

Valentine W N & Beck W S. Biochemical studies on leucocytes. I. Phosphatase activity in health, leucocytosis, and myelocytic leucemia.

J. Lab. Clin. Med. 38:39-55, 1951.

[School of Medicine, University of California, Los Angeles, CA]

This paper reported quantitative data on the alkaline and acid phosphatase content of separated human leukocytes. Markedly different alkaline phosphatase activity patterns were demonstrable. In chronic myelocytic leukemia (CML) activity was very low; in most nonleukemic granulocytosis it was strikingly elevated. [The SC[®] indicates that this paper has been cited in over 215 publications since 1961.]

William N. Valentine
Department of Medicine
School of Medicine
Center for the Health Sciences
University of California
Los Angeles, CA 90024

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"In 1948, I came to the newly founded UCLA medical school with J.S. Lawrence, the first chairman of its department of medicine. Earlier research work at the University of Rochester had centered on thalassemia and hematologic aspects of radiation biology. However, I had become convinced that studies of blood cell metabolism at the molecular level should widen the vistas of classical morphology. My coauthor, Bill Beck, now professor of medicine at Harvard and director of the Hematology Research Laboratory at Massachusetts General Hospital, joined our laboratory after his residency at Wadsworth Veterans Administration Hospital. We determined to investigate the phosphatase activity of human leukocytes (isolation techniques were now available), and correlate this quantitatively with hematologic parameters and disease entities.

"This fortunate choice was motivated largely by the fact that certain leukocytes were known to possess alkaline phosphatase activity, and the techniques involved were within the capabilities of our modest laboratory. We soon became ex-

cited by the uniformly low activity in chronic myelocytic leukemia (CML) and the contrastingly striking elevations in most nonleukemic granulocytosis. Perhaps more exciting was the observation that in polycythemia vera (PRV) and certain myeloproliferative syndromes, granulocyte populations morphologically similar to those of CML possessed very high alkaline phosphatase activity (reported in a companion paper¹). At one point, with the help of John H. Lawrence, director of the Donnor Laboratory, Beck and I packed up our instrumentation and traveled to Berkeley. There, in 48 hours, we studied 15 subjects with CML, PRV, and other myeloproliferative syndromes. These were patients in the large clinic supervised by Lawrence. The companion report¹ also documented the characteristically low alkaline phosphatase activity in the leukocytes in paroxysmal nocturnal hemoglobinuria. Although it had received essentially no attention by clinicians and we initially had missed it, Beck and I soon realized that what we believed to be a 'first' was not. Wachstein had observed similar metabolic patterns in CML and PRV utilizing histochemical techniques.²

"Beck later left Los Angeles to work with Severo Ochoa and to be recruited by the late Walter Bauer to the Harvard faculty. During the next several years, my laboratory made additional observations on the high and low activity patterns in different morbid states, the effect of corticosteroids on leukocyte alkaline phosphatase, and on the role of Zn^{++} and the substrate specificities of the enzyme. The widely variant patterns in morphologically similar cells in myeloproliferative syndromes strongly suggested heterogeneous etiologies. The observation that a few (but by no means most) therapeutically induced remissions in CML were accompanied by apparent reversion of leukocyte alkaline phosphatase to normal with restoration of normal responsiveness to corticosteroids prompted us to raise the possibility that in CML a suppressed normal clone would still exist in conjunction with a dominant leukemic clone.^{3,4}

"This paper has been highly cited largely because of the interest in the correlations of enzyme activity with certain disease states such as those observed in various myeloproliferative disorders. Recently, Hayhoe and Quaglino⁵ have extensively reviewed the literature on leukocyte alkaline phosphatase in health and disease."

1. Beck W S & Valentine W N. Biochemical studies on leucocytes. II. Phosphatase activity in chronic lymphatic leucemia, acute leucemia, and miscellaneous hematologic conditions. *J. Lab. Clin. Med.* 38:245-53, 1951.
2. Wachstein M. Alkaline phosphatase activity in normal and abnormal blood and bone marrow cells. *J. Lab. Clin. Med.* 31:1-17, 1946.
3. Valentine W N, Follette J H, Solomon D H & Reynolds J. Biochemical and enzymatic characteristics of normal and leukemic leukocytes (with particular reference to leukocyte alkaline phosphatase). (Rebeck J W, Bethell F H & Monto R W, eds.) *The leukemias: etiology, pathophysiology, and treatment*. New York: Academic Press, 1957. p. 457-65.
4. Valentine W N. The metabolism of the leukemic leucocyte. *Amer. J. Med.* 28:699-710, 1960.
5. Hayhoe F G J & Quaglino D. *Haematological cytochemistry*. London: Churchill Livingstone, 1980. p. 105-45.