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In Memoriam: G. Jeanette Thorbecke 1929–2001

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In Memoriam
G. Jeanette Thorbecke
1929–2001

To laugh often and much.

To win the respect of intelligent people and the affection of children.

To earn the appreciation of honest critics and to endure the betrayal of false friends.

To appreciate beauty; To see the best in others.

To leave the world a bit better, whether by a healthy child, a garden patch, or a redeemed social condition.

To know when one life has breathed easier because you have lived.

This is to have succeeded.

Ralph Waldo Emerson

In early November 2001, G. Jeanette Thorbecke, M.D., Ph.D., and Professor of Pathology at the New York University School of Medicine, traveled to Hawaii at the invitation of the Society for Leukocyte Biology to receive the 2001 Marie T. Bonazinga Award at the Cytokine Odyssey 2001 meeting. Following the meeting, Dr. Thorbecke, a lover of the sea, went swimming in the Pacific and was stung by jellyfish, resulting in complications from which she died unexpectedly on November 16, 2001 at the age of 72. This ended a career marked by more than five decades of contributions and achievements in the biological sciences.

Dr. Thorbecke received her medical and graduate education in The Netherlands at the University of Groningen. Her doctoral dissertation involved a study of in vitro antibody and gamma globulin formation in hematopoietic organs. She spent two years as a postdoctoral fellow at the Lobund Institute for Germfree Animals at the University of Notre Dame (Notre Dame, IN), and then returned to Holland as an assistant in the Department of Pathology at the University of Leiden. Dr. Thorbecke came to the United States again in 1957, joining the faculty of the New York University (NYU) School of Medicine in the Department of Pathology. By 1970, she had achieved the rank of Full Professor. She remained at NYU School of Medicine throughout her career.

Dr. Thorbecke was an outstanding and internationally renowned scientist, who made numerous and significant discoveries that had enormous impact on our understanding of immunological mechanisms. She authored or co-authored over 430 research articles in leading scientific journals. Her scientific contributions were diverse, but with a principal focus in areas of tumor immunology, B cell development and function, autoimmunity, aging, immunosuppression, and tolerance induction.

Dr. Thorbecke contributed immensely to the early knowledge on histologic and functional aspects of lymphoid tissue development, and her work illuminated the relationship of germinal center formation to the development of immunological memory. Her early studies mapped the migratory journey of activated B cells and showed that the maximal development of the germinal centers coincided with the peak of antibody formation on days 4–5 after initial intravenous injection of antigen, and that, when animals previously primed with antigen were challenged with the same antigen, the antibody-secreting immature plasma cell foci developed more rapidly and contained more cells.

Dr. Thorbecke's interest in normal germinal centers led to over 30 years of research into their abnormal counterparts. She used the SJL/J mouse strain to study the development of spontaneous reticulum cell sarcomas, which closely resemble Hodgkin's disease in humans. The dependence of SJL lymphomas on host $CD4^+$ cells for their growth, mediated by the presentation of tumor cell antigens to $CD4^+$ cells, led to the birth of the concept of "reverse immune surveillance". In this model, the host response against the tumor cells promotes rather than inhibits tumor growth. The responding syngeneic $CD4^+$ T cells produce copious amounts of cytokines, including IL-2, IL-4, IL-5, and IFN-γ, some of which support lymphoma growth. It took two decades of work before a breakthrough was made in identifying the stimulating antigen on the SJL lymphoma cells: a viral superantigen, vSAg29, which is encoded by mouse mammary tumor virus *Mtv29*. Considering that the human genome is laden with endogenous retroviral sequences, Dr. Thorbecke's work provides a model for continuing study of the role of retroviral sequences in human lymphoma development.

Another of Dr. Thorbecke's primary interests evolved during the 1970s when the existence and physiologic role of IgD was beingdefined. She and her colleagues showed that in vivo depletion of IgD-positive lymphocytes had no significant impact on the ability of mice to generate T-dependent or T-independent antibody responses, but that production of certain Ig isotypes was increased. They concluded that compensatory mechanisms exist that allow the animal to make a normal immune response. These findings were elaborated on in additional reports demonstrating the functional effects of anti-IgD treatment on B cell development and showing that indirect mechanisms were involved. Further studies revealed immunoregulatory mechanisms in which IgD played an important role. Thus, in studies of the mouse model of myeloma, it was shown that mice bearing IgD myelomas had significantly enhanced antibody responses, in contrast with mice bearing myelomas

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that produced other Ig classes. This phenomenon was not observed in athymic mice leading to the discovery that IgD immune enhancement was T cell mediated and could be transferred to naive mice using T cells exposed to oligomeric IgD. Dr. Thorbecke's curiosity, scientific instincts and playfulness were well displayed in her response to this discovery. In discussing the new findings with Dr. Benjamin Pernis, Dr. Thorbecke made a bet that the Th cells would be the mediator of the phenomenon; Dr. Pernis bet on suppressor T cells. Dr. Thorbecke won the bet (a bottle of wine), which she shared with Dr. Pernis and the rest of the lab when they showed that murine Th cells express the IgD receptors involved in this phenomenon.

In 1988, Dr. Thorbecke's pivotal work provided insight into the possible physiological significance of IgD receptors when it was demonstrated that B cells with cross-linked IgD could up-regulate IgD receptors on Th cells. This finding suggested that Dr. Thorbecke's earlier in vivo studies showing indirect augmentation of certain Ig isotypes following anti-IgD treatment appeared to involve T cell induction of IgD receptors. Connecting the findings obtained with anti-IgD treatment and IgD treatment was both personally satisfying and professionally useful; Dr. Thorbecke conveyed her enthusiasm with the results by reminding those in her lab to "Always celebrate the little things in life—don't wait for the big things."

More studies on this phenomenon followed. Her lab discovered that IgD receptors could be released as soluble molecules, were up-regulated by T cell activation signals including cytokines and various intracellular second-messenger systems where tyrosine kinase activity is required, and that they bind to *N*-linked glycans associated with Fd and Fc regions of IgD. Further studies followed, showing that, unlike mouse $CD4^+$ T cells, human IgD receptors could be up-regulated on both $CD4^+$ and $CD8^+$ cell subsets, but that in both mice and humans, there was deficient expression of IgD receptors in T cells from aged individuals.

With the advent of IgD-knockout mice, Dr. Thorbecke's early findings on the compensatory mechanisms in the absence of IgD-positive cells were unequivocally confirmed. These findings stimulated new questions, and Dr. Klaus Rajewsky agreed to supply Dr. Thorbecke with the mice. This brought to the fore, in a confrontation with the U.S. Customs Department, one of Dr. Thorbecke's key characteristics: her impatience with incompetence. The U.S. Customs Department refused to allow entry of the knockout mice into the U.S. because of their erroneous concerns about potential infectious diseases carried by the mice, "such as anthrax". It required three shipments of mice, the careful tutelage by Dr. Thorbecke of her fellows in dealing with incompetent bureaucrats, and three trips to Customs at JFK International Airport to finally acquire the mice. With much celebration in the lab, the IgD knockout mice were received and used to show that enhancement of antibody responses by T cells with up-regulated IgD receptors depends upon the availability of IgD-expressing B cells.

Jeanette Thorbecke's interests extended to several other areas of immunology: the production of autoanti-idiotype antibodies during the normal immune response and the changes in idiotype repertoire with aging, carcinogen-induced fibrosarcomas in chickens and their relationship to delayed-type hypersensitivity, Langerhans cells as representatives of the accessory cell system, and their distinction from interdigitating cells and lymphoid dendritic cells, the involvement of TNF-α and TGF-β in the induction of arthritis, the modes of tolerance to arthritis induced by type II collagen, the mechanism by which TGF-β protects against experimental allergic encephalomyelitis, and the use of antigen-specific TGF-β1 transduced Th1 cells in gene therapy for experimental allergic encephalomyelitis and allergen-induced hyperactivity.

Dr. Thorbecke was a member of the Dutch and British Societies of Immunology, the American Association of Immunologists, as well as numerous other scientific societies. She served these organizations in many capacities. She was extremely active in promoting the candidacy of Dr. Marian Koshland as the first woman president of the American Association of Immunologists, and Dr. Thorbecke, herself, became the second woman president of the American Association of Immunologists (1989–90). She served on numerous scientific advisory boards at the national and international levels for governments, for voluntary health foundations, and for industry.

Dr. Thorbecke received numerous honors and awards during her distinguished career in science. She was the recipient of a Research Career Development Award from the Health Research Council of the City of New York, and was elected as a correspondent of the Royal Dutch Academy of Arts and Sciences in 1980. Her native country honored her with the prestigious van Loghem Award, which not only recognized her accomplishments as an outstanding scientist, but also as a person with vision for the future. In 1989, Dr. Thorbecke received the Outstanding Woman Scientist Award from the American Women in Science organization, and in 1999 she received the Rose Hirschler Award in Dermatology for her work on Langerhans cells. Most recently, she was nominated for the Chugai Award for Excellence in Mentoring and Scholarship from the American Society for Investigative Pathology, and, as mentioned above, she had just received the Marie T. Bonazinga Award before her untimely death.

In addition to her achievements in science, Dr. Thorbecke was a wife, mother, friend, and mentor. She shared many scientific pursuits with her husband, Dr. Gerald Hochwald, a noted neurobiologist and fellow NYU faculty member with whom she raised three handsome and talented sons, Bert, Neal, and Steve, who now pursue their own careers in science and medicine. Dr. Thorbecke's extended "scientific family" includes over 60 scientists who either performed their doctoral studies under her tutelage, or selected her laboratory in which to do postgraduate research. Many went on to achieve positions of leadership in academe and industry in a variety of areas in Immunology. All were instilled with the Thorbecke enthusiasm for scientific inquiry and high standards for excellence. Her devotion to her students and fellows was legendary. She understood the importance of guiding young people entering the field, and was known to demand uninterrupted time with students interviewing for admission to the graduate program so that she could be sure she understood their motivation and had correctly assessed their intelligence so that she could judge their abilities and advise them at the very beginning of their graduate careers.

Beyond all of her scientific achievements, what also made Jeanette Thorbecke so outstanding was her awareness, concern, and involvement with people. All who worked with her are quick to comment on her superb character—one of a caring and concerned mentor, colleague, and friend. She had endless energy, infectious enthusiasm, and uncanny insight. In the words of a former trainee, "She leads by splendid, and exhausting, example, demanding nothing of those who work with her that is much a fraction of what she demands of herself." Dr. Thorbecke was fond of art and music, and was quite well known for her choreographic abilities on the dance floor and for her passion for painting. She combined her enthusiasm for the arts with her science at every opportunity.

"In all great people I have met," said Ralph Waldo Emerson, "I notice directness, truth spoken more truly, as if everything of obstruction, of malformation, had been trained away. For it is not what talents or genius a person has, but how he is to his talents, that constitutes friendship and character." Jeanette Thorbecke exemplified these qualities.

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