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# This Week's Citation Classic®

**Bodmer W F.** Evolutionary significance of the HL-A system.
*Nature* **237**:139-45, 1972.
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*Polymorphism, complexity, and selective forces* operating on the HLA system were reviewed. Recombinational and functional data indicated a complex genetic region with many loci whose functions were correlated with the immune system and cellular differentiation and were also somehow interrelated with the immunoglobulins. [The SCI® indicates that this paper has been cited in over 325 publications.]

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I started work that led to the definition of the LA (now A) locus of the HLA system with Rose Payne, and my wife, Julia Bodmer, at Stanford at the beginning of 1963.[1] My contribution, as a population geneticist and statistician trained under the great Sir Ronald Fisher, was initially in approaches to the analysis of the data and their interpretation. By 1972 two major loci had been defined; immune response genes linked to H2 (and, therefore, presumably their counterparts to HLA) had been identified by McDevitt and Benacerraf; the importance of HLA matching for transplantation was being realised; and the association with, but genetical separation from the serological determinants, of the mixed lymphocyte culture reaction had been analysed by Bach and Amos.[2] A small meeting was organised in 1971 at NIH, bringing together some of the main workers in immune response and the HLA field who for many years had been involved in working together in the international collaborative workshops through which the system had very largely been defined. This meeting was to discuss the present state of knowledge of the HLA system, especially in relation to its function, and I was assigned the evolutionary and genetic questions.

The paper in *Nature* grew out of a report I had prepared for the meeting. It emphasised the extraordinarily high level of polymorphism for the system and the ways in which natural selection could generate this through immune response differences that influenced resistance to pathogens. This can create a form of frequency-dependent selection, which is still the most plausible mechanism for maintaining HLA polymorphism despite the explosion in knowledge about the system following the application of biochemical and recombinant DNA techniques.

Even the limited recombination data then available suggested a complex region containing many genes. Included amongst these, it was suggested, would be the immune response genes, and further genes involved in the control of the mixed lymphocyte culture reaction. The suggestion was made that there may also be further genes for differentiation antigens and their "recognisers," both involved in the control of cellular differentiation. These suggestions foreshadowed the discovery in 1974 by Zinkernagel and Doherty[3] of their restriction phenomenon, now interpreted in terms of interactions between the T-cell receptor and HLA region products. The paper finished with a discussion of the possible interrelationships between HLA products and immunoglobulins, a discussion stimulated by a hypothesis that had been put forward by Jerne[4] suggesting that germ line immunoglobulin genes had specificity against the histocompatibility antigen determinants, which I felt was untenable and has not been substantiated. My suggestion in the paper of a direct relation between HLA and immunoglobulins, together with one made independently at about the same time by Gally and Edelman,[5] turned out to be correct but, I now believe, mainly for the wrong reasons.

Knowledge of the HLA system has advanced extraordinarily rapidly,[6,7] and this, in turn, has naturally influenced ideas on the evolution of the system. Unexpected functions such as those of the complement and 21 hydroxylase genes have been found, but so far little or no evidence for differentiation antigens exists, other than in the control of the immune system. Nevertheless, the complexity of the region is still much as predicted in 1972 and many of the ideas suggested then about the generation of polymorphism by selection still remain valid.

1. **Payne R, Tripp M, Weigle J, Bodmer W & Bodmer J.** A new leukocyte isoantigen system in man. *Cold Spring Harbor Symp.* **29**:285-95, 1964. (Cited 115 times.)
2. **Bach F & Amos D B.** Hu-1: major histocompatibility locus in man. *Science* **156**:1506-8, 1967. (Cited 245 times.)
3. **Doherty P C & Zinkernagel R M.** A biological role for the major histocompatibility antigens. *Lancet* **1**:1406-9, 1975. (Cited 205 times.)
4. **Jerne N K.** The somatic generation of immune recognition. *Eur. J. Immunol.* **1**:1-9, 1971. (Cited 680 times.)
5. **Gally J A & Edelman G M.** The genetic control of immunoglobulin synthesis. *Annu. Rev. Genet.* **6**:1-46, 1972. (Cited 265 times.)
6. **Möller G,** ed. Molecular genetics of class I and II MHC antigens 2. *Immunol. Rev.* (Whole issue.) (85), 1985. 168 p.
7. **Albert E D, Baur M P & Mayr W R,** eds. *Histocompatibility testing. 1984.* Berlin: Springer-Verlag, 1984. 764 p.

 