In The Beginning

Noel R. Rose BS AM MD PhD FCAP FAAAAI

Department of Pathology and Department of Molecular Microbiology and Immunology, The Johns Hopkins Schools of Medicine and Public Health, Baltimore, MD, USA

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In 1957, an article published in the *Journal of the American Medical Association* (*JAMA*) changed the immunologic world [1]. It summarized over 3 years of intensive research by a team of investigators at the State University of New York at Buffalo, proving for the first time that a common human disease, chronic lymphocytic (Hashimoto) thyroiditis, is due to autoimmunization. This review summarizes my own involvement in this body of work, initially at Buffalo and then at Johns Hopkins. I recount my personal background that brought me to it, and describe the subsequent changes in immunologic thinking and medical practice that stemmed from the original discovery.

THE DECADE OF THE 1950S AND BEFORE: GENESIS

My interest in biomedical research was ignited in the seventh grade. Our biology teacher brought into class his personal monocular microscope and gave us, as young students, the opportunity to look at our own bodies in a new way. I was amazed, as was Anton van Leewenhock two centuries before, at this unseen world of microorganisms thriving on our skins and between our teeth. Enthralled by the observation, I decided at an early age that studying the effects of our microbial inhabitants on human health and disease would be my future career.

In the subsequent years, I pursued all of the courses and research opportunities available in microbiology first at Yale University as an undergraduate and then at the University of Pennsylvania as a graduate student. Following receipt of a PhD degree from the University of Pennsylvania, I accepted a junior faculty appointment at the University at Buffalo with a commitment to complete my medical training and thus receive qualifications in both medicine and basic biologic science.

In Buffalo I joined the recently created Department of Bacteriology and Immunology under the leadership of Professor Ernest Witebsky who was already world famous for isolating the blood group A and B substances. He was long interested in the organ-specific antigens that distinguish the specialized cells of the body. Frequently called tissue-limited antigens, these substances reflect the unique function of each cell within the organ and provide valuable insights into the fundamentals of cellular differentiation and metabolism. Witebsky predicted that organ-specific antigens would be of great importance in understanding normal physiology as well as disease, and in developing immunologic therapy for cancer [2].

Most of Witebsky's personal research was conducted using alcoholic extracts of tissues which probably represented glycolipids of cell membranes. The rationale for this approach was based on the extensive studies of cardiolipin, the alcohol-soluble antigen used in the serologic test for syphilis. Witebsky was following the precepts of his teacher Hans Sachs, himself one of the two key students of the great immunologist, Paul Ehrlich.

When I joined his department, Witebsky suggested that I look at the organ-specific antigen from the thyroid gland, thyroglobulin. At that time it was considered one of the rare proteins with clear-cut organ specificity. However, the methods for studying proteins in their native state were still limited, and Witebsky suspected that the organ specificity of thyroglobulin might be an artifact due to denaturation of the protein during its preparation. Since I had good training in biochemistry, I set about developing a gentle method of preparing thyroglobulin by the step-wise addition of ammonium sulfate to simple saline extracts of thyroid. It was quite easy to prepare thyroglobulin with nearly 90% purity. By making thyroglobulin from a number of different species and then immunizing rabbits with the products I readily confirmed that this protein antigen is strongly organ specific. The rabbit antibodies reacted strongly with thyroglobulin and barely, if at all, with any other organ of the species. Moreover, rabbit antisera induced by thyroglobulins of one species cross-reacted with similarly prepared thyroglobulins from other mammalian species.

Despite my great care in preparing the thyroglobulin in a gentle fashion, Witebsky was still concerned that it may have been denatured. I decided, therefore, to perform the critical experiment. All of us as medical students had learned the dictum of Ehrlich, *horror autotoxicus*. It taught us that the body refuses to produce autoantibodies because they would inflict harm. As a disciple of Ehrlich and as a blood grouper, Witebsky was a strong, vocal advocate of the validity of the *horror autotoxicus* law and agreed that a native protein injected into the same animal would fail to induce antibody formation. Therefore, I

carefully prepared rabbit thyroglobulin and immunized rabbits with this material. Since the amount of thyroglobulin was very limited, I adopted a then new method of immunization employing complete Freund adjuvant. My first results were highly disturbing; injection of rabbit thyroglobulin into rabbits indeed did induce thyroglobulin-specific antibody. Fearing there might be allogeneic differences among rabbits, I went on to prepare thyroglobulin from a single rabbit and injected it into the same animal. Once more, autoantibodies appeared.

Despite these results, I felt strongly that I had prepared thyroglobulin in the most careful fashion. Suppose, I reasoned, I had actually immunized the rabbits with thyroglobulin in a natural (or nearly natural) state, what would happen to the rabbit's own thyroid gland? Therefore, I removed thyroids from the immunized animals and asked Kornel Terplan, professor of pathology, to examine them. He soon reported that the glands were grossly infiltrated with monocytic cells and granulocytes with evidence of fibrosis and even germinal center formation. It was, he suggested, a replica of the human disease, chronic lymphocytic (Hashimoto) thyroiditis.

In those days, the only autologous antigens known to induce an autoimmune response were the sequestered antigens in "privileged sites." They included antigens from the brain, the lens of the eye, and sperm. The idea that the thyroid gland, a well-vascularized tissue, could contain an autoantigen capable of inducing disease seemed highly unlikely. Before he would accept these startling results, Witebsky insisted that I reproduce the phenomenon in other species. I succeeded in doing so in guinea pigs and dogs. Some of the dogs, in fact, produced particularly severe thyroiditis. As a final step, I performed the ultimate experiment of preparing thyroglobulin from one lobe of a rabbit, used to immunize the very same animal. Its remaining thyroid lobe could then be shown to develop thyroid infiltration. For these surgical experiments, I turned to the chairman of surgery, Dr. John Paine, and his assistant, Dr. Richard Egan.

When all these results were assembled, Witebsky had to accept the reality that Ehrlich's biologic dictum of *horror autotoxicus* did not apply to thyroglobulin and that this human disease, chronic lymphocytic thyroiditis, was likely the result of autoimmunization. Through Dr. Paine's connections, we laboriously collected about a dozen sera samples from patients with various thyroid diseases and found that at least four of them contained potent antibodies to human thyroglobulin. These four patients had severe thyroiditis.

After 3 years of intensive work, we agreed that we had completed the circle of evidence to prove that human chronic lymphocytic thyroiditis is an example of a human disease caused by autoimmunization. In order to announce these results, Witebsky contacted Dr. John Talbot, former professor of medicine at Buffalo, who had just become Editor-in-Chief of *JAMA*. They agreed this journal was the appropriate one since it would be read not only by practicing physicians but also by the leading medical investigators. Witebsky and I spent a great deal of time preparing the article as thoroughly, but cautiously, as possible. As we concluded our labors and prepared to submit the paper, Witebsky exclaimed that it may well demolish an accepted medical dogma. Many enigmatic human diseases might now be attributed to autoimmunity. There should be some way, I decided, of critically evaluating the evidence before declaring a human disease to be autoimmune. Koch's Postulates had served infectious disease research very well for almost a century. A similar set of postulates might provide valuable guidelines for future studies of autoimmunity. From that came the four "Witebsky Postulates" which established a rational basis for declaring a human disease to be autoimmune in etiology.

The *JAMA* article created quite a stir. It was one of the 100 most cited papers in biology at that time. It generated, as Witebsky predicted, numerous claims that a particular human illness is due to autoimmunization. Years later, I revisited the original postulates and developed a three-tiered approach to decide that a human disease is due to autoimmunity based on direct, indirect and circumstantial levels of evidence [3].

As our work was being publicized, another line of investigation appeared that led to general acceptance of autoimmunity as an important cause of many human diseases. Dr. Peter Miescher, then in Basel, Switzerland, provided compelling evidence that the lupus erythematous (LE) cell described in the bone marrow of lupus patients by Hargraves represented phagocytosis of nuclear material [4]. This phagocytic phenomenon resulted from opsonization of the nucleus by antinuclear antibodies. As thyroiditis became the prototype of a large group of diseases that are mainly restricted to a single organ, lupus has served as the model for many other diseases in which broad autoimmune responses induce systemic effects.

The impact of the *JAMA* article not only influenced clinical medicine, it changed our fundamental understanding of the immune response. We soon had visits from two of the key figures who shaped modern immunology. Peter Medawar came from England and added self-tolerance in his formulation of immunologic tolerance acquired in embryonic life. F.M. Burnet from Australia incorporated in his theory of clonal selection the concept of clonal deletion to establish normal self-tolerance and the chance origin of forbidden clones to explain the exceptional occurrence of autoimmune disease. Thus, our paper had far-reaching and lasting effects on both basic and applied immunology.

THE DECADE OF THE 1960S: MECHANISMS

By 1960, the concept of autoimmune disease had become well entrenched. The number of human diseases believed to be of autoimmune origin increased almost daily. My own research program followed two pathways. The first was to apply the

new methods that I had learned to detecting autoantibodies and also to demonstrating cell-mediated responses to other immune related diseases, including immediate and delayed hypersensitivity responses [5,6]. I also tried to show that another organ-specific antigen, insulin, was capable of producing insulitis in rabbits [7]. The goal of an experimentally induced insulitis in animals has still not been achieved.

The second and more prominent direction of my research in the decade of the 1960s was to determine the actual mechanisms of pathogenic autoimmunity. While we could not consistently transfer thyroiditis by passive infusion of antiserum, thyroglobulin-specific antibodies were capable of inducing thyroiditis especially if the thyroid gland were genetically vulnerable, damaged or inflamed [8,9]. On the other hand, antigen-specific T cells could adoptably transfer thyroiditis to syngeneic but not allogeneic recipients [10].

As more information emerged on the differentiation of T cells in the thymus, we turned to quantitative studies of thymic depletion and restoration [11]. An unexpected finding of these experiments was the diversity of immune responses in thymus cell-restored mice, suggesting that the early thymus itself may actually contain cells that retard rather than promote the immune response. This led to a number of studies continuing for the next ten years showing that timed neonatal thymectomy hastened spontaneous thyroiditis in the OS chicken and the BUF rat [12,13]. These experiments suggested the presence in the thymus of natural thymic suppressors, which we later built into our conceptual models of the mechanism of self-tolerance and autoimmunity based on clonal balance [14-16].

A further question was the actual mechanism of tissue damage. To address that issue we developed cell cultures of thyroid cells, taking care that they retained their organ specificity by producing thyroglobulin. Using intricate cell culture techniques, we could show that direct contact between thyroglobulin-specific T cells and cultured thyroid cells induced injury and death of thyroid follicular cells [17,18].

A series of experiments began a detailed antigenic mapping of the thyroglobulin molecule. The first experiments involved separation of the peptide fragments following proteolytic digestion [19]. A number of years later **t**he results led to the discovery that autoantibodies to thyroglobulin present in normal euthyroid individuals differed from additional antibodies formed later in patients with clinical thyroiditis [20]. These findings clarified our earlier concepts of the difference between naturally occurring, benign autoimmunity and pathogenic autoimmune disease [21,22].

Another informative study related to a second organ-specific antigen of the thyroid gland, thyroperoxidase. Other investigators had shown that most thyroiditis patients produce antibody to thyroperoxidase in addition to antibody to thyroglobulin. In our hands, rabbits injected with thyroid cell suspension did not produce antibody to rabbit thyroperoxidase, in contrast to rhesus monkeys given rhesus thyroid cell suspensions [23]. The primates immunized with thyroid extracts produced antibody to thyroglobulin first. After lesions appeared in their thyroids they produced additional antibodies to thyroperoxidase. Based on these experiments we later suggested that *escalation* of the autoimmune response was an early signal of pathogenic autoimmunity [24].

As the 1960s ended, we were able to achieve another major goal, the induction of experimental thyroiditis in mice [25]. This task was accomplished largely through careful attention to the adjuvant as well as the strain of mouse used in active immunization. It opened the doors to studies of the genetics of autoimmune diseases.

THE DECADE OF THE 1970S: GENETICS

The 1970s opened with the first demonstration that the susceptibility of different strains of mice to experimentally induced thyroiditis was genetically determined. The most prominent genes regulating susceptibility were part of the major histocompatibility complex (MHC) [26]. This finding was soon confirmed in the spontaneous model of thyroiditis in the OS chicken, as well as both induced and spontaneous thyroiditis in the rat [27-29]. Today, virtually every autoimmune disease in experimental animals and humans is regulated by genes of the major histocompatibility complex. This MHC association represents one of the fundamental characteristics (the "common threads") shared by all autoimmune diseases. Within the MHC, we were able to resolve the active immunization process into the induction steps that depend primarily on MHC class II genetic determinants and severity of lesions in the thyroid gland, which resides mainly in MHC class I [30,31]. Subsequently, we took up studies of the genes outside of the MHC, which together account for more than half of the inherited susceptibility to thyroiditis. In this case, however, there is no single predominant family of genes, but rather a large number of disparate traits [32]. Each contributes a small amount to the final susceptibility. Most of the genes that have been studied were found to regulate the immune response.

These early investigations on thyroiditis in experimental animals are reflected in our current understanding of genetics of autoimmune disease generally. The induction of the immune response depends first upon recognition of the candidate antigen by genes of the MHC. Together they determine the specificity of the immune response. Non-MHC genes represent a consortium of non-antigen-specific traits that collectively regulate the normal homeostasis in the immune response on a daily basis. In the case of autoimmunity, there is a gradient from highly susceptible to relatively resistant mice in response to the candidate antigen [33]. Present evidence suggests that a similar situation occurs in human autoimmune disease.

By the end of the 1970s, we gained a good understanding of the inherited susceptibility to thyroiditis and witnessed its application to other autoimmune diseases. Collectively, however, all of these genetic traits seem to provide less than half of the actual risk. Some of the risk may be associated with hormonal influences or random post-genomic, epigenetic changes in the immune system itself. However, the largest contribution to risk seems to arise from environmental mediators. They represent the "triggers" of autoimmunity.

THE DECADE OF THE 1980S: ENVIRONMENT

In humans, many examples of environmental agents that precipitate autoimmune diseases in genetically susceptible individuals have been described, yet in only a few instances has a cause-and-effect relationship been established [34,35]. In experimental animals, the most common environmental mediators appear to be infections.

In 1981, I moved with a number of colleagues to the Johns Hopkins University [Figure 1]. Johns Hopkins provides a particularly favorable setting for combined fundamental and clinical research. As the first university in the United States founded specifically to support advanced research and education, the medical school has, from the beginning, accepted only students who have completed a broad undergraduate curriculum. In fact, modern American medical education is modeled after the Hopkins plan. Two years of intensive study of the basic biologic sciences underlying health and disease are followed by 2 years of applied clinical clerkships in a university academic hospital. Although modified many times in many ways, this basic plan transformed medicine from a trade to a scholarly discipline. The Hopkins model now marks medical education throughout the world.

Figure 1. Dr. Rose examining a gel in his laboratory at Johns Hopkins, 1982

At Johns Hopkins, I had the opportunity of establishing a department devoted to infection and immunity. To emphasize the role of microbial infection in the induction of autoimmune disease we expanded our earlier investigations of inflammatory diseases of the heart instigated by viral infection. From detailed study has come the first clear evidence of how infection could initiate autoimmune disease. Briefly, we found that coxsackievirus B3, one of the common viral causes of myocarditis in humans, induces acute infectious myocarditis in all strains of mice [36]. Although most mice recover from the viral disease spontaneously, a few inbred strains develop a chronic disease that we established as the result of an organ-specific immune response to cardiac myosin [37,38].

This model, the first example of virus-induced autoimmune disease where the antigen was defined, has proved to be of incredible value in discovering the underlying immunopathic mechanisms [39]. Virus-induced damage inflicted on the cardiac cells induces expression of the intracellular cardiac myosin. In the presence of cardiac inflammation, also induced by the virus, the antigen is presented to CD4 T helper cells, which are able to initiate pathogenic autoimmunity. Recent investigations have shown that the Th17 pathway is essential for the induction of inflammatory myocarditis [40]. However, the signature cytokine, interleukin (IL)-17, does not determine the severity of inflammation. Instead, IL-17 is the critical component in determining whether a mouse with autoimmune myocarditis will proceed to further fibrotic remodeling of the heart in the form of dilated cardiomyopathy [41,42].

These experiments have provided the opportunity to dissect the step-wise progression from viral infection to autoimmune inflammatory myocarditis to subsequent fibrotic cardiac remodeling and dilated cardiomyopathy. Although somewhat chaotic on first observation, the steps can be predictable. It provides hope that human immune mediated disorders can be assessed in terms of the inflammatory pathways activated and the future outcome determined [43]. Equally important, identification of the key inflammatory mediators provides opportunities to prognose, predict and intervene therapeutically. By the end of the 1980s, we could see our goal of moving from reductionistic, mechanistic experiments to translational investigations involving earlier diagnosis, more accurate prognosis and more targeted interventions [44].

THE DECADE OF THE 1990S: EPIDEMIOLOGY

In 1997, our group published another highly cited article that changed the immunologic landscape [45]. Starting with 24

well-defined autoimmune diseases, we assembled the existing publications on incidence and prevalence based on the most reliable data available. Three autoimmune diseases are relatively common in North America and Western Europe: Graves' disease, chronic lymphocytic thyroiditis and rheumatoid arthritis. All of the other autoimmune diseases are relatively rare. As a group, the autoimmune diseases are among the largest clinical and public health problems in the industrialized countries. Many of these diseases are increasing in incidence. Interestingly, all the autoimmune diseases co-occur with some other autoimmune conditions, signifying some measure of shared genes. The autoimmune diseases are truly a family [46].

This knowledge of the relatedness of the autoimmune diseases also points to the prospect that genetic data combined with biochemical and immunologic early biomarkers may soon be able to predict, on an individual basis, the onset of some autoimmune diseases. By defining the precise causative antigen, early interventions to prevent or abort the condition may be feasible [47].

THE DECADE OF THE 2000S: POLICY ISSUES

Part of the responsibility of an investigator is to share the essence of his research findings with professional colleagues and with the general public. Much of my recent activity relates to promoting the concept that autoimmune diseases are a family of related human diseases. Basic science has shown that the autoimmune diseases share common threads [48]. They represent a category of disease based on their common etiology, loss of self-tolerance. The autoimmune diseases, collectively, are among the major causes of illness and death in the industrialized countries. They are comparable in prevalence to other main categories of disease, cancer and heart disease, although they are still relatively unrecognized. Health professionals must realize that autoimmune diseases as a group are relatively common and that they can be life-long and life-threatening. Although cures for any autoimmune disease are not presently at hand, most patients can be maintained by supportive treatment. However, many of the most effective treatments are risky and expensive. Our vision turns to prevention [47].

The general public has begun to read about autoimmune diseases in widely circulating journals and newspapers. Patients and their families need to understand more about their causation and course. That the incidence is increasing suggests that the industrialized environment may be an important factor in their etiology. There is some suggestion that autoimmune diseases are now rising in other lesser developed countries as industrialization proceeds. Autoimmune diseases are an international health priority.

A proportion of my own efforts has been to develop a Research Center for Autoimmune Disease at Johns Hopkins. It is designed to bring together the many faculty members in the university community who work on any aspect of tolerance and autoimmunity. Especially important is its mission of connecting investigators and clinicians interested in different autoimmune diseases and discovering the parallels and synergies. I was pleased to have the opportunity of chairing the Autoimmune Disease Coordinating Committee of the National Institutes of Health, which is charged with coordinating research policy at the national level. On the public side, I work with the American Autoimmune Related Disease Association to increase public awareness and understanding of all the autoimmune diseases. Finally, the International Congresses of Autoimmunity have promoted research on autoimmunity as a major cause of disease throughout the world.

For the past 60 years, I have been privileged to see autoimmunity emerge as an important component of human medicine, to witness the importance of studying autoimmunity as a part of the normal physiology, to participate in expanding the scope of autoimmune disease research, both inward to the molecular and genetic levels and outward to the clinic. It has been a wonderful journey of discovery but we still have many miles to go.

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Correspondence

Dr. N.R. Rose

Dept. of Pathology, The Johns Hopkins Schools of Medicine and Public Health, Baltimore, MD 21205, USA

email: nrrose@jhmi.edu

References

1. Witebsky E, Rose NR, Terplan K, Paine JR, Egan RW. Chronic thyroiditis and autoimmunization. *JAMA* 1957; 164: 1439-47.
2. Witebsky E, Rose NR, Shulman S. Studies of normal and malignant tissue antigens. *Cancer Res* 1956; 16: 831-41.
3. Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 1993; 14: 426-30.
4. Miescher P. The antigenic constituents of the neutrophilic leukocyte with special reference to the L.E. phenomenon. *Vox Sang* 1957; 2 (3): 145-58.
5. Arbesman CE, Rose NR, Kantor SZ, Beede RB. Immunologic studies of ragweed-sensitive patients. I. Specificity and sensitivity of hemagglutination reactions. *J Allergy* 1960; 31: 317-32.
6. Girard JP, Rose NR, Kunz ML, Kobayashi S, Arbesman CE. In vitro lymphocyte transformation in atopic patients: induced by allergens. *J Allergy* 1967; 39: 65-81.
7. Fellenberg von R, Rose NR. Antigenicity of insulin. *Int Arch Allergy* 1968; 33: 454-72.
8. Vladutiu AO, Rose NR. Transfer of experimental autoimmune thyroiditis of the mouse by serum. *J Immunol* 1971; 106: 1139-42.
9. Jaroszewski J, Sundick RS, Rose NR. Effects of antiserum containing thyroglobulin antibody on the chicken thyroid gland. *Clin Immunol Immunopathol* 1978; 10: 95-103.
10. Twarog FJ, Rose NR. Transfer of autoimmune thyroiditis of the rat with lymph node cells. *J Immunol* 1970; 104: 1467-75.
11. Mayhew B, MacGillivray MH, Rose NR. Immunologic restoration of thymectomized mice by thymus cell suspensions and the duration of their effect. *Proc Soc Exp Biol Med* 1968; 128: 1217-21.

12. Welch P, Rose NR, Kite JH Jr. Neonatal thymectomy increases spontaneous autoimmune thyroiditis. *J Immunol* 1973; 110: 575-7.
13. Silverman DA, Rose NR. Neonatal thymectomy increases the incidence of spontaneous and methylcholanthrene-enhanced thyroiditis in rats. *Science* 1974; 184: 162-3.
14. Rose NR. The role of the thymus in spontaneous autoimmune thyroiditis. *Ann N Y Acad Sci* 1975; 249: 16-24.
15. Rose NR. Current concepts of autoimmune disease. *Transplant Proc* 1988; 20: 3-10.
16. Rose NR, Talor E. Antigen-specific immunoregulation and autoimmune thyroiditis. *Ann N Y Acad Sci* 1991; 636: 306-20.
17. Rose NR, Kite JH, Jr, Doebbler TK, Brown RC. In vitro reactions of lymphoid cells with thyroid tissue. In: Amos B, Koprowski H, eds. Cell-Bound Antibodies. Philadelphia: Wistar Institute Press, 1963: 19-33.
18. Creemers P, Rose NR, Kong YM. Experimental autoimmune thyroiditis: in vitro cytotoxic effects of T lymphocytes on thyroid monolayers. *J Exp Med* 1983; 157: 559-71.
19. Stylos WA, Rose NR. Splitting of human thyroglobulin. II. Enzymatic digestion. *Clin Exp Immunol* 1969; 5: 285-97.
20. Bresler HS, Burek CL, Hoffman WH, Rose NR. Autoantigenic determinants on human thyroglobulin. II. Determinants recognized by autoantibodies from patients with chronic autoimmune thyroiditis compared to autoantibodies from healthy subjects. *Clin Immunol Immunopathol* 1990; 54: 76-86.
21. Esquivel PS, Rose NR, Kong YM. Induction of autoimmunity in good and poor responder mice with mouse thyroglobulin and lipopolysaccharide. *J Exp Med* 1977; 145: 1250-63.
22. Rose NR, Mackay IR. Introduction – autoimmunity versus autoimmune diseases. In: Rose NR, Mackay IR, eds. The Autoimmune Diseases, Chapter 1. Orlando, FA: Academic Press, Inc, 1985: xxv-xxvi.
23. Andrada JA, Rose NR, Kite JH, Jr. Experimental thyroiditis in the rhesus monkey. IV. The role of thyroglobulin and cellular antigens. *Clin Exp Immunol* 1968; 3: 133-51.
24. Rose NR. Autoimmune regulation: through the crystal ball. *Clin Exp Immunol* 2007; 147: 9.
25. Rose NR, Twarog FJ, Crowle AJ. Murine thyroiditis: importance of adjuvant and mouse strain for the induction of thyroid lesions. *J Immunol* 1971; 106: 698-704.
26. Vladutiu AO, Rose NR. Autoimmune murine thyroiditis. Relation to histocompatibility (H-2) type. *Science* 1971; 174: 1137-9.
27. Bacon LD, Kite JH Jr, Rose NR. Relation between the major histocompatibility (B) locus and autoimmune thyroiditis in obese chickens. *Science* 1974; 186: 274-5.
28. Rose NR. Differing responses of inbred rat strains in experimental autoimmune thyroiditis. *Cell Immunol* 1975; 18: 360-4.
29. Lillehoj HS, Beisel K, Rose NR. Genetic factors controlling the susceptibility to experimental autoimmune thyroiditis in inbred rat strains. *J Immunol* 1981; 127: 654-9.
30. Tomazic V, Rose NR, Shreffler DC. Autoimmune murine thyroiditis. IV. Localization of genetic control of the immune response. *J Immunol* 1974; 112: 965-9.
31. Beisel KW, David CS, Giraldo AA, Kong YM, Rose NR. Regulation of experimental autoimmune thyroiditis: mapping of susceptibility to the I-A subregion of the mouse H-2. *Immunogenetics* 1982; 15: 427-30.
32. Beisel KW, Kong YM, Babu KSJ, David CS, Rose NR. Regulation of experimental autoimmune thyroiditis: influence of non-H-2 genes. *J Immunogenetics* 1982; 9: 257-65.
33. Rose NR, Kong YM, Okayasu I, Giraldo AA, Beisel K, Sundick RS. T-cell regulation in autoimmune thyroiditis. *Immunol Rev* 1981; 55: 299-314.
34. Nyland JF, Caturegli P, Rose NR. Environment/drug-induced human autoimmune disease. Immune System Toxicology. In: Lawrence D, ed. Comprehensive Toxicology. Philadelphia: Elsevier Academic Press, Ltd, 2010; 5: 440-51.
35. Miller FW, Pollard KM, Parks CG, et al. Criteria for environmentally associated autoimmune diseases. *J Autoimmunity* 2012; 39(4): 253-8.
36. Wolfgram LJ, Beisel KW, Herskowitz A, Rose NR. Variations in the susceptibility to coxsackievirus B_3-induced myocarditis among different strains of mice. *J Immunol* 1986; 136: 1846-52.
37. Wolfgram LJ, Beisel KW, Rose NR. Heart-specific autoantibodies following murine coxsackievirus B_3 myocarditis. *J Exp Med* 1985; 161: 1112-21.
38. Neu N, Rose NR, Beisel KW, Herskowitz A, Gurri-Glass G, Craig SW. Cardiac myosin induces myocarditis in genetically predisposed mice. *J Immunol* 1987; 139: 3630-6.
39. Rose NR, Beisel KW, Herskowitz A, et al. Cardiac myosin and autoimmune myocarditis. In: Evered D, Whelan J, eds. Ciba Foundation Symposium 129: Autoimmunity and Autoimmune Disease. Chichester, UK: John Wiley & Sons, Ltd, 1987: 3-24.
40. Cihakova D, Rose NR. Pathogenesis of myocarditis and dilated cardiomyopathy. *Adv Immunol* 2008; 99: 95-114.
41. Baldeviano GC, Barin JG, Talor MV, et al. Interleukin-17A is dispensable for myocarditis but essential for the progression to dilated cardiomyopathy. *Circ Res* 2010; 106: 1646-55.
42. Wu Lei, Ong SuFey, Talor MV, et al. Cardiac fibroblasts mediate IL-17A-driven inflammatory dilated cardiomyopathy. *J Exp Med* 2014; 211(7): 1449-64.
43. Rose NR. Critical cytokine pathways to cardiac inflammation. *J Interferon Cytokine Res* 2011; 31: 1-6.
44. Rose NR. Prediction and prevention of autoimmune disease: a personal perspective. *Ann NY Acad Sci* 1007; 1109: 117-28.
45. Jacobson DL, Gange SJ, Rose NR, Graham NMH. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997; 84: 223-43.
46. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmunity* 2007; 29 (1): 1-9.
47. Rose NR. Moving from prediction to prevention. *The Scientist* 2007 May (Suppl): 76-78.
48. Rose NR. Autoimmune diseases: tracing the shared threads. *Hosp Practice* 1997; 32: 147-54.