

Bach F & Hirschhorn K. Lymphocyte interaction: a potential histocompatibility test in vitro. *Science* 143:813-4, 1964.

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Lymphocytes from two unrelated individuals, cultured together in the same tube, undergo morphological transformation to large cells and divide. Both of these parameters may be estimated quantitatively. There is a correlation between the degree of this response and the degree of cross-reactivity of grafts from the two individuals placed on a third unrelated recipient. [The *SCI*® indicates that this paper has been cited in more than 490 publications.]

## The Importance of MLC

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The opportunity afforded one in writing a commentary on a paper that has achieved *Citation Classic* status is most unusual. It allows one, by specific invitation from the editor, to reflect personally on what was a well-nigh unique aspect of one's scientific career—in this case, my involvement with K. Hirschhorn in the description of the mixed leukocyte culture (MLC) test, at the same time that Bain and her colleagues published similar data.<sup>1</sup> This was a singular "moment" in my scientific life.

In the very early 1960s, I attended a lecture by Peter B. Medawar, on transplantation. At that time, in a brief interchange, I brazenly suggested to him that such a complex system might best be analyzed in vitro. I reasoned that if lymphocytes carried transplantation antigens and were able to respond to such antigens by blast formation and proliferation (as shown by Medawar, Gowans, L. Brent, and others), then such a response should take place if lymphocytes of two individuals were mixed in culture, i.e., the MLC test. The hope was that the MLC would help address both of the issues about which he had spoken: the antigens recognized and the cellular basis of allograft rejection.

Studies with the MLC have contributed to the description of the MHC in humans (HLA), helped to define the antigenic determinants to which T cells presumably react, and given evidence of the importance of MHC-encoded antigens as the target moieties to which T cells respond.<sup>2,3</sup>

From the perspective of the cells mediating allograft rejection, it must still be a matter of question to which degree the information learned in vitro has helped us to understand allograft rejection in vivo. Certainly our observations that helper T cells ( $T_h$ ) respond preferentially to class II antigens, that cytotoxic T cells ( $T_c$ ) respond primarily to class I antigens, and that the combined class II/class I response leads to collaboration between the  $T_h$  and  $T_c$  to generate the strongest cytotoxic response,<sup>3</sup> is of great importance and has relevance in at least some situations of allografting.<sup>4</sup> (It is this series of observations relating to the MLC that I have always thought are of the greatest importance of those that came from my laboratories.)

I am grateful to the reviewer of the first grant that I ever submitted to the NIH when I established my own laboratory, then at the University of Wisconsin, for his/her generosity of intellect and spirit. The grant was funded with high priority and funding as requested (it was a different age of funding in 1966). However, it included a final comment as follows: "We hope that the applicant, who appears to be a promising young investigator, does not become too enamored by this new test of his...which clearly has limited applicability." Funding of that grant allowed me to continue my studies with the MLC and point to some of its applications. Equally important, it has furnished me, and so many of my students, with decades of great fun.

I have recently discussed many of these issues in greater detail.<sup>5</sup>

1. Bain B, Vas MR & Lowenstein L. The development of large immature mononuclear cells in mixed leukocyte cultures. *Blood* 23:108-16, 1964. (Cited 635 times.)
2. Bach FH & Amos DB. Hu-1: major histocompatibility locus in man. *Science* 156:1506-8, 1967. (Cited 260 times.)
3. Bach FH, Bach ML & Sondel PM. Differential function of major histocompatibility complex antigens in T-lymphocyte activation. *Nature* 259:273-81, 1976. (Cited 550 times.)
4. Bach FH & van Rood JJ. The major histocompatibility complex—genetics and biology. *N. Engl. J. Med.* 295:806-13; 872-8; 927-36, 1976. (Cited 580 times.)
5. Bach FH. The T lymphocyte perspective of HLA: a personal reflection. (Terasaki P, ed.) *History of HLA: ten recollections*. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1991. p. 189-211.

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