJ, Welsh KI. Phototyping: comprehensive DNA typing for HLA-A, B, C, DRB1, DRB3, DRB4, DRB5 & DQB1 by PCR with 144 primer mixes utilizing sequence-specific primers (PCR-SSP). Tissue Antigens 1995;46:355–367.
16. Mielants H, Veys E, Joos R, Noens L, Cuvelier C, DeVos M. HLA antigens in seronegative spondyloarthropathies. Reactive arthritis and arthritis in ankylosing spondylitis: relation to gut inflammation. J Rheumatol 1987;14:466–471.
17. Brown MA, Kennedy LG, Darke C, Gibson K, Pile KD, Shatford JL, Taylor A, Calin A, Wordsworth BP. The effect of HLA-DR genes on susceptibility to and severity of ankylosing spondylitis. Arthritis Rheum 1998;41:460–465.
18. Mielants H, Veys E, Cuvelier C, DeVos M, Gecmaer S, DeClereq L, Schatterman L, Gyselbreche L, Elevant D. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. J Rheumatol 1995;22:2279–2284.
19. Mielants H, Veys E, Cuvelier C, DeVos M, Gecmaer S, DeClereq L, Schatterman L, Gyselbreche L, Elevant D. The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. J Rheumatol 1995;22:2273–2278.
20. Selby W, Janossy G, Mason D, Jewell D. Expression of HLA-DR antigens by colonic epithelium in inflammatory bowel disease. Clin Exp Immunol 1983;53:614.
21. Cuvelier C, Mielants H, de Vos M, Veys E, Roels H. Major histocompatibility complex class II antigen (HLA-DR) expression by ileal epithelial cells in patients with seronegative spondyloarthropathy. Gut 1990;31:545–549.
22. Hermann E, Fleischer B, Mayet WJ, Poralla T, Meyer zum Buschenfelde KH. Response of synovial fluid T cell clones to *Yersinia* enterocolitica antigens in patients with reactive *Yersinia* arthritis. Clin Exp Immunol 1989;75:365–370.
23. Calin A, Fries JF. An ''experimental'' epidemic of Reiter's syndrome revisited. Follow-up evidence on genetic and environmental factors. Ann Intern Med 1976;84:564–566.
24. Hillarby M, Davies E, Donn R, Grennan D, Ollier W. TAP2D is associated with HLA-B44 and DR4 and may contribute to rheumatoid arthritis and Felty's syndrome susceptibility. Clin Exp Rheumatol 1996;14:67–70.
25. Fraser PA, Stern S, Larson MG, Marcus-Bagley D, Awdeh Z, Glass DN, Alper CA. HLA extended haplotypes in childhood and adult onset HLA-DR4 associated arthropathies. Tissue Antigens 1990; 35:56–59.

Received July 2, 1999. Accepted October 27, 1999.

Address requests for reprints to: T. R. Orchard, M.D., University of Oxford, Radcliffe Infirmary, Gastroenterology Unit, Woodstock Road, Oxford OX2 6HE, England. Fax: (44) 1865-224829.

Supported by a grant from the National Association for Crohn's and Colitis and the Arthritis Research Campaign.