

This Week's Citation Classic

Stiehm E R & Fudenberg H H. Serum levels of immune globulins in health and disease: a survey. *Pediatrics* **37**:715-27, 1966.

[Dept. Pediatrics and Hematology Unit, Dept. Med., Univ. California Sch. Med., San Francisco, CA]

Serum levels of IgG, IgM, and IgA immunoglobulins were determined on 296 normal infants and children at various ages and in 30 adults. The technique employed radial immunodiffusion in agar, using monospecific antisera. The marked alterations of immunoglobulins with age, particularly in the first year of life, necessitate comparison of the immunoglobulins obtained on any pediatric patient with appropriate age-matched controls. [The SC[®] indicates that this paper has been cited over 425 times since 1966.]

E. Richard Stiehm
Department of Pediatrics
School of Medicine
University of California
Los Angeles, CA 90024

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"This paper, prepared during a pediatric immunology fellowship in Hugh Fudenberg's laboratory at the University of California-San Francisco Medical Center, was conceived because of three factors. The need throughout pediatrics for standard values of immunoglobulins at different ages; the availability of a then unpublished new method, radial immunodiffusion, for quantitating immunoglobulin levels with a minimum of antiserum and effort; and the availability of 300 sera from infants and young children at various ages as a result of an ongoing trial of killed measles vaccine.

"In 1963, when this work was started, the only study of IgG, IgM, and IgA immunoglobulin levels in infants and children was by C.D. West, R. Hong, and N.H. Holland, in which the levels for IgA and IgM were reported in units, and the method was a cumbersome and inaccurate quantitative immunoelectrophoresis.¹ J.P. Vaerman of Belgium, a postdoctoral scholar in Fudenberg's laboratory, had worked with radial immunodiffusion in the laboratory of the late J.F. Heremans, and taught it to me prior to

publication. We prepared rabbit antisera against human IgG (Cohn Fraction II), IgA myeloma, and IgM macroglobulinemia proteins, and absorbed them repeatedly with agammaglobulinemic serum, and other immunoglobulins until they were monospecific. The antisera available commercially at that time was of limited availability and of poor strength and specificity.

"The method was an important advance, permitting 20 or more analyses with .1-.2 ml of antisera and with reproducibility of $\pm 10\%$. Subsequently, it was (and is) used, with minor modifications, by numerous hospital laboratories and in commercial kits. The paper usually quoted for the radial immunodiffusion method is J.L. Fahey and E.M. McKelvey² or G. Mancini et al.³

"The marked alterations in immunoglobulin levels with age and the expanding recognition of primary antibody immunodeficiencies in young infants necessitated this detailed study to correctly interpret immunoglobulin levels at any age. The tables and graphs of IgG, IgM, and IgA changes with age have been reproduced in innumerable textbooks of pediatrics, immunology, and laboratory methods; they are still the standard reference in most studies of immunoglobulin levels in children.

"Two other aspects of this study have been frequently quoted. One is the immunoglobulin abnormality of mongolism (high levels of IgG and IgA, and low IgM) which has contributed to an extensive literature on the immunologic defect in this genetic disorder. Second, and considerably more important, is the IgM level in cord blood from normal infants. Elevated levels of cord blood IgM (> 20 mg/dl) were noted in a sub-sequent study of newborns with congenital infection (i.e., rubella, cytomegalovirus, etc.).⁴ This led to the IgM screening test used in nurseries to identify infants with suspected congenital infection. Without the normal values established by the 1966 paper, we would not have been able to recognize the subtle but definite IgM elevations present in congenitally infected infants."

1. **West C D, Hong R & Holland N H.** Immunoglobulin levels from the newborn period to adulthood and in immunoglobulin deficiency states. *J. Clin. Invest.* **41**:2054-64, 1962.
2. **Fahey J L & McKelvey E M.** Quantitative determination of serum immunoglobulins in antibody-agar plates. *J. Immunology* **94**:84-90, 1965.
3. **Mancini G, Carbonara A O & Heremans J F.** Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* **2**:235-54, 1965.
4. **Stiehm E R, Ammann A J & Cherry J D.** Elevated cord macroglobulins in the diagnosis of intrauterine infections. *N. Engl. J. Med.* **275**:971-5, 1966.