

This Week's Citation Classic

Bain B, Vas M R & Lowenstein L. The development of large immature mononuclear cells in mixed leukocyte cultures. *Blood* **23**: 108-16, 1964.

In mixed leukocyte cultures prepared' from pairs of normal unrelated donors, some of the lymphocytes became transformed to large cells capable of mitosis. Subsequent experiments indicated that transformation was stimulated by genetically determined factors in leukocytes. A relationship to transplantation immunity was suggested. [The SC® indicates that this paper has been cited over 505 times since 1964.]

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"My observation of the mixed leukocyte reaction is a classical example of a discovery that was bound to happen. It happened to me because I was in the right place at the right time.

"In the early 1960s, Magdalene Vas came to the Royal Victoria Hospital in Montreal to do research on leukocyte cultures. I was employed as her technician, and I soon became so interested in these studies that I wanted to continue them as a Ph.D. student. Our chief, the late Louis Lowenstein, was enthusiastic about the idea and had me enrolled at McGill University before I had a chance to change my mind.

"Just around this time, Peter Nowell published a paper showing that the bean extract phytohemagglutinin (PHA) could induce normal leukocytes to undergo mitosis¹. Vas and I (undoubtedly along with many others) tried the technique and found that it

worked. Very soon thereafter, it was demonstrated that tuberculin caused mitosis in leukocyte cultures from sensitive individuals, and evidence accumulated that small lymphocytes were the responding cells. It was suggested that PHA and tuberculin stimulated lymphocytes in a manner analogous to immune responses *in vivo*.

"These notions were roaming around inside my head when I read a paper by Schrek and Donnelly, in which they reported large, primitive mitotic cells in a culture containing mixed leukocytes from two donors.² Their main objectives in the study were along other lines, so they made no further comment on this phenomenon. Because of the way my mind was tuned at the time, I suspected that the changes observed in the mixed culture were the result of antigenic differences between the two donors. I immediately recruited two of my colleagues to donate blood for cultures, and five days later I found primitive cells, mitoses, and a topic for my Ph.D. thesis

"My initial assumption, based on no logic whatsoever, was that ABO blood group differences were causing the stimulation. Therefore my first pairs of donors were A and B combinations. I then decided to run a 'negative' control using Vas and myself, both group O. The result was by no means negative, which disproved my poorly conceived hypothesis and cleared the way for a more rational approach to the mixed leukocyte reaction.

"I believe that the interest in my work was due to the novelty of the observation, set against a background of progress and excitement in the areas of lymphocyte function and transplantation immunity. As I indicated at the beginning of this article, I was very fortunate to have a head start in the discovery of the mixed leukocyte reaction: Chapman and Dutton,³ and their rabbits, were close behind!"

REFERENCES

1. **Nowell P C.** Phytohemagglutinin: an initiator of mitosis in cultures of normal human leukocytes. *Cancer Res.* **20**: 462-6, 1960.
2. **Schrek R & Donnelly W J.** Differences between lymphocytes of leukemic and non-leukemic patients with respect to morphologic features, motility, and sensitivity to guinea pig serum. *Blood* **18** : 561-71, 1961
3. **Chapman N D & Dutton R W.** The simulation of DNA synthesis in cultures of rabbit lymph node and spleen cell suspensions by homologous cells. *J. Exp. Med.* **121**: 85-100, 1965.