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This Week's Citation Classic

Giblett E R, Anderson J E, Cohen F, Pollara B & Meuwissen H J. Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. *Lancet* 2:1067-9, 1972. [King County Central Blood Bank, Inc., Seattle, WA; Children's Hosp. Michigan, Dept. Pediat., Wayne State Univ., Detroit, MI; and Dept. Pediat., Albany Med. Coll., Kidney Dis. and Birth Defects Insts., State of NY Dept. Health, Albany, NY]

This paper describes two unrelated children with severe immunodeficiency whose blood cells contain no adenosine deaminase activity. It suggests that the parents in each case are heterozygous and the children homozygous for a 'silent' allele and that adenosine deaminase may be necessary for normal immune function. [The SCI® indicates that this paper has been cited over 555 times since 1972.]

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"Working in a blood bank provides an excellent opportunity to investigate human genetic systems involving blood cell antigens, electrophoretic polymorphisms, and plasma protein variants. Studies of such genetic markers formed the basis of a book I wrote in 1969,[1] and I often receive blood specimens sent for tests to evaluate, for example, the fate of transplanted bone marrow. In 1972, Albany pediatricians Hilaire Meuwissen and Bernard Pollara asked me to determine the red cell antigens and isozymes of a child with combined immunodeficiency and her mother, the potential bone marrow donor. In Seattle, Jeanne Anderson (my assistant) and I were astonished to find that adenosine deaminase (ADA, a polymorphic enzyme) was missing from the child's blood cells, and her (consanguineous) parents had very low ADA levels. These findings suggested that the parents were heterozygous and the child homozygous for a 'silent' allele at the structural gene locus for ADA. Several weeks later, I received a telephone call from my old friend Flossie Cohen—a pediatric immunologist visiting Seattle from Detroit. I asked her if she had any patient with severe immunodeficiency disease whose blood we might test for ADA and she said yes. To our amazement, we found the same ADA anomalies in that patient and family. We reported this remarkable coincidence of two cases of ADA deficiency with immunodeficiency in the *Lancet* paper. Subsequently, over 30 more cases have been described.

"Because of our serendipitous finding, we set up assays for several additional enzymes in the purine, pyrimidine, and nucleic acid pathways. In 1975, Arthur Ammann, Diane Wara, and Louis K. Diamond at the University of California sent us blood from a child with normal B cells but a numerical and functional T-cell deficiency. We found that her blood cells had normal ADA but no measurable purine nucleoside phosphorylase (PNP) activity, and her (consanguineous) parents had low PNP levels.[2] Ten more children with this inherited anomaly and selective T-cell dysfunction were later described.

"The paper on ADA deficiency is frequently cited because it demonstrated the unique importance of purine metabolism in lymphoid cells and showed that some cases of immune deficiency have a biochemical basis. Many laboratory investigators were stimulated into action by that paper; I wish there were sufficient space to mention all their names, especially my colleagues at the University of Washington. Most participated in two 1978 symposia that brought together the genetic, immunologic, biochemical, clinical, and therapeutic findings in ADA and PNP deficiency.[3,4] The impaired immunity in these patients is now ascribed to the unique kinases in lymphoid cells that (in the absence of ADA or PNP) cause accumulation of deoxyribonucleotides. The latter inhibit the action of ribonucleotide reductase and thereby the synthesis of DNA. Inhibition of S-adenosylhomocysteine hydrolase may also play a role. Differences between the kinases, and perhaps the nucleotidases, in B and T cells account for the selective susceptibility of T cells to PNP deficiency.[5] I am confident that further research will uncover additional biochemical defects that cause immunodeficiency."

1. **Giblett E R.** *Genetic markers in human blood.* Oxford: Blackwell Scientific Publishers, 1969. 629 p.
2. **Giblett E R, Ammann A A, 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.
3. **Pollara B, Pickering R J, Meuwissen H J & Porter I H, eds.** *Inborn errors of specific immunity: proceedings of a Symposium on Inborn Errors of Specific Immunity, held in Albany, New York, 16-18 October 1978.* New York: Academic Press, 1979. 469 p.
4. **Elliott K & Whelan J, eds.** *Symposium on Enzyme Defects and Immune Dysfunction, London, 1978.* Amsterdam: Excerpta Medica, 1979. 289 p.
5. **Carson D A, Lakow E, Wasson D B & Kamatani N.** Lymphocyte dysfunction caused by deficiencies in purine metabolism. *Immunol. Today* 2:234-8, 1981.