

# This Week's Citation Classic

Gatti R A & Good R A. Occurrence of malignancy in immunodeficiency diseases: a literature review. *Cancer* 28:89-98, 1971.  
[Depts. Pediatrics and Pathology, Univ. Minnesota, Minneapolis, MN]

**This report reviews the frequency and types of cancer which are seen among patients, mainly children, with various forms of immunodeficiencies. While the frequency we originally reported was probably overestimated, it is still a dramatic fact that such patients develop cancer between 100-1,000 times more commonly than the general population of similar age. Lymphoid cancer far predominates other kinds, although this spectrum alters slightly from one primary immunodeficiency to another. [The SCI® indicates that this paper has been cited over 285 times since 1971.]**

Richard A. Gatti  
Department of Pathology  
School of Medicine  
University of California  
Los Angeles, CA 90024

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"This report added great credibility to the then-incubating hypothesis that defective immunosurveillance mechanisms might underlie the pathogenesis of cancer. When I arrived for my fellowship in immunology with R. A. Good, there was a consensus that the cancer incidence was higher than normal among patients with immunodeficiencies and those receiving long-term immunosuppression following renal transplants. In the literature, I found mainly anecdotes and hypotheses about immunosurveillance, so Good and I felt it important to document the frequency and types of malignancy in patients with immunodeficiencies.

"With time, tumor-specific antigens were shown to be tumor-associated. Law's neonatally thymectomized mice with abundant tumors were overshadowed by the observation that nude mice, born without thymuses, develop little or no cancer.<sup>1</sup> The idea that blocking antibodies protect neuroblastoma cells from destruction by circulating killer lymphocytes bogged down in technological controversy. The latest fashionable hypothesis is that interferon turns on natural killer cells and that these cells may be important in immunosurveillance, if that exists. What remains the single most convincing observation to support a role for immunosurveillance is our review showing

that patients with primary immunodeficiencies do develop cancer with a consistently high frequency. No doubt this accounts for the frequent citing of the reference.

"Good suggested that we establish an international Immunodeficiency-Cancer Registry so as to learn more about this provocative relationship. In late 1971, shortly before I left Minneapolis to join George Klein's department of tumor biology at the Karolinska Institute, I handed over my bulging files to Kersey and Spector, who then initiated such a registry. The registry now contains over 350 case reports.<sup>2</sup> The expanded data base has confirmed the dominance of lymphoid cancer among immunodeficiency patients. It has also made us recognize that if immunodeficiency were the primary defect responsible for oncogenesis, the spectrum of cancers seen in these patients would not differ substantially from those seen among the general population.

"That 'a major role for immunity in oncogenesis seems almost certain,' now seems uncertain. A minor role now seems more certain! Immunologic responses are a secondary or, possibly even, tertiary event in tumor development: the initial transformation occurs at a genetic level. Our recent focus on immunogenetics is now yielding more basic information as we try to map cancer susceptibility genes in high-cancer risk families.<sup>3</sup> Perhaps we jumped too quickly away from biochemistry and virology, then too quickly again from serological immunology into the vagaries of cellular immunology. Perhaps after the basic mechanisms of malignant transformation have been elucidated, the principles of tumor immunology will take on new significance, for example, in immunotherapy.

"Anecdote. The degree of 'DABP' (as appears after MD in the original publication) was my way of rebelling against pediatricians who often cite in their papers the title 'FAAP' (i.e., Fellow of the American Academy of Pediatrics). The difference, if you pass your pediatrics board exams, you become a Diplomat of the American Board of Pediatrics (DABP). If you then contribute \$180.00 a year, you are an FAAP. DABP seems the more relevant of the two."

1. Law L W. Studies of thymic function with emphasis on the role of the thymus in oncogenesis. *Cancer Res.* 26:551-74, 1966.
2. Spector B, Perry G & Kersey J. Genetically-determined immunodeficiency diseases (GDID) and malignancy. Report from the Immunodeficiency-Cancer Registry. *Clin. Immunol. Immunopathol.* 11:12-29, 1978.
3. Gatti R A, Spence A, Sparkes R, Harris N & Freidin M. Association of cancer susceptibility with the major histocompatibility complex (MHC). *Proc. Amer. Assn. Cancer Res.* 22:67a, 1981.