

This Week's Citation Classic®

Rose N R & Witebsky E. Studies on organ specificity. V. Changes in the thyroid glands of rabbits following active immunization with rabbit thyroid extracts. *J. Immunol.* 76:417-27, 1956.

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Totally thyroidectomized or partially thyroidectomized rabbits injected with extracts of their own thyroid glands produced antibodies reacting with their own thyroglobulin. Histological examination showed severe inflammatory changes in the residual thyroid tissue of the immunized animals. [The *SCI*® indicates that this paper has been cited 315 times. It was part of a series of articles that have been cited in more than 900 publications.]

Experimental Autoimmune Thyroiditis

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This paper showed that it is possible to immunize an animal with antigenic material from its own body and thereby to induce an autoimmune disease. It represented a clear violation of Paul Ehrlich's famous dictum, *horror autotoxicus* (fear of self-poisoning), which, in 1956, was universally accepted and interpreted to mean that such autoimmunization is impossible. There were, in fact, several earlier examples of autoimmunity involving the lens of the eye, the brain, and the sperm, but these exceptions to the rule were attributed to the anatomical isolation of these tissues. It was difficult to extend the concept of inaccessible antigen to a well-vascularized tissue like the thyroid gland.

These studies caused a profound change in immunologic thinking. They entered directly into Burnet's reasoning when he propounded his selective theory of antibody formation. They were equally important in creating a new area of clinical immunology.

The remarkable similarity of the histological changes in autoimmunized rabbits and in patients with certain forms of chronic thyroiditis stimulated Ernest Witebsky and me to study patients with that disease. We were soon able to show that autoantibodies to thyroglobulin are present in the sera of many patients with chronic

inflammatory thyroid disease. These findings were published separately during the following year.¹ Similar results were obtained independently by a British group.² In our article, we speculated that many other human diseases might prove to be due to autoimmunization, and we set forth a series of criteria to establish the autoimmune etiology of a human disease.

As we predicted, a number of autoimmune diseases, such as diabetes and myasthenia gravis, are now believed to be attributable to autoimmunization. Chronic thyroiditis and its experimental counterpart, however, have remained a valuable paradigm of autoimmune disease. Among the "firsts" discovered with this model were the association of autoimmune disease with the major histocompatibility complex³ and the suppression of autoimmunity by large doses of soluble antigen.⁴ A recently published book on organ-specific autoimmunity, authored by former students and colleagues, provides an indication of the lively research continuing in this field.⁵

One may wonder why an article on experimental immunization is included in a series entitled "Studies on organ specificity." Research in this area began when I joined Witebsky's Department of Bacteriology and Immunology at the University of Buffalo, New York, in 1951. My arrival provided the opportunity for resuming research Witebsky had begun in Germany, before his departure in 1932, centering on antigens that are unique for particular tissues. Witebsky felt strongly that these antigens had to be related to the specialized functions of differentiated cells and that they would be useful in demonstrating differences between normal and malignant cells. It occurred to us later that organ-specific antigens, so limited in their distribution, were the constituents of the body most likely to engender an autoimmune response. In more modern parlance, these antigens are least capable of inducing clonal deletion in the thymus or of avoiding other homeostatic mechanisms that normally prevent immunological self-destruction.

1. Witebsky E, Rose N R, Terplan K, Paine J R & Egan R W. Chronic thyroiditis and autoimmunization. *J. Amer. Med. Assn.* 164:1439-47, 1957. (Cited 310 times.)
2. Roitt I M, Doniach D, Campbell P N & Vaughan Hudson R. Auto-antibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet* 2:820-1, 1956. (Cited 415 times.)
3. Vladutiu A O & Rose N R. Autoimmune murine thyroiditis. Relation to histocompatibility (H-2) type. *Science* 174:1137-9, 1971. (Cited 250 times.)
4. Kong Y M, Okayasu I, Giraldo A A, Beisel K W, Sundick R S, Rose N R, David C S, Audibert F & Chedid L. Tolerance to thyroglobulin by activating suppressor mechanisms. *Ann. NY Acad. Sci.* 392:191-209, 1982. (Cited 30 times.)
5. Bigazzi P E, Wick G & Wicher K. *Organ-specific autoimmunity*. New York: Dekker, 1990.

*Received August 3, 1990