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ROBERT ALAN GOOD
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A Biographical Memoir by
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Biographical Memoir

Robert A. Taft

ROBERT ALAN GOOD

May 21, 1922–June 13, 2003

BY RAYMOND D. A. PETERSON

Robert A. Good was born on May 21, 1922, in Crosby, Minnesota (the Iron Range), and died on June 13, 2003, in his home in St. Petersburg, Florida, with his wife and family at his bedside. In our last conversation he reflected on his 80 revolutions around the sun and said he'd like nothing more than to start that same journey again. Bob was the second of four children born to parents that were professional educators. His father died of cancer when Bob was six years old, and he and his brothers were raised by their mother in Minneapolis, where "Grandma Good," as we all called her, taught school and piano lessons. Bob was a precocious and curious boy, and so too were his brothers, all of whom went on to obtain M.D. or Ph.D. degrees and to excel in their chosen careers. All were enthusiastic about life. One example being brother Tom who became a well-recognized pediatric endocrinologist and, as a hobby, roped and broke wild mustangs in Utah and Nevada.

Upon graduating from Central High School in Minneapolis, Bob entered the University of Minnesota and in 1947 became the first student to simultaneously obtain M.D. and Ph.D. degrees. His Ph.D. was in anatomy, where he developed a special interest and expertise in the morphology of hematopoietic cells. His mentor in this area was Dr. Hal

Downey, well known for his description of the cells that characterize mononucleosis. Among other beloved mentors Bob often spoke of were Barry Campbell and Fred Kolough. With Campbell he studied experimental allergic encephalomyelitis, an experience that began his career in experimental immunopathology. Kolough was a graduate student interested in plasma cells, and when he left his research career to pursue other endeavors he charged Bob with the challenge of further characterizing these cells. At that time plasma cells were only one of the many cell types suspected to be players in the orchestration of the immune response. So, at the beginning of his career Bob began his journey down a path that came to be strewn with contributions that immensely advanced our knowledge of the ontogeny and phylogeny of the immune system, the interactions of the many components of the system, and the clinical implications of disorders of this system. Finally, he conceived of ways to significantly affect genetic aberrations of the system and proceeded to correct them.

Finishing his formal schooling, he entered the pediatric training program and came under the tutelage of Dr. Irvine McQuarrie, a relationship that was to profoundly influence and facilitate his career. McQuarrie was one of the founders of modern pediatrics, an accomplished scientist, but most of all a scout for talent. He imbued Bob with his passion (i.e., the utilization of what he termed "Experiments of Nature") to direct the study of fundamental biological phenomena. Bob followed this admonition his entire career. McQuarrie also facilitated Bob's move to the Rockefeller Institute in 1949. There he interfaced with many of the leaders in medical research and began his independent path of research.

Bob often told a story about that move that reveals the self-starter characteristics that so typified him. He recounted how he reported, on his first day in New York, to the office of

Maclyn McCarty, his proposed mentor. McCarty greeted him and said he was on his way out for an extended vacation and would see him on his return. Bob was charged up for what he thought would be a directed research endeavor with one of the most prestigious scientists of his time, but once that disappointment was over he moved ahead with his own ideas and made contact with many of the outstanding investigators at the Rockefeller. By the time McCarty had returned, Bob was well on his way to delving into the exciting research bed present in that environment. Later, back at Minnesota when I had become one of the more "senior" fellows, I would tell Bob about a new fellow that was seemingly sitting around looking for something to do. Bob's response, while loving, was always the same. In keeping with his Rockefeller experience he had concluded that fellows should be provided with encouragement, a rich intellectual climate, physical facilities, and finances to pursue what they thought was important. He didn't want fellows to be technicians working on his ideas. Most caught on and moved on with amazing successes. A few did not and moved down other career paths.

Back in Minnesota Bob followed the Experiments of Nature trail and it led to research endeavors that would otherwise not have been apparent. Preeminent of those observations (experiments) was one provided by a patient referred to him by Dr. Richard Varco, a very astute and progressive surgeon at the university. The patient had a thymoma, but of special note, agammaglobulinemia. (This combination is now known as the "Good syndrome.") The significance of this observation was to lead to the discovery of the role of the thymus, at the time an organ without a known function and often considered to be a vestigial remnant.

The syndrome of agammaglobulinemia had been recently described by Col. Ogden Bruton, and stimulated by that observation Bob had begun studying the serum immuno-

globulins of children with decreased resistance to infections. These patients offered a unique opportunity to study the relationship of lymphoid tissues, including plasma cells, to the production of immunoglobulins. This was still in the early days of immunoglobulin characterizations and the techniques required for their study were established and carried out in collaboration with Dr. Bob Bridges, an intense perfectionist in the laboratory and an invaluable associate. Bridges wouldn't tolerate anyone in his lab who didn't appreciate the need to be precise in the Kjeldahl nitrogen determinations, paper and gel electrophoreses, immunoelectrophoresis, and the other labor-intensive, evolving technologies of those days. These studies led to the discovery of a great many syndromes, each with unique abnormalities of their immune systems. Once identified by phenotypic characteristics, it became possible to begin the process of defining the cellular and eventually the molecular basis of the diseases, a process that continues today. These Experiments of Nature are akin to the genetic knockout animals created by modern molecular techniques.

Defects in other host defenses were also presented by these children. The phagocytic defect responsible for chronic granulomatous disease was revealed by Beulah Holmes and Good. Several complement deficiencies were likewise revealed. The C2 deficiency associated with decreased resistance to infection and lupus was identified by Noorbibi Day-Good and Good. Henry Gewurz worked out aspects of the alternate complement pathway and other selected defects in complement that mimicked some of the immunoglobulin deficiencies.

As his clinic continued to accrue and study patients with various types of immunodeficiencies, Bob focused his laboratory studies on understanding the thymus-agammaglobulinemia observation. Together with a very special collabo-

rator, Dr. Carlos Martinez, Bob launched a major research project Carlos was an experimental physiologist trained by the famous Professor Bernardo Houssay in Argentina. He was not only extremely well versed in physiology he was also the most gracious member of the growing team of people joining Bob's enthusiastic and intense search for understanding the thymus-immune system relationship. Under his tutelage, thymectomies were performed on a variety of species to determine whether such a procedure would influence antibody production. No effect was noted in these experiments using adult animals. Then the observations of Bruce Glick, a graduate student in poultry science at Ohio State, came to his attention. Glick had shown that bursectomy of newly hatched chickens resulted in their incapacity to produce antibodies to injected antigens.

The bursa is a hind-gut lymphoid organ in birds that, like the thymus, was also without known function. Glick was excising the organ, in the motif of Claude Bernard, "to cut it out and see what happens." The effect on antibody production was totally unanticipated but was serendipitously immediately recognized by Glick to be noteworthy. Bursectomy early in life prevented the birds from producing antibodies to injected antigens. This observation prompted Bob and his colleagues to begin a study of neonatal thymectomy in mice, and an effect on antibody production was immediately observed. Neonatally thymectomized mice were deficient in antibody production, and in subsequent studies shown to be also deficient in rejecting skin grafts. Immunoglobulin levels in these animals were not significantly affected and the diminished antibody responses were not observed with all types of antigens. These nuances were later to be clarified, but at that moment the fact that the thymus was involved in the development of immunocompetence was definitively shown.

The discovery of the role of the thymus was monumental and a credit to the Experiments of Nature trail that Bob was following. A huge organ occupying the chest of young animals now had a function never before known. The discovery was also the consequence of the relentless pursuit of understanding that experiment and of the enthusiastic group of colleagues that were stimulated to join him in this quest. Bob never asked anyone to work with him. They did because it was exciting and, indeed, fun.

It is not surprising that elsewhere in the scientific world someone else made the same discovery while coming from an entirely different direction. J. F. A. P. Miller, then working at the Chester Beatty Cancer Institute in England, was following the lead of Jacob Furth when he independently came to the conclusion that the thymus was the source of the cells later to become central to the immune response. In 1944 Furth had shown that early thymectomy would prevent the spontaneous leukemia that occurs in the AKR strain of mice. Furth hadn't removed the thymuses until a few weeks of age, and as a consequence did not encounter the immunologic effects of neonatal thymectomy. Miller did thymectomies at birth, and observed the same phenomenon as seen in Minnesota.

Because of this simultaneous independent discovery there existed some contention regarding the credit, but Good always was clear in acknowledging Miller's work. The reverse was not always the case. Soon many other investigators jumped on this discovery, with the result that it was independently confirmed many times over.

The next seminal laboratory studies were prompted by the observation that the children with agammaglobulinemia were able to exhibit delayed hypersensitivity reactions. The children lacked plasma cells and germinal centers in their lymph nodes but possessed the lymphocytes that mediated delayed reactions. In the course of defining this dichotomy

Bob exhibited his insatiable enthusiasm during one of our weekly Thursday night transplantation seminars. We had a Latvian patient, named Egalis, with agammaglobulinemia. In the course of the discussion regarding how to fully define cellular immunity in these patients, Bob suddenly became inspired and said, "Let's transplant Egalis." Those that didn't know the patient assumed he had referred to *eagles* and were concerned Bob had crossed over the hill with his enthusiasm. Until the matter was clarified the seminar turned into a ridiculous deliberation with Bob insisting on transplanting Egalis and others trying to dissuade him.

While many options were entertained to clarify this dichotomy I presented one that paid off in a major way. Although it was rewarding to conceive of and conduct this series of experiments, in the context of this memoir of Bob, the most important point was that Bob encouraged everyone to pursue their hunches. He created the fertile soil for others to plant with their ideas. This particular idea would not have surfaced in any environment other than the one created by Bob. With the exception of putting down the proposal to transplant eagles no one was ever told his fledgling idea was not worthy of consideration.

The experiments were to be performed in chickens because they had the two organs suspected to be critical in the ontogeny of the immune system: the thymus and "bursa of Fabricius." Two approaches were taken. In one set of experiments normal chickens were utilized. They were bursectomized or thymectomized at hatching and then given a sublethal dose of radiation to destroy lymphocytes that we postulated may have emigrated from these central lymphoid organs prior to the surgery. Subsequently their immunologic capabilities and lymphoid tissues were analyzed.

The second experimental approach analyzed the consequences of bursectomy or thymectomy on the development of

a viral-induced lymphoma. These were conducted in collaboration with Dr. Ben Burmester, an eminent scientist and a wonderful gentleman who had first described this disease and then directed the U.S. Department of Agriculture's Regional Poultry Laboratory in East Lansing, Michigan. He graciously made available to us the substantial facilities of that institution, including the isolation facilities, the inbred chicken line, the oncogenic virus, and the considerable staff required to monitor the study. My colleagues and I developed the protocols and performed the operations. Burmester and his staff did the rest. I know Dr. Burmester tolerated a fair amount of criticism from some of the veterinarians on his staff for offering their services to some pediatricians that seemingly (in fact truly) knew very little about chickens.

The results of both experiments definitively showed there are two populations of lymphocytes in the body: those originating and migrating from the bursa and those originating and migrating from the thymus. Thus, the two major classes of lymphocytes—T lymphocytes, from the thymus, and B lymphocytes, from the bursa—were delineated. Normal chickens subjected to bursectomy and radiation were profoundly deficient in antibody synthesis to injected antigens but exhibited normal delayed hypersensitivity. Those thymectomized produced antibodies but did not develop the capacity to manifest delayed hypersensitivity. Chickens infected with the avian lymphoma-inducing virus went on to develop the lymphomas if thymectomized but not if bursectomized. The malignant transformation occurred in bursal cells that then metastasized to the liver and elsewhere. The thymic cells were not involved.

Upon presenting these data at a national meeting, Max Cooper, a collaborator in those studies, was challenged with the statement that "men aren't chickens." He acknowledged this was true, but the underlying implication deserved a

serious answer. Over the next few years the origin of B cells in mammals was addressed but not clearly answered. The fetal liver and/or liolymphocytes described by Fichtelius are likely sources, but in any case the T- and B-cell dichotomy has proven invaluable in understanding immunodeficiency states and also malignancies of the lymphoid tissues.

Bob's clinic continued to identify children with decreased resistance to infection, and as a consequence numerous syndromes were identified and the underlying defects delineated. The clues from these children gave direction to laboratory studies and soon new fundamental data were obtained that facilitated a systematic study of the patients. A few examples follow.

The first practical operational classification of immunologic diseases was based on the recently discovered two components of the lymphoid tissues: T and B cells. Now several clinical entities previously known only by names given to them by the investigators could be classified as deficiencies of T cells, B cells, or both. This classification permitted further studies focused on the underlying cellular defects and eventually on the molecular defects responsible for the syndrome. Thus, Bruton's agammaglobulinemia was categorized as an isolated B-cell deficiency. The Swiss-type deficiency was recognized as a lack of both T and B cells. A subset of patients with the severe combined deficiency were later found by two "Good guys," as students of Bob's were known, Ben Pollara and Helaire Meuwissen, to have a deficiency of adenine deaminase. This led another Good guy, Michael Blaese, to perform the first human gene transplantation. Thus, once the dichotomy was established, the next logical steps became apparent and led on to subsequent studies.

In a similar manner the malignancies of cells of the lymphoid lines could now be defined as being of T- or B-cell lineage at various stages of the differentiation. All have proven

to be monoclonal. This perspective has totally changed the way these malignancies are diagnosed, studied, classified, and treated. By these criteria most childhood leukemias were of B-cell lineage, some composed of very immature cells and others of more mature cells. T-cell leukemias were quite different, both in the course of the disease and response to treatment. Great strides now have been made in further characterizing these malignancies and in developing targeted, effective therapy.

Bob and his group described many other syndromes based on these early studies, but one additional discovery deserves mention because it heralded the appearance of a major catastrophic epidemic. We reasoned that because the thymus was critical in the ontogeny of immune competence, an "acquired" defect in the thymus might also have an impact on the development of immune competence. At the time we were working with Ludwig Gross's passage A leukemia virus. Gross took great interest in our studies and was an invaluable colleague. Like the leukemia in Furth's AKR mice, the Gross virus also induced a leukemia that could be prevented by thymectomy. We sought evidence that infected mice might become immunodeficient in the months prior to the appearance of their leukemia. Indeed they did, manifesting a diminished antibody response to selected antigens and an inability to reject skin grafts from an unrelated donor. This acquired immunodeficiency set the stage for understanding the immunodeficiency following the HIV infection in humans.

These experiences plus years of studying transplantation in the laboratory, another of his multifaceted arenas of study, led Bob directly to apply this knowledge to patients with immunodeficiencies. He performed the first successful human bone marrow transplant in the world in 1968 with his student Dick Gatti. The patient was an infant with a profound

inherited immune deficiency of both T and B cells. The disease had killed 11 male children in this extended family. The patient was cured with the marrow donated by his sister. He is now a healthy adult and the father of twin boys. Good went on and used bone marrow transplantation to cure a fatal acquired aplastic anemia and the enzyme deficiency, adenosine deaminase. Continuing experience has shown bone marrow transplantation to be useful in treating some 75 diseases, including leukemias and other fatal disorders.

In addition to these seminal studies of the ontogeny of the immune system he went on to initiate a parallel study of the phylogeny of the immune system. He and his colleagues collected every available species of swimming creatures imaginable. His grasp of the phylogenetic tree was remarkable. Not only was the venture scientifically profitable it was fun as well. One of my contacts with this group was a night at the home of Karl-Eric Fichtelius ("Figge"), a pioneer lymphologist in Uppsala, Sweden. He grilled hagfish, the possessor of the most primitive immune system known, and we washed it down with aquavit.

In 1973, following this long and productive research career in Minnesota, Bob was recruited to become president and director of the Sloan-Kettering Institute for Cancer Research and director of research at Memorial Hospital in New York City. During his next 10 years there, he assembled an impressive faculty and addressed many different aspects of immunobiology. These ranged from very fundamental studies of cellular differentiation, transplantation, and the impact of nutrition on autoimmune diseases and cancer, to the wider use of bone marrow transplantation for a variety of otherwise fatal diseases. His colleagues there, as in Minnesota, came because they wanted to work alongside Bob and enjoy his positive, enthusiastic approach to science and life. Bob left a big footprint in New York. The major bone marrow

transplantation program remained there under the care of Richard O'Reilly, and many of his colleagues in transplantation and immunology also remained. They and their students continue Bob's legacy.

Thereafter he joined the Oklahoma Health Sciences Center in Oklahoma City as member and head of the Cancer Research Program, professor of pediatrics, Research Professor of Medicine, and professor of microbiology and immunology.

In April 1985 he made his last move, to the All Children's Hospital and the University of South Florida in St. Petersburg. There he spent 18 years in developing a major clinical and research center in immunology. Here his research team received millions of dollars in federal and private research grants to study such issues as how to eliminate the hazards of graft-vs.-host disease in recipients of transplants and creation of immunologic tolerance in these patients. The role of nutrition in the aging process was also a subject of major study. In addition to activities in the research labs, he helped to train more than 100 future physicians through residency and fellowship programs at All Children's Hospital and the University of South Florida.

Bob clearly pioneered the field of bone marrow transplantation and continued this endeavor into the last year of his life. On one of my visits to the All Children's Hospital, I remember his gentleness as he comforted a teenage girl with leukemia who had just received a marrow transplant. She had begun exhibiting the skin rash typical of graft-vs.-host disease and was convinced she was doomed. Bob sat on her bed and explained how this could be managed and, indeed, was a good sign that the graft would facilitate the rejection of the leukemia. He was always kind and thoughtful, especially with the children under his care.

For these and other pioneering discoveries Bob was the recipient of many honors and awards. He was elected to membership in the National Academy of Sciences in 1970. Throughout his more than half a century Bob was the recipient of more than 100 international and national awards, including:

- The Albert Lasker Clinical Medical Research Award, for uniquely important contributions to our understanding of the mechanisms of immunity, discovery of the role of the thymus, and launching an era of cellular engineering (1970).

- The Gairdner Foundation Award (Toronto, Canada) in recognition of many contributions to the understanding of host defense mechanisms (1970).

- The American College of Physicians Award for distinguished contributions to science as related to medicine (1972).

- The John Howland Award of the American Pediatric Society for a lifetime of distinguished contributions to the field of pediatrics (1987).

- Charter Member, International Bone Marrow Transplant Registry award for pioneering work in bone marrow transplantation (1989).

- Ronald McDonald Children's Charities Award of Excellence, for advancing children's health through his work in bone marrow transplantation, immunology, and immunodeficiency disease (1991).

- The Order of the Sacred Treasure, Gold and Silver Star, conferred by the Emperor of Japan, for great achievements in academic research and further development of scientific exchange between the United States and Japan (1998).

- Achievement Award, American Society for Blood and Marrow Transplantation, recognizing Dr. Good as one of the three giants of blood and marrow transplantation along with George Santos, M.D., and E. Donnall Thomas, M.D. (2000).

• Establishment of the Robert A. Good Chair in Pediatric Immunology, Children's Research Institute at University of South Florida/All Children's. This multimillion-dollar endowment was made possible by donations from the Eleanor Naylor Dana Charitable Trust in recognition of Dr. Good's scientific achievements. Good had been a Dana trustee since 1982 (2001).

Bob received more than a dozen honorary degrees from prestigious academic institutions in the United States, and around the world, including Sweden, Korea, Japan, and Italy. He authored or coauthored more than 2000 publications and wrote or edited some 50 books.

Rather than listing all Bob's other honors, I think he'd like to be remembered by others as who he actually was. He often used that quote about honors and flattery: "A little flattery doesn't hurt, just don't inhale." He seldom inhaled.

Poetry, for reasons I never asked, really filled his mind. He could and would with the slightest encouragement recite Lewis Carroll's "The Hunting of the Snark." On a sailing trip on my boat we were heading south down the Florida coast at sunrise. I was at the helm and Bob and others were below decks sleeping. Because the sunrise was so striking, and I also thought it time for the others to get up, I loudly proclaimed one of my few memorized lines of poetry from the "Road to Mandalay:" "And the dawn comes up like thunder outer Burma 'crost the Bay." No sooner out of my mouth but Bob's booming voice came forth from the darkness below and said, "outer China 'crost the Bay." And of course, he was right. He gave many of us a copy of poems by his favorite poet, Robert Frost. His copy and mine fall open to "The Road not Taken." This was clearly his paradigm.

All this being said, a final note about Bob's real legacy, the reason he will be remembered by those of us fortunate to have known him. His greatest legacy is not the many major scientific contributions he made but the impact he had on his students. He "passed it on" in the profoundest

sense of this expression. Others, that he often spoke of, had passed on their gifts to him and he in turn passed on those priceless gifts of friendship, respect, and the thirst for new knowledge to so many of us. In the Buddhist philosophy our lifetime accomplishments and spiritual growth is passed on through our spirit to better those that have been fortunate enough to receive and recognize it. The recipients that stand on the backs of giants can then see farther down "the road not taken."

He is survived by his widow, Noorbibi Day-Good, Ph.D.; five children by his long-deceased first wife, Jean; two stepsons; 17 grandchildren; 6 great-grandchildren; and most notably hundreds of what Bob called his intellectual children and grandchildren.

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