

Giblett E R, Ammann A J, Wara D W, Sandman R & Diamond L K.

Nucleoside-phosphorylase deficiency in a child with severely defective T-cell immunity and normal B-cell immunity. *Lancet* 1:1010-13, 1975.
[King County Central Blood Bank, Inc., Seattle, WA and Divs. Pediatric Immunol. and Hematol., San Francisco Medical Ctr., Univ. California, CA]

This paper describes a child with normal B-cell function but severe T-cell deficiency resulting in severely restricted cellular immunity. Her blood cells contain no purine nucleoside phosphorylase (PNP) activity, and her parents have less than half normal levels. These findings suggest an autosomal recessive defect primarily affecting T cells. [The SCI® indicates that this paper has been cited in over 410 publications since 1975.]

nucleoside phosphorylase (PNP). Since the PNP activity of her consanguineous parents was well below normal, we postulated, again in *Lancet*, that this syndrome was also inherited as an autosomal recessive and that the PNP deficiency caused the T-cell dysfunction. Ten more patients with a similar clinical syndrome and selected T-cell deficiency associated with defective PNP have subsequently been reported from various parts of the world.^{2,3}

A very recent symposium at the New York Academy of Sciences⁴ showed the extent to which our initial findings have been expanded. The symposium was composed of papers on the relationship of purine metabolism to immune deficiency, the use of ADA and PNP substrate analogs in the treatment of lymphoid malignancies, and the molecular biology of the two enzymes, whose genes have both been cloned.

Our papers on ADA and PNP deficiencies have been frequently cited because they described the first known examples of "inborn errors" of metabolism specifically affecting lymphocytes, and, thereby, immune function. Also, our findings led to the discovery that the intracellular accumulation of deoxyadenosine and deoxyguanosine, which occurs in ADA and PNP deficiencies respectively, is toxic to lymphocytes. This toxic effect appears to be due to inhibition of ribonucleotide reductase activity, thus impairing the synthesis of DNA. The increased susceptibility of T cells to deoxyguanosine toxicity reflects different complements of nucleoside kinases and, possibly, nucleotidases, in T cells as compared with B cells. It has also been postulated that inhibition of s-adenosylhomocysteine hydrolase is another metabolic deterrent in ADA deficiency.⁵

Although there is no convincing documentation that other inherited enzymopathies cause specific immune defects, I feel certain that such instances will eventually be uncovered.

I was elected to membership in the National Academy of Sciences in 1980. No doubt part of the reason for my selection was our discovery of these two enzyme deficiencies. However, I would like to believe it was also based on our much more extensive work on the genetic markers in blood.⁷

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In 1972, my pediatrician colleagues and I described two unrelated children with severe combined immunodeficiency disease whose blood cells lacked adenosine deaminase (ADA).¹ We suggested that the defective immunity was caused in some way by the enzyme deficiency and that the condition was inherited as an autosomal recessive.

That paper, published in *Lancet*, was widely read and subsequently became a *Citation Classic*.¹ It stimulated other investigators to look for similar cases (over 30 more were soon found) and to explain the biochemical basis for the immune defect. I was stimulated to search among immunodeficient patients for defects in other enzymes of the purine, pyrimidine, and nucleic acid metabolic pathways. In 1975, Arthur Ammann, Diane Wara, and Louis K. Diamond at the University of California sent a blood specimen to my lab from a child whose B-cell function was normal, but whose T cells were sparse and hypofunctional. We found that her blood cell ADA levels were normal, but there was no measurable activity of purine

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2. Pollara B, Pickering R J, Meuwissen H J & Porter I H, eds. *Inborn errors of specific immunity*. New York: Academic Press, 1979. 469 p.
3. Elliot K & Whelan J, eds. *Enzyme defects and immune dysfunction*. Amsterdam: Excerpta Medica, 1979. 289 p.
4. Tritsch G L, ed. Adenosine deaminase in disorders of purine metabolism and in immune deficiency. *Ann. NY Acad. Sci.* To be published, 1985.
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6. Giblett E R. *Genetic markers in human blood*. Oxford: Blackwell Scientific, 1969. 629 p. (Cited 645 times.)