

This Week's Citation Classic

Nezelof C, Jammet M L, Lortholary P, Labrune B & Lamy M. L'hypoplasie héréditaire du thymus: sa place et sa responsabilité dans une observation d'aplasie lymphocytaire, normoplasmo-cytaire et normoglobulinique du nourrisson. *Arch. Fr. Pédiat.* 21:897-920, 1964.

This paper reports a new form of hereditary immunodeficiency, characterized by peripheral lymphocytosis, thymic hypoplasia, and the presence of plasma cells and normal or subnormal serum immunoglobulins. This form demonstrates in man the functional, morphologic, and genetic delineation in lymphoid tissue development. [The SC[®] indicates that this paper has been cited over 155 times since 1964. This is the most cited paper from this journal 1961-1980.]

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"In 1961, I was a pediatrician and was just finishing my training as a pathologist. Clinical immunology was still in its infancy and, at the time, to most pediatricians, could be summed up as the findings of immunoelectrophoresis and antibody evaluation. The thymus was then considered to be an organ for storing lymphocytes which somehow aided growth.

"By chance, in the department of the esteemed Maurice Lamy at Hôpital des Enfants Malades in Paris, we encountered a 14-month old boy who, from the age of three months, had suffered from repeated digestive and respiratory infections.

"This history and a persistent blood lymphopenia suggested a primary immune deficiency, of course, but this diagnosis was finally and resolutely eliminated on the basis of normal electrophoreses and the presence of a small amount of anti-APC antibodies. The child died at 16 months and his autopsy revealed two disturbing facts: first, a thymic tissue lacking both thymocytes and corpuscles, so unusual that I had some difficulty in identifying it as such; and secondly, a peripheral lymphocytosis affecting essentially the small lymphocytes but, strangely and unexpectedly,

sparing the plasma cells.

"Perplexed by the contradictory findings published in the 1960 *Ciba Foundation Symposium on Cellular Aspects of Immunity*,¹ I did not immediately grasp the significance of the case. Fortunately, through reading the excellent general review published by G. Fabiani and A. Delaunay² and attending a symposium organized by R.A. Good in the Netherlands, I became acquainted with the experimental work done by J.F.A.P. Miller³ and Good and his co-workers⁴ on the role of the thymus in the development of cellular immunity and on the probable dichotomy of lymphoid tissue.

"From then on, the almost experimental character of the case history became clear, for it demonstrated for the first time that the lymphocytic and plasmocytic lineages were independent. These lineages were soon to be dubbed 'thymodependent' and 'thymus-independent.' It also revealed the crucial nature of thymic lesions.

"This paper has been highly cited for the following reason: like the cases of congenitally absent thymus, reported by Di George in 1966,⁵ this publication was well received and drew a large audience because it appeared at the right moment, that is to say, at a time when immunologists needed to document in humans the experimental findings of T and B dichotomy of lymphoid tissue, already well established in chickens, and to demonstrate in man the vital role of thymic epithelial tissue in the maturation of peripheral lymphoid tissue, as well as to establish a coherent classification of primary immunodeficiency diseases. Furthermore, it kindled hopes of discovering, in man, the equivalent of the bursa of Fabricius. The golden age of thymology had begun.

"Fifteen years later, we are still surprised by the success which this single case history has had, because, in fact, it reported only clinical pathological findings and did not contain any real immunological investigation. At any rate, this case report opened up the gates of immunopathology for me, which at the time were narrow, and allowed me to deal with T cell immunodeficiencies."⁶

1. Wolstenholme G E W & O'Connor M, eds. *Ciba Foundation Symposium on Cellular Aspects of Immunity*. Boston: Little, Brown, 1960. 495 p.
2. Fabiani G & Delaunay A. Un probWme d'actualité- la place du thymus en immunologie. *Biol. Méd.* 52:446-91, 1963.
3. Miller J F A P. Immunity and the thymus. *Lancet* 1:43-5, 1963.
4. Good R A, Martinez C, Archer O K & Papermaster B W. Role of the thymus in development of immunity. *J. Clin. Invest.* 41:1361, 1962.
5. Di George A M, Dacou C, Lischner H W & Arey J B. Congenital absence of the thymus and its immunologic consequences concurrent with congenital hypoparathyroidism. *Program and abstracts: Seventy-Sixth Annual Meeting of the American Pediatric Society. 27-28 April 1966. Atlantic City. St. Louis: American Pediatric Society, 1966. p. 29.*
6. Gosseye S & Nezelof C. T system immunodeficiencies in infancy and childhood. *Pathol. Res. Pract.* 171:142-58, 1981.