

This Week's Citation Classic

Brewerton D A, Caffrey M, Hart F D, James D C O, Nicholls A & Sturrock R D.
Ankylosing spondylitis and HL-A 27. *Lancet* 1:904-7, 1973.
[Westminster Hospital, London, England]

The inherited antigen now known as HLA B27 was found in 72 of 75 patients with the rheumatic disease ankylosing spondylitis and in three of 75 matched controls. The same antigen was also present in 31 of 60 first-degree relatives. [The SC[®] indicates that this paper has been cited over 385 times since 1973.]

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"It was lunch in the common room at Westminster Hospital on a hot summer day in 1971. As a rheumatologist I had been fascinated for many years by the enigma of ankylosing spondylitis, which is primarily a chronic inflammation of the spine. Its aetiology was unknown except that family studies had indicated a hereditary component. My colleague, David James (head of our tissue-typing laboratory), had recently returned from an international conference at which there were reports of associations between histocompatibility antigens and inherited immune responses in mice and a paper indicating a possible link between HLA antigens and Hodgkin's disease. Over the salad we decided to investigate the frequency of HLA antigens in ankylosing spondylitis.

"There were delays while grantgiving bodies declined to support the project. Caffrey joined James to do the tissue-typing. Nicholls helped me in clinical assessments. Hart and Sturrock were planning a drug trial of patients with spondylitis. Once we had started, the association between HLA B27 and spondylitis

was obvious. Although it now seems strange, we made a joint decision in 1972 that James and Caffrey would write a brief (laboratory oriented) report for *Nature*,¹ while I wrote a longer (more clinical) paper for the *Lancet*. At first the research results appeared too good to be true. We worried that they might be false results produced by an unrecognized component of the disease or by treatment, so we turned to the first-degree relatives, most of whom would not have spondylitis or received treatment. The *Lancet* article was delayed until we learned—to our relief—that 31 of 60 relatives had B27.

"Unknown to us, the association between B27 and spondylitis had been discovered independently by a team in Los Angeles led by Bluestone and Terasaki. Their article in the *New England Journal of Medicine*² was published between our *Nature* and *Lancet* reports, all three appearing within a few weeks. Subsequently, James, Bluestone, and I shared the Robecchi (European) and Geigy (International) prizes for arthritis research. I won the Bose prize of the Royal College of Physicians.

"Before writing the *Lancet* article, we had already established that HLA B27 was also strongly associated with acute anterior uveitis (iritis), seronegative limb arthritis, Reiter's disease, and the spondylitis in patients with psoriasis, ulcerative colitis, and Crohn's disease. In the article we hinted that this might be so but held back the material for three subsequent articles in the *Lancet*. A review was published in 1978.³ From the outset we hoped that B27 would help in the identification of infective agents. The hunt for such agents is now our main endeavour. We received one criticism of our article: it contained no statistical proof that 96 percent and 4 percent were significantly different."

1. Caffrey M F P & James D C O. Human lymphocyte antigen association in ankylosing spondylitis. *Nature* 242:121, 1973.
2. Schlosstein L, Terasaki P I, Bluestone R & Pearson C M. High association of an HLA antigen, W27, with ankylosing spondylitis. *N. Engl. J. Med.* 288:704-6, 1973.
3. Brewerton D A. Inherited susceptibility to rheumatic disease. *J. Roy. Soc. Med.* 71:331-8, 1978.