CYTOKINES

STRESS AND IMMUNITY

Second Edition

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In Memoriam: Robert A. Good

by Diana Pickett, M.D., Ph.D., and Noorbibi Day-Good, Ph.D.

> Quid edit beificium taceat; narret qui accepit. *(*Let him who has done a good deed be silent; let who has received it tell it.*)*

INTRODUCTION

Robert A. Good, B.A., M.D., Ph.D., D.Sc., FACP, the father of modern immunology and cellular engineering, will always be remembered for his extensive studies of X-linked agammaglobulinemia bisecting the immunological universe, the universe of the lymphoid system, and the universe of viruses. He identified and defined numerous primary immunodeficiencies of humans, and especially identified and defined chronic granulomatous disease (CGD) of childhood. His research achievements include the discovery of the function of the thymus and the definition of the two distinct major cellular components of the immunity system, and performance of the first successful bone marrow transplantation in a human.

Good was like Paul Bunyan, the legendary figure who hailed from his home state of Minnesota: super sized in all that he did. If ever the field of medicine and medical research needed a recruitment model to induce bright young minds to follow a career in the sciences, the life and legend of Bob Good would be a great choice.

> Ab ovo usque ad mala. (To the stars through difficulties.)

He overcame the death of his father at an early age and a crippling bout of Guillain–Barré that left him partially paralyzed. He turned the challenge of hours when he was unable to play sports into an advantage and used them to study science and medicine. He demanded the best from himself and others and yet was always supportive, seemingly when needed most. He out-published, out-worked, and outshined most of his colleagues but it did not turn his head; instead, his feet were planted, in those famous tennis shoes, firmly on the ground. He said he felt more at home and in his element patting the fontanels and rubbing the abdomens of his little patients than on stage giving a speech. Good loved every minute of life and life returned the compliment. Bob Good has not left us; he has merely gone on ahead, as he always has.

THE TRANSLATIONAL PHYSICIAN SCIENTIST

Good is considered one of the greatest figures in 20th century medicine and medical research. He was one of the very first "translational physician scientists" to set the standard beginning at bedside, by observation and conversation, with his patients, his greatest teachers. Information gleaned and questions posed were taken to both the clinical and experimental laboratories for dissection and analyses. Results were gathered and returned via translation to the patient's bedside, with answers, treatments, and many times cures for their illnesses.

> All life is an experiment.
>
> **Ralph Waldo Emerson**

Scientific Compass, Tenacity, and "Experiments of Nature"

Good was a visionary who could seemingly see around scientific corners and intuitively know in which direction research in immunology was headed and what were the important and necessary issues to explore at that particular moment in time. He maintained his theories and interests even if it sometimes meant temporarily setting them aside on a "mental bench." He never gave up until all avenues had been explored and exhausted. The story of his theory, formed in 1953, on the role of the thymus in mammalian immunity and the two different sets of rabbit thymectomy experiments, separated by a pregnant pause, was a perfect example of step-wise experiments and Good's tenacity in staying the scientific course until the answer was forthcoming.

> You'll have to repeat that experiment. That's why we call it RE-search!
>
> **Robert A. Good**

He was able to visualize and analyze unwell areas in body systems responsible for "dis-ease" in his patients, and then connect the dots leading from the clinical presentation to the diagnosis, etiology, treatment, and, in many cases, cure. He wanted to be able to understand it all: how, why, when, and where immunity was responsible in defining health and disease. Questions developed from observing and conversing with patients regarding these fabled "experiments of nature," a term used by one of Good's first mentors, Irving McQuarrie at the University of Minnesota, when he gave the young Bob Good advice on how he should approach his career in medicine and medical research by becoming a pediatrician and observing "experiments of nature." Bob was so impressed by that intriguing and eloquent description of illness that from that moment forward "experiments of nature" became his hallmark signature phrase.

The Good Methodology: In Pursuit of Excellence

> Salus populi suprema lex esto. (Let the welfare of the people be the supreme *law.*)

Good's methodology of placing the patient first and his or her welfare as the focus and driving force of his research steered his research and clinical efforts. Tenacity;

incisive questioning over and again; challenging current dogma and those who proposed it; voluminous reading, writing, and publishing; critiquing theories and results; innate intelligence and 20-hour workdays led Bob Good to become one of the finest pediatricians and clinical and basic immunologists of all times.

Continuing Tradition

> We are what we repeatedly do. Excellence, then, is not an act, but a habit.
>
> **Aristotle**

Bob Good was the consummate people person, professor, mentor, team player, and even better team leader. He trained over 300 young scientists worldwide, many of whom distinguished themselves as professors, chairmen, heads of departments and institutions, and leaders in their fields. Good was extremely pleased to see his former students and fellows, whom he affectionately called his intellectual children and grandchildren, develop their own careers and become distinguished professionals. Bob, to his credit, gave female scientists the respect of not being treated differently from their male counterparts; for him, the only criterion was the degree of excellence.

Good practiced the adage that sharing is strength, learning from and sharing with others throughout his entire life. He generously gave to others as he received, in kind, from his own mentors, E. Lyon, I. McQuarrie, L. Thomas, H. Kunkel, Mac McCarthy, professors, colleagues, and students. As a young professor at the University of Minnesota, Good said of his own dean:

> Harold S. Diehl conveyed this heritage [the "Golden Age" of scholarship at the University of Minnesota] to me as my dean, and I shall always think of him in this role. A fine scholar in his own right, he cherished good research. He opened many doors for me, created innumerable opportunities, and fostered my development as a student, young faculty member, and ultimately professor.

EDUCATION AND ACADEMIC OPPORTUNITIES

Education and academic opportunity were the cornerstones of Good's upbringing and would become his constant, welcome, and challenging companions throughout his lifetime. Good was a straight A student and completed all his pre- and post-graduate studies at the University of Minnesota in Minneapolis. After receiving a bachelor's degree in 1944, he continued his academic studies by matriculating concurrently in both the medical and graduate schools in the first honors M.D./Ph.D. program at the university. Good studied and worked in the laboratory day and night throughout the year. In 1947, a short three years after beginning the programs, he graduated with honors and became the first student at the University of Minnesota to receive both degrees in the same ceremony.

The pursuit of excellence in all that he did was his true North Star. Encouraging others to do better than they think they can do was the scientific mantra he repeated over and over again to remind others as well as himself to continue their efforts. He never talked down to people nor did he confront them, even when their performances were lacking. He gave everyone the opportunity to rise to a challenge and self-correct.

He believed in working hard — if at first you don't succeed, then keep at it until you do. Making the best use of time, as exemplified by his own daily schedule and monumental scientific work product, was important to him.

His intellectual capacity, creativity, and sheer volume of professional accomplishment were more than vast. His work at the bench and with patients spanned almost 60 years; it was prodigious in both depth and scope. He cast his intellectual, clinical, and scientific nets far and wide. He captured many "experiments of nature" first observed at his patients' bedsides and brought them to the laboratory bench to analyze and solve their mysteries for the benefit of his patients. His encyclopedic knowledge and recall of pediatric and adult medicine were well known among his colleagues and yet he always made the time to listen to patients, colleagues, and students. Good never thought he knew all there was to know on a subject and was always willing and eager to learn something new and fill any existing lacunae in his knowledge base. In fact, two of his famous sayings were:

> All I can say is that the last word has not been written on the subject.

> A medical problem can always be analyzed in terms of how it fits into phylogeny, ontogeny, or pathology.

Influence on Others

Nowhere are the character of Bob Good and his influence on others better portrayed than in the quotes of students, colleagues, and others whose lives he touched.

> In our lives, we meet many people and they all influence us in one way or another. However, the person who influenced me most is my dear teacher, Dr. Robert A. Good, one of the greatest medical scholars in the world. Dr. Good taught me how to do research and how to approach it. He encouraged me to study hard and not to be afraid of making mistakes. When I would make a mistake, he warmly told me not to become discouraged but instead to learn from my experience. He said we will all succeed in the end, if we do not give up.
>
> **Chih-Hsin Chen, M.D.**

Good was known to often give sage and direct advice, based on his own productive life and decades-long career:

> Experiential docet. (Experience teaches.)

> Be selfish. Think of your own career first. No one else will!

> Some of my fondest memories are when we get together and discuss science and ideas and we keep on working right through lunchtime.

> We are so very lucky.

> This is no kitten ball game.

Good always made sure he gave everyone credit, both orally and in publications. He never made an unkind comment about anyone and always found something positive to say about everyone:

That fellow's feelings of inferiority are totally justifiable. I cannot praise him highly enough!

Good told his students, as he was told by his mentors, that to stand out from the crowd one must ask critical questions, accept only definitive answers, put both mind and body to the task, and proceed.

Trahimur omnes laudis studio. (We are all led on by our eagerness for praise.)

Good also said that he was told by one of his mentors that a little bit of acclaim is good as long as you don't swallow it!

Carpe diem. (Seize the day.)

It was hard to catch Good for one-on-one time. He started his days at 4 A.M., worked at home, and saw his fellows for early morning meetings until 8 A.M. He then went on rounds at the hospital to see his patients and worked in his lab. Evening schedules were just as tight. More than one colleague has told of how he exchanged cutting Good's hair for a morning appointment because of Good's active schedule! Another told of a breakfast meeting in New York and his astonishment when the breakfast menu consisted of steak and French fries. When he commented on the menu, Good retorted that it was already lunchtime! These are only a few of the many stories about the long and fulfilled days in the life of Robert A. Good.

UNIVERSITY OF MINNESOTA, 1944

Outstanding people have one thing in common: an absolute sense of mission.

Zig Ziglar

Good's dual careers as a clinician and clinical and basic researcher spanned almost 60 years, from 1944 to 2003. He remained at his alma mater, which always held a special place in his heart and mind, in his beloved home state of Minnesota, for 28 years. He served on the medical school faculty from 1950 to 1972 as an instructor, assistant professor, associate professor, American Legion Memorial research professor, professor of pediatrics, professor of microbiology, and professor and head of the Department of Pathology. His greatest scientific accomplishments were fostered during his time in that exceptional clinical and teaching environment.

Good wanted to be remembered foremost as a pediatrician, immunologist, and teacher. In following his own scientific trail, as he did so eloquently when writing about E. Lyon, one can see exactly how he fosters independence and originality as well as sharing and inviting others to join him in generating excitement, and pursuing ideas, concepts, and theories among his colleagues and medical and graduate students.

Keywords in Good's Scientific Lexicon

> It is always the challenge of a new day, this feeling of excitement.
>
> **Robert A. Good**

Were Good able, in 1944, to see his future scientific trajectory spread out before him, the core of his research legacy and scientific contributions would certainly be the dense, compact, and mysterious immune system. Much like fission, the nuclear core would explode into myriad discrete areas of the human immune response to be explored; described by a string of keywords that would have been, with each learning experience and observed "experiment of nature," added to the increasing fund of knowledge to help solve the puzzle and balance the equation between ease and dis-ease.

To the student interested in analyzing Good's scientific opus, the titles of his early papers incorporate the seminal and recurring themes found throughout the corpus of his vast bibliography. Plasma cells, bone marrow, inflammation, allergic reactions, reticuloendothelial system, kidney and liver disease, autoimmune disorders, pathology viewed by the electron microscope, and hypersensitivity were Good's constant themes. He worked at relating them to each other, bit by bit to connect the dots and form matrices bridging the gaps and providing answers and treatment cures caused by malfunctioning immunological systems. His scientific course was set after only a dozen papers published before he was 27 years old!

SCIENTIFIC CONTRIBUTIONS

> Throughout the centuries there were men who took first steps down new roads, armed with nothing but their own vision.
>
> **Ayn Rand**

Plasma Cells and Antibody Production, 1944

Beginning with the armature of the immune system and in particular, the plasma cell, Good contributed to the further understanding of its function beginning in 1944 on work published as the subject of his doctoral dissertation in 1947. He demonstrated that plasma cells were indeed the major antibody-producing cells in the immune system. His investigations were independent of but contemporaneous with contributions of Astrid Fagraeus of Sweden. This knowledge was soon applied to patients with X-linked agammaglobulinemia. Good discovered that these patients lacked both plasma cells and germinal centers but had normal lymphocyte numbers and cell-mediated immunities. The study of the plasma cell would become the core of research throughout Good's life. His studies of patients with severe agammaglobulinemia showed that not only do two distinct immunological systems exist (later called T and B cell systems), but his patient's "experiments of nature" were examples of bisections of the bacterial, viral, lymphoid, and immunologic universes (1954–1956) — a most amazing and insightful observation made by Good.

ROCKEFELLER INSTITUTE, 1949

As a recipient of a Helen Hay Whitney Fellowship, Good was obliged to take a year of training away from the University of Minnesota. This would be the first time Good spent living outside his beloved home state. The world was waiting for him and him for it. He chose, upon the recommendation of McQuarrie, the Rockfeller Institute — a veritable Mt. Olympus or prestigious ivory tower. He joined the rheumatic fever laboratory of Maclyn McCarty, of DNA fame. New York City energized Good and vice versa. In fact, New York was probably the only city that could keep pace with Good as he began to cut a wide scientific and clinical path for himself and others. He loved the culture, music, art, food, and most of all the incredibly interesting people he met there.

Lessons Learned from Hodgkin's and Multiple Myeloma Patients

Good did not initially find his own unique scientific niche in those first few months at the Rockefeller, but thanks to a circuitous route that included Henry Kunkel, an early mentor, who happened to need large amounts of myeloma serum to continue immunochemical studies on proteins, Good was brought into contact with a myeloma patient and the characteristics of that particular disease. Good was known in some circles as a very successful plasma cell hunter and obtained all the sera Kunkel needed. In exchange for sera contributions, Kunkel taught the young Bob Good about the emerging fields of immunochemistry and serum globulin proteins. Good still had not found the perfect fit or research area to which he could devote his time and make a contribution.

Al Stetson suggested that Good crystallize CRP which presumably would have made Maclyn McCarty, Good's boss in the rheumatic fever laboratory, happy. David Karnofsky of the newly established Sloan-Kettering Institute recommended using pleural and peritoneal effusions from Hodgkin's patients as copious sources of CRP as starting materials. This led Good to see another spectrum of diseases involving the immune system in Hodgkin's patients whose susceptibilities were completely opposite to those found in myeloma patients.

Quod erat demonstrandum. (Which was to be proved.)

These were the scientific happenstances and underpinnings that combined to create the critical mass that would precipitate the major focus of Good's long-standing research interests: T and B cells, their progenitors, and their progeny. Good would find his own niche and embark on what would become his own particular course in an area he would later term "clinical immunology" steadied by the keel and rudder in the form of the plasma cell and cell-mediated immunity and the two "experiments of nature": multiple myeloma and Hodgkin's disease, whose secrets he would later decipher in collaboration with his colleagues and students when he returned to his clinical work and laboratory in Minnesota.

Scientific Symphony

> Organized activity and maintained enthusiasm are the wellsprings of power.
>
> **Paul J. Meyer**

Trying to get one's arms around and grasp Good's research and the clinical issues in which Good was involved is like reading several books at the same time. One must be able to follow parallel paths and remember the plots and characters of each scientific study when reading his bibliography. His research as seen from a distance was much like a symphony: "Variations on a Theme of Immunology in G Major," played by an orchestra of different instruments with Good as the conductor most of the time, co-conductor some of the time, or sitting in the back giving support and advice to others. There were many "first violins" brought up through the ranks along the way — promising young and brilliant scientists who today are prominent in their fields. Good published over 2,100 publications, many times shared with over 1,200 co-authors, along with 50 books, countless articles and abstracts, and other contributions to the communities where he lived and worked.

BEGINNING OF GOOD'S GOLDEN YEARS

> Every great institution is the lengthened shadow of a single man. His character determines the character of the organization.
>
> **Ralph Waldo Emerson**

The Genesis (1944) and Demonstration (1965) of the Two-Component System of Cell-Mediated and Humoral Immunity

Good's studies of patients with severe agammaglobulinemia showed that two distinct immunological systems, later designated T and B cells, existed. Also, the expression of his patient's diseases bisected the bacterial/viral microbial universe divided into the high grade encapsulated bacterial pathogen and the acid-fast bacilli, fungi, and some viruses.

In 1952, before discovering the role of the thymus in immunology, Good showed through his investigations of agammaglobulinemia, Hodgkin's disease, and multiple myeloma, that two major arms of immunity exist. Antibody production based on plasma cells was shown to represent the major defense against encapsulated bacterial pathogens; the other thymus-dependent arm of immunity based on lymphocytes represented the major defense against many viruses, fungi, and facultative intracellular bacterial pathogens. A work Good published in 1964 with senior fellow Ray Peterson and Max Cooper, a young fellow in Good's laboratory, clearly delineated and demonstrated Good's 1952 theory of a two-component immune system consisting of humoral and cell-mediated immunity. Peterson and Cooper brought the proof of that theory to fruition in experiments with chickens. Unlike other animal models,

chickens provided an excellent opportunity to tease out the two-component theory of immunity in that they have two morphologically and distally separate lymphoid organs: a cell-mediated thymus-dependent system and a bursa that was found to be responsible for humoral immunity.

Good, his colleagues, fellows, and student associates were about to make scientific history again. Their findings were published in *Immunologic Deficiency Diseases in Man* under the title of "The two-component concept of the lymphoid system," authored by Cooper, Perey, Peterson, Gabrielsen, and Good.

In addition to receiving the first E. Meade Johnson Award and performing otherwise recognized work on the Shwartzman phenomenon, Good was about to begin one of the most exciting and challenging periods of his career. He opened his green pediatric journal one day in 1952 and read about Col. Ogden Bruton's 8-year-old male pediatric patient whose serum electrophoretic pattern was void in the pattern area of gamma globulin.

Extending Col. Bruton's initial findings, Good was eager to test his plasma cell theory that certain immunologically challenged patients would not develop plasma cells. The anticipated opportunity to test his theory was soon presented to him by three of his own pediatric patients. Two were brothers, which suggested a genetic component to their agammaglobulinemic illness. He found, as he predicted, neither plasma cells nor gamma globulin Schlieren patterns in the sera of the children. Germinal centers were absent as was the development of lymphocytes. Good extended his studies to include patients from neighboring hospitals and soon had a dozen patient profiles. He was to call this syndrome Bruton's agammaglobulinemia to "recognize the unique contributions made by Col. Ogden Bruton."

Good found several different types of agammaglobulinemia within the patient population, including XLA, hypogammaglobulinemia, and delayed allergic reactions.

Good's Syndrome: Thymoma with Immunodeficiency, 1953

A most telling experiment of nature.

Robert A. Good

In 1953, Good was asked to consult on an adult patient who had previously presented to Richard Varco's chest clinic in 1951 with far too many recurrent bouts of pneumonia. Soon thereafter, Varco extirpated a 565-g benign stromal epithelial anterior mediastinal tumor. Removal of the tumor did not restore the patient's immunological response. Good tested the patient's serum and found the presence of "some" plasma cells, indicating hypogammaglobulinemia, rather than an XLA patient devoid of all plasma cells and agammaglobulinemic. This led Good to question the role played by the thymus, if any, in the immune response. He postulated, based on both patient and experimental observations, that it did play an essential part in immunity, but confirmation of that theory would be left to the rabbits; however, the glory did not go to the class of 1954, the 4- to 5-week old group, but to the class of 1959; the "hot little newborns," as Good called them.

This was the beginning of a lifetime of study of immunodeficiency diseases in humans with the ogammaglo bulinemic patient providing a challenging and perplexing "experiment of nature."

In order to experimentally test Good's theory regarding the thymus, 4- to 5-week old rabbits were thymectomized to test for their subsequent ability to produce antibodies, thus demonstrating the role of the thymus. Laboratory findings for that particular experimental construct were published from 1954 through 1957. While the instant experiments confirmed the 1945 published work of Harris, they did not demonstrate Good's theory that the thymus was intimately involved in the immune response and that thymectomy would disrupt that process. Successful and promising results of subsequent rabbit experiments were submitted to the American Association of Immunologists (AAI) in December of 1960, demonstrating that, indeed, the thymus was found to be critical to the immune process when thymectomy in rabbits was performed during the neonatal period.

How the Rabbit Experiments Began, 1954

Good, one of Varco's fellows named L.D. MacLean, and Sol Zak, a medical student of Good, set about doing that first set of unremarkable rabbit thymectomy experiments in 1954 and 1955. The experimental design was based upon earlier publications beginning with Bruton's 1952 paper on his agammaglobulinemic patient and Good's plethora of papers on agammaglobulinemia, plasma cells, and thymoma. Based on the evidence, it was reasonable to assume that a difference should be demonstrated by thymectomized rabbits.

Good was familiar with the immunological states of newborn humans, rabbits, and other experimental animals. What was not calculated then was the timing of maturity of the rabbit's immune system. Thymectomy at 4 to 5 weeks of age seemed a sound supposition physiologically and ontogenetically, but it was too late in immunological development to show the desired effect of thymectomy. Had the experiments been done in mice whose immunological apparatus matured later than those of rabbits at the 4- to 5-week-old mark, the defining history of the crucial role played by the thymus in mammalian immunity might have been told at an earlier date.

In their 1956 paper titled "Thymic tumor and acquired agammaglobulinemia: a clinical and experimental study of the immune response," MacLean, Zak, Varco, and Good boldly began by stating with great conviction and logic that

> the simultaneous occurrence of acquired agammaglobulinemia and benign thymoma in humans suggested that the thymus might participate in the control of antibody formation.

Despite what were disappointing results, they continued to insist that

> the thymus does not participate in the control of the immune response under the conditions described herein is indicated by the experimental findings. In spite of the data obtained in this investigation, which indicate that the normal thymus does not exercise a controlling influence on the immune response in the rabbit, it still seems likely that some essential relationship exists between the thymic tumor and the acquisition of acquired agammaglobulinemia.

Those final words do not seem to be ones reflective of a mindset of surrender in deciphering the mysteries of the thymus. Indeed, the authors, in closing, entreat further research in the area: "Determination of the nature of the relationship awaits further investigation." And just like MacArthur and others with determination, the authors did return in 1959 to complete the mission.

Definitive Second Rabbit Experiments, 1959

In 1959, at a spring meeting of the Federation of American Societies for Experimental Biology (FASEB), Harold Wolfe, a friend and colleague, sought Good out after a presentation to tell him about a 1956 paper by Glick et al., unknown to most immunologists. The paper discussed the effects of neonatally bursectomizing chickens and their subsequent failure to produce antibodies. This was, indeed, important news. Wolfe also told Good about his own recent laboratory findings in Wisconsin with Mueller and Meyer that confirmed Glick's work and extended their own studies in bursectomized chickens.

Good said he then knew what the problem had been with the earlier rabbit experiments. The rabbits were thymectomized too late in their immunological development! Ben Papermaster, a fellow in Good's lab with whom Good had published work on antibody production in neonatal chickens, went to visit Wolfe in his Wisconsin lab to learn more about the lab's bursectomy experiments. When Papermaster returned, Good, his colleagues, and his students began a series of neonatal thymectomy experiments in rabbits, mice, and other animal models.

Exciting New Results, 1960

As an AAI member, Good communicated the results of the first animal experiments in abstract format. He directed the work of master's student Olga K. Archer and James C. Pierce, Varco's surgical fellow. The abstract was submitted in December of 1960, published in *Federation Proceedings* in March of 1961, and orally presented by Archer in April of 1961 at the FASEB meeting in Atlantic City, New Jersey. The title of the abstract was "Role of [the] thymus in [the] development of the immune response." The bottom line of the abstract was that "the thymus is necessary for the normal development of the immune response in the rabbit." After the presentation, Good, who chaired the session, presented an in-depth report on their latest experimental results with co-authors John Kersey, Carlos Martinez, Gus Dalmasso, and Ben Papermaster. The report covered findings with rabbits, chickens, and mice and clearly indicated that thymectomy or prevention of thymus development very early in life prevented the normal development of both humoral and cell-mediated immunities.

Additional Evidence

Their evidence also showed that thymectomy prevented homograft or allograft rejection of normal tissues and prevented rejection of both allogeneic and syngeneic tumors. Graft versus host reaction (GVHR) was inhibited due to surgical or hormonal

thymectomy. Good also discussed their extensive and convincing research on skin graft rejection across multiple minor and major histocompatibility barriers. These celebrated findings led Good to state in his usually audacious way that at long last they had established the essential function of the thymus! A series of more than twenty papers flowed on the subjects of the thymus and the demonstration of the two-component system of immunity from Good and his colleagues and fellows.

Immunodeficiency Diseases

Chronic Granulomatous Disease, 1957

Good said that one of the most rewarding and challenging areas of his work came from opportunities offered by observing and conversing with patients and learning about "experiments of nature," evidenced by the different forms of genetically determined and acquired immunodeficiency diseases. He was dedicated to every one of his patients and called them his best teachers. Studying the various forms of immunodeficiency diseases afforded a means to dissect immunological development and function. Good identified and provided the initial descriptions of at least eight distinct varieties of primary immune deficiency disease (PIDD) in humans in clinical and pathological detail. One was chronic granulomatous disease (CGD) of childhood. He linked hypergammaglobulinemic disease to phagocytes and established that this disease was based on a failure of phagocytic cells to kill ingested catalase-positive bacteria and generate hydrogen peroxide, one of the activated states of oxygen. Because CGD patients exhibited increased susceptibility to infection by catalase-positive bacteria, but not to catalase-negative bacteria, Good looked once again to the bisected microbial universe for answers, according to the specific mechanism of bodily defense toward potential pathogens.

Phylogeny, Ontogeny, Pathology, and Complement, 1964

Good's seminal and elegant work, beginning in 1964, on the phylogeny and ontogeny of the origins and development of the immune system using the lamprey, hagfish, and other species showed that immunity including the complement system appeared much earlier in evolution than had been imagined — dating back 400 million years. Good, despite the belief among certain members of the Boston group that isolated complement deficiencies were not associated with disease, was the first to refute that and demonstrate that patients with infections and collagen-like diseases most certainly had isolated complement deficiencies. These early observations by Gewurz, Pickering, and Day were followed by many more studies of additional patients with complement deficiencies.

> A medical problem can always be analyzed in terms of how it fits into phylogeny, ontogeny, or pathology.
>
> **Robert A. Good**

Transplantation: Genesis, 1955

Good's first published manuscript on transplantation in humans was a February of 1955 *JAMA* article titled "Successful homograft of skin in a child with

agammaglobulinemia." One of Good's patients, it was reported, kept a skin graft for more than a year while others vigorously rejected them. This led Good to begin experiments on the transferability of delayed allergic responses from agammaglobulinemic patients to normal recipients. Good was beginning to fine tune the different types of immunodeficient patients, based upon their clinical presentations and the courses of their diseases. The title of one of Good's papers published in 1963 with co-authors Martinez and Gabrielsen gave another hint of how close the possibility of success was: "Progress toward manipulation of the transplantation barrier."

Good was keenly interested and active in the area of transplantation many years before success could be claimed. Carefully planned research, insights derived from solid education and training in several disciplines, constant contacts with patients that focused on "experiments of nature," a network of colleagues and students to inspire and from whom to receive inspiration and lessons all led to the promise of success once the theoretical feasibility of organ transplantation had been established.

Cellular Engineering and Transplantation, 1967

Good coined the phrase *cellular engineering* to describe a methodology for treating disorders of the immune system and was the first to successfully use fetal liver cells and bone marrow transplantation as examples.

FIRST BONE MARROW TRANSPLANTATION PATIENT, 1968

In August of 1968, Good and a group of his fellows put into practice his earlier published theory of the possibility of curing an X-linked congenital form of severe combined immunodeficiency disease (SCID) by bone marrow transplantation (BMT). The first successful transplantation and the first cure of an X-linked SCID by cellular engineering were achieved. The 4-month-old male SCID patient developed aplastic anemia, a complicating acquired immunodeficiency disorder that compromised the initial successful transplant necessitating in November of the same year a second allogeneic bone marrow transplantation with the same matched (B, C, D loci) sibling donor. This second BMT corrected and subsequently cured the acquired aplastic anemia developed, most likely Good said, from an A antigen mismatch between donor and recipient in the first BMT.

Details of First BMT

Jerome L'Heureux, a pediatrician in Meriden, Connecticut, knew of Good's work and interest in immunodeficiency diseases and the promising area of BMT. L'Heureux was convinced that Bob Good held the only chance for the survival of his 4-month-old male patient. Eleven male babies on the child's mother's side of the family succumbed to this SCID before their first birthdays. No male child had survived in eight years. L'Heureux's patient had already faced several bouts of life-threatening pneumonia, each one staved off by antibiotics. He gave the child little hope of survival unless Bob Good had an idea that would save the child from a certain and early death.

The child was found to be suffering from the X-linked form of SCID. He had four healthy sisters but he was getting weaker every day. Good examined the child and determined that he was a likely candidate for BMT as an effort to try to cure the X-linked SCID (XSCID) from which he suffered. If a reasonable major histocompatibility complex (MHC) matched donor could be found, they would proceed with the transplant.

Only one of the patient's sisters appeared compatible enough to allow doctors to attempt the procedure, but one chance was all that was needed. Good assembled the transplant team. Richard Hong was an independent colleague and associate professor who helped Good train fellows clinically and in the laboratories and treated children with both primary and secondary immunodeficiency diseases. Edmond Yunis had become director of the University of Minnesota blood bank and brought the group to the cutting edge of research on lymphoid and hematopoietic transplants in experimental animals. Carlos Martinez and Yunis had earlier shown that it was possible to achieve lymphoid cell transplants without producing GVHD — a critical factor in successfully transplanting bone marrow and having it engraft in the recipient without killing him. Hilaire Meuwissen, a senior fellow interested in carrying out transplants of stem cells from marrow to treat SCID, would supervise the surgery. Richard Gatti had just joined Good's group as a research fellow. Gatti, with assistance from Hugh Allen, a clinical resident, would make history by actually performing the transplant.

The patient and his sister were later shown to be less compatible than previously thought, by a single antigen attributed to an A locus mismatch due to a previous genetic cross-over event in the recipient. No prophylactic myeloablative treatment was used. The transplant was deemed a success. Both T and B cells were reconstituted within the recipient within a month. The second part of the story is well known in that the first BMT, while successful in curing the XSCID, created a complicating and life-threatening aplastic anemia due to an antigenic mismatch unknown at the time of the first transplant. The majority opinion was to destroy the first transplant that caused the anemia, but Good felt that would bring the patient back to ground zero — still suffering from the fatal XSCID that would soon claim another victim. Good's reasoning prevailed and with the family's consent a second bone marrow transplant was performed in November of 1968 in an attempt to cure the fatal anemia that developed as a result of the first transplant. The same brave little sibling donor was asked to donate more of her bone marrow to her ailing brother. This time, the little patient was completely cured; neither XSCID nor aplastic anemia was present after the second transplant. Good described his young patient's new immune system thus:

> Mature red blood cells, white blood cells, and platelets promptly appeared in the circulating blood. The patient's red blood cell type switched over entirely from cells of the patient's genetic A type to production of red cells from the marrow that were now entirely of donor origin-blood group O cells.

Now, almost 40 years later, the patient is completely cured of his congenital and acquired diseases, is married, and has two healthy twin sons.

BMT, a form of cellular engineering, has been applied to more than 75 otherwise fatal diseases. It has been demonstrated to be a viable method of reconstituting a

hereditarily defective immunological system and to correct both structure and function of a hematopoietic system affected by an acquired disease.

Recognition by Esteemed Colleagues

Good was nominated many times for the Nobel Prize, which he no doubt should have won for myriad clinical and scientific contributions and discoveries in various areas over the span of his six-decade-long career. The committee, in 1990, however, favored Dr. E. Donnell Thomas and Dr. Joseph Murray to share the prize in medicine and physiology for Thomas's perfection of bone marrow transplantation and Murray's first successful kidney transplant from one identical twin to the other. Good was, nonetheless, brought before that august podium in Stockholm, if not in person, then by everlasting words spoken by his colleague and friend E. Donnell Thomas, upon delivery of his Nobel Lecture on December 8, 1990:

> In November of 1968* Dr. Robert Good and his colleagues carried out the first marrow transplant from a matched sibling for an infant with an immunological deficiency disease.** Our team carried out our first transplant using a matched sibling donor for a patient with advanced leukemia in March 1969.

Good was held in such high esteem by his colleagues that when it came time to select the keynote speaker for the special lecture honoring Thomas at his own institution in Seattle, Good it was often said, received the popular vote. People needn't have been worried whether Good, who did not receive the Prize for the BMT he was the first to perform, would be upset to be asked to congratulate his competitor and recipient of the prize. Good said that he felt honored to be able to laud the successes of his colleague and friend, Don Thomas, for his accomplishments in the field of marrow transplantation in leukemia. Seattle gave Good his own award by naming the conference room where the event was held in his honor.

NEW YORK AND SLOAN-KETTERING INSTITUTE 1973

Cancer

Good's extensive work in the fields of congenital, acquired, and/or induced oncological diseases meant it was time to create a separate section in his research portfolio. He delineates the relationship of cancer and immunity in an editorial article titled "The cancer–immunity interface in a hospital practice."

Cancer and Immunodeficiency Diseases

In 1973, Good became president of the Sloan-Kettering Research Institute. He appeared on the cover of *Time* and was featured in the March 19 issue of the magazine. Good noted in the article that he and his co-workers observed a high

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* The first BMT was actually performed in August of 1968; the second was in November of 1968.

** Gatti, R.A., Meuwissen, H.J., Allen, H.D., Hong, R., and Good, R.A., *Lancet* ii, 1366–1369 (1968).

correlation between cancer and the immunodeficiency diseases and that "in order for cancer to occur and persist, there must be a failure of the immunological process." These "failures" provided the stimulation for Good to devote his life to the study and understanding of immunological "experiments of nature," finding ways to correct the imbalances and relieve the suffering of all creatures, large and small. He said:

> Understanding the immune system will enable us to do far more than treat allergies or immunodeficiency diseases or to control cancer; it will enable us to understand the basic processes of life.

Nutrition, Calorie Restriction, Longevity, Autoimmunity, and Cancer

Good, with colleagues Day and Engelman, analyzed in detail the molecular biology, cellular biology, and virology of the bases by which calorie restriction inhibits development of breast cancer in mice. Most striking were the observations that calories, on energy intake restriction, control and reduce proliferation of vegetative cell systems and reproductive organs while enhancing cell proliferation essential during immune responses and tissue regeneration. In studies extending over a 24-year period, Good and his students and younger colleagues were at the forefront in making many important contributions to analyses of the influence of nutrition, impacts of individual nutriments on immune function, and the development of immunologically based diseases. In addition, Good and Gabriel Fernandes showed reduced calorie consumption made it consistently possible to double, often triple, and occasionally quadruple the life spans of genetically short-lived autoimmune-prone mice and prevent the immunologic involution that occurs with aging in these animals. Using diets high in both calories and saturated fats, Good and his colleagues produced striking models of arthrosclerosis and arteriosclerosis in autoimmune-prone mice, but not in autoimmune-resistant strains.

Additional Significant Contributions

Good, his colleagues, and his fellows made other important contributions in the areas of nutrition and immunity, longevity and cancer, autoimmune diseases, systemic lupus erythematosus (SLE), kidney and liver diseases, virology, and other areas of interest.

- Good was the first to publish in-depth research demonstrating the immunosuppressive qualities of viruses.
- A 1973 paper on pneumocystis carinii pneumonia that Good co-authored with Burke is still considered a classic in the field of medicine.
- Among the most important contributions was the definitive analysis of the crucial role played by zinc in thymic function and in the development and maintenance of immunologic functions of both T and B cells.

PUBLICATIONS AND AWARDS

Good published more than 2,100 scientific papers. He authored, co-authored, or edited more than 50 books and wrote countless articles in his almost 60-year career at the laboratory bench and the patient's bedside. Good literally supported the pencil industry by writing all of his works in long hand in pencil. His archives house thousands of pages of handwritten papers, notes, articles, and other memorabilia. He was lauded as the most cited scientist in any discipline during a 15-year period from 1961 to 1976 by the Citation Index.

He was the recipient of more than 250 awards, honors, and recognitions including the Albert Lasker Clinical Medical Research Award; the Emperor's Sacred Treasure; the Gold and Silver Star, the highest honor Japan can bestow on a non-Japanese scientist; the prestigious Canadian Gairdner Foundation Award; the Claude Bernard Prize; the E. Meade Johnson Award; the Lila E. Gruber Award for his work on the Shwartzman phenomenon; the Parke-Davis Award; the Borden Award; the International Bone Marrow Transplant Registry 25th Anniversary Award; the John Howland Award, the highest honor granted by the American Pediatric Association; the David Karnofsky award for cancer research; and the Ronald McDonald Award of Excellence, to name but a few. Good was a generous patron of local and national charities and often donated his prize monies to charities.

Good received 13 honorary doctorates from Hahnemann Medical College; Catholic Medical College of Seoul, South Korea; University of Uppsala, Sweden; New York Medical College; Medical College of Ohio, Toledo; College of Medicine and Dentistry of New Jersey; University of Chicago; University of Rome; St. John's University; Chicago Medical School; Miami Children's Hospital; University of Minnesota; and Shinshu University School of Medicine. His research throughout his long career was funded by the National Institutes of Health, the American Cancer Society, and other agencies. His last honor was a merit award from the National Institutes of Health. He also served for several years on study sections of the NIH, NCS, and other agencies.

Memberships and Contributions to the Community

Good was a founder and/or member of myriad professional organizations. He served as president of the American Association of Immunologists, the American Association of Pathologists, the American Society for Clinical Investigation, the American Society for Experimental Biology and Medicine, and the International Society for Preventive Oncology, among others. Good was a charter member of the Institute of Science and when he arrived in Florida in 1985, he was the only member of the National Academy of Sciences in the Department of Medicine at the University of South Florida. He sat on over 40 editorial boards and served as an untiring consultant to many others. He was in demand as a lecturer and was able to present science in its simplest terms to lay audiences.

National Marrow Donor Program and Registry

Good was honored before the Congress of the United States by the Hon. Bill Young of Florida in 1994 for his pivotal, seminal, and sustaining role in establishing the first National Bone Marrow Registry Program in the U.S. in 1987. To date, over 93 million potential donors have been registered under this program and over 4 million transplants have been performed under the National Marrow Donor Program.

Bone Marrow Transplantation Programs

Good started the first BMT programs at the University of Minnesota, New York's Sloan-Kettering Institute, the University of Oklahoma, and All Children's Hospital in St. Petersburg, Florida. Mrs. Eleanor Naylor Dana donated $1 million toward the transplant unit in New York. She also named Good a trustee of the Eleanor Naylor Dana Trust and he served on the board for 28 years.

CELEBRATIONS AND ENDOWED CHAIRS

Hines Chair

Good was a recipient of the Hines Chair at All Children's Hospital in St. Petersburg Florida and the University of South Florida (USF) at Tampa. He generously gave up the chair to recruit a molecular geneticist for the Department of Pediatrics at the university.

Fifty Years of Medicine and Medical Research

In May of 1994, in St. Petersburg, Florida, on the occasion of his 78th birthday and 50 years in medicine and medical research, Dr. Good was honored by USF in a three-day celebration, organized by Professor Richard Lockey, director of the Allergy and Immunology Program, and attended by distinguished leaders in the fields of medicine and medical research. Over 500 colleagues, and members of academic and professional societies to which he belonged joined in the celebration. The highlight of the event was an important scientific symposium entitled: Perspectives in Immunology and Medicine I: A Symposium in Honor of Dr. Robert A. Good, 1944–1994.

Robert A. Good "Super" Chair

The University of South Florida again honored Good by establishing the Robert A. Good Chair in immunology. The Dana Foundation contributed a second million dollars in support of continuing the legacy of Bob Good and his research efforts. Both contributions were matched by the state and the university to become a phenomenal $5.2 million "super" chair in immunology.

Honored by the U.S. Congress

The Hon. Bill Young, a member of the House of Representatives, honored Dr. Good on the floor of the U.S. Congress for his outstanding contributions and pioneering role in establishing the National Marrow Donor Program in 1987. The President of the University of South Florida; Ambassador and Mrs. Marker; the President of All Children's Hospital, Dennis Sexton; and many others also paid tribute to the man who inspired and infused the university and hospital through his talent and generosity.

Tribute of Dr. Edmond Yunis

Dr. Edmond Yunis, a celebrated colleague and good friend, honored Good with a special tribute — a poem excerpted below:

When I was young we walked
through the wooded fields
near the tall trees close to the night,
when the loon sang distant songs.
Other times when was cold
the winter evenings with the bright snow
and the moon giving certain blue taint
showed lights covering the ground.
But, it was at dawn when often
we shared precious moments
of excitement and inquiry; new questions
and the challenge for answers.

We have all been there
and again we are here,
a gathering of the young and not so young
with binding forces like chains.
Today, we celebrate his life
one half a century, a triumph.
A natural contingency,
a miraculous chance.
Fifty years and more will come
and, when we meet again
we shall look at the sea,
and the warm breeze near our faces
with invisible birds above,
will fly together unfinished trips
beyond shadows and winds.

Then a toast to Robert, the scientist
our friend, the teacher and the physician.

The Robert A. Good Lecture Series

In February of 2001, the University of South Florida College of Medicine at Tampa honored Good in a special three-day tribute. The endowed annual Robert A. Good Lecture was established to carry on the legacy he established at the university and within the state of Florida.

PERSONAL GLIMPSES

Robert Good was a physically commanding, attractive, larger-than-life, warm, brilliant, eccentric, generous, optimistic, constantly energized, impressive, and charismatic man. He slept fewer than four hours a night throughout his life. What daylight did not give freely he stole from the night. It was quite normal for him to start his day at 4 A.M. by meeting with colleagues, fellows, and students at home over a pot of coffee. He often said:

> Your day can always be expanded at the front end, i.e., get up a little earlier!
>
> If you can't sleep, then get up and work!
>
> I can think of no greater punishment than to be made to stay in bed till 7 A.M.!

EARLY YEARS, MINNESOTA, 1922

Good was born on May 21, 1922, in Crosby, Minnesota, a small town north of Minneapolis, with a population of 2,065. He was the second of four sons born to educators Roy Homer Good and Ethel Whitcomb, both born in Hennepin County, Minnesota. Good's paternal grandparents, Charles and Emma Good, moved from Canada to Wisconsin and then to Minnesota before his father was born in 1861. Charles Good's family emigrated to Canada from England in 1874. Emma Good was born in England in 1866. Her family emigrated to Canada from England in 1864.

Roy Homer Good was completing his Ph.D. program in education in 1927 when he died of testicular cancer at the age of 37. Bob Good was only 5 then; his three brothers were all under 7 years of age. His mother decided not to remarry and continued to teach school while raising and supporting her four boys, all of whom grew up to become outstanding doctors. Bob collaborated with his brother Tom, a dermatologist, in writing several papers.

Guillain–Barré, 1941

In June of 1941, at age 19, during his pre-med university years, Good suffered a mild case of what Good later said was Guillain–Barré (GB) — not polio nor amyotrophic lateral sclerosis. At the time of diagnosis, doctors did not know whether Good would ever be able to walk again or, what surely must have been a worse prognosis, be able to continue his university studies and realize his dream of becoming a doctor and helping to cure cancer — a promise he made to his father when he was only 5 years old.

The illness started suddenly and quickly left him paralyzed from the neck down, but did not necessitate the use of artificial ventilation or an "iron lung" as the device was known in the days of polio epidemics that crippled lives as well as bodies. Fortunately, Good suffered only a mild case of GB and gradually regained control of his muscles. The illness resolved within the year but left him with paralysis below the knees and lacking knee jerk reflexes. This led to his early and understandable interest in the two-nerve two-axon studies he conducted in Berry Campbell's neurophysiology lab while he was still a graduate student, before Fred Kolouch wooed him away with alluring studies of plasma cells.

Good, always an A student, was among the first 14 students to be selected for admission to medical school in March of 1943. Upon hearing of Good's illness, the dean arbitrarily deleted Good's name from the list. When Good found out, he naturally went to see the dean and ask why his name had been eliminated. The dean said he "assumed" Good would not be entering medical school because he had Lou Gehrig's disease. Good's minor paralytic disease left him lame below the knees, not above the neck, and certainly did not preclude him from thinking and writing! The dean put Good's name back on the roster and the rest is history. Good's lameness necessitated his somewhat eccentric but vastly more comfortable wearing of tennis shoes instead of more elegant oxfords.

Family Life

Good married and had five children, beginning in 1948 with Robert Michael, followed by Mark Thomas, Alan Maclynn, Margaret Eugenia, and Mary Elizabeth. As of 2003, his children had presented him with 14 grandchildren. He acquired three more grandchildren from the family of his wife, Noorbibi Day-Good, for a total of 17 little children to spoil and read to. Good said with so many children and grandchildren he memorized the stories so that he could be ready at a moment's notice when a little face was upturned toward his and asked for a story. One of his granddaughters is carrying on the family pediatrician tradition.

Good, divorced from his first wife, remarried and divorced a second time. He found happiness both professionally and privately when he married his long-time friend and colleague, Noorbibi Day, Ph.D., a Kenyan of Indian descent and a well-known scientist in her own right. They had known each other since 1957 when she interviewed with Good for a position in his laboratory. He said that she was welcome to work but asked if she had to work wrapped up in those swaddling clothes. Noorbibi said the garment was a sari and that she was used to working in one. Noorbibi went to work with Good and wore her sari. Bob and Bibi both had families of their own then and were professional colleagues and friends. When they married years later, their families including Bibi's two sons Kahlil Day and Selim Day melded together very nicely. The two families still remain in close contact. Life is unpredictable. While it may not offer an entire lifetime of happiness, it provided several decades' worth in Bob and Bibi's case.

Noorbibi Day-Good published her first paper from Good's laboratory in 1958. Their professional relationship continued more than 45 years and produced more than 175 papers along with a dozen books and articles. They shared 20 years as

husband and wife. They were usually the first on the dance floor and the last to sit down. Theirs was a good marriage based on a lifetime of friendship and respect.

Memories of Bob Good

Bob loved animals, especially dogs. His personal library contains many books about dogs. A photo of his last cocker spaniel, KD (the dog was a gift from Kahlil Day, and Bob named the dog in Kahlil's honor) remains on display in the library along with photos of family members, friends, and colleagues. He loved American football, especially when his hometown team, the Tampa Bay Buccaneers, won the Super Bowl in Tampa! He loved classical music, opera, and poetry, especially that of Robert Frost, good conversation, and gourmet food he prepared. Good was convinced that all great scientists must by nature be great chefs! He loved to travel the world and see all that could be seen by one man who lived life to the hilt.

The End of a Chapter

Robert A. Good retired from his lab and from this life on Friday, June 13, 2003, after 81 revolutions around the sun. He died at home, surrounded by his family, friends, and one of his student fellows. This was the end of a chapter but not the end of the book that has yet to be written about Bob Good. He suffered but never complained during a long and valiant battle with esophageal cancer, a fatal "experiment of nature" diagnosed in 1997. Despite three surgeries, radiation treatments and all that goes with battling such illness, he nevertheless continued to work, teach courses, attend lectures and events, and mentor his beloved students and fellows. His body was wearing down, but his mind was razor sharp until the end. He was reading a book on DNA on his terrace in St. Petersburg, Florida, looking east at the vast expanse of the blue-green waters of the Gulf of Mexico he loved so well. Boats were in the harbor and small private planes were taking off and landing at Albert Whitted airport in front of his 23rd floor condominium. The sky was brilliantly blue and cloudless on the day Bob died. He never tired of being alive until the very end when he was told that the cancer returned with a vengeance and nothing more could be done. When his wife asked whether there was anyone he wanted to see, he replied, "my students." Bob closed his book and as the sun set, called it a Good day and a Good life. He never forgot us and we will never forget him.

Memorials

Two memorial services honored Good. The first one was in June of 2003 at All Children's Hospital in St. Petersburg. The second one was held in November of 2003 at All Souls Unitarian Church in New York City and was followed by a major memorial symposium at Rockefeller University — the site of Bob's early work in Maclyn's lab that allowed him to find his own scientific niche studying myeloma and Hodgkin's patients. The symposium was sponsored by Bob's long-time friends

Fred and Vicki Modell, who founded the Jeffrey Modell Foundation in honor of their son who died of PIDD. Scientists and dignitaries from around the world, friends, and family members gathered to remember and pay their respects to a man who had given his life to the well-being of others.

The Modells, generous patrons who have devoted their lives to finding cures for diseases like the one that stole their son, are building an impressive state-of-the-art immunology center at Harvard Medical School to commemorate the 20th anniversary of their foundation. The library at the center will be named in Bob Good's honor as testimony to his contributions to the field of immunology. It is hoped that bright young minds will find inspiration by learning about the life of Robert A. Good and that the torch he has passed to others will not be extinguished and will burn even more brightly in years to come.

Fred Rosen

One keynote speaker at Good's memorial service was Fred Rosen, who passed away in May of 2005. Rosen was a favorite of Good's, a good friend, erudite scholar, exceptional physician scientist, and healthy competitor, hailing from Harvard and the Boston group. Rosen spoke thus of Bob Good:

Fred Rosen's Tribute to Good

In 1865, in his *An Introduction to the Study of Experimental Medicine*, Claude Bernard wrote:

> Great men may be compared to torches shining at long intervals, to guide the advance of science. They light up their time, either by discovering unexpected and fertile phenomena, which open up new paths and reveal unknown horizons, or by generalizing acquired scientific facts and disclosing truths, which their predecessors had not perceived.

How can I sum up the career of one such great man, Bob Good, in one thousand words, without shortchanging his memory and his larger-than-life presence in the medical science arena for half a century? Many things have been said of Bob Good since he left us, but there is one word that I have not heard. He was, after all is said and done, extremely intelligent. His scintillating, smart mind dominated any assembly where he was present. An example of this occurred in the early 1950s.

Gitlin and Janeway, my mentors, had presented at a meeting of the Society for Pediatric Research in Atlantic City an abstract on children with susceptibility to infection and hypergammaglobulinemia. On the spot he pointed out that this was absurd, that the latter was a consequence of the former and not the cause. He went home and quickly demonstrated in a similar cohort of patients that this phenomenon was due to a phagocyte defect, namely chronic granulomatous disease. Along with his colleague Beulah Holmes, he showed that this disease results from a fault in bacterial killing and that the hypergammaglobulinemia

was the consequence of persistent antigenic stimulation. In one stroke, he opened a new field of scientific endeavor in the economics of phagocytic function that provided scientific employment for many who proceeded to exploit this extraordinary observation. The time allotted to me does not allow further digressions to illustrate this point. It happened over and over again.

Bob was deeply humanistic and perhaps because of his own infirmities he always expressed his personal and caring concerns to others. He harassed me for years about all my bad habits, about smoking and being overweight, and I never took offense at his telling me these things because they were expressed with compassionate concern. Of course, his feelings for his own patients bore the same imprimatur of commitment and caring, He was after all a consummate physician.

He had a puckish sense of humor, sometimes eliciting the prankster in him. Once many years ago, while seated next to him at a meeting in St. Pete Beach, Florida, we listened to one of his research fellows present a talk, which I thought was awful. When he was done, I leaned over to Bob and said, "This guy is a preacher, not a scientist." Later that day, at a cocktail reception, this young man approached me and said, "Bob Good says you think I'm a preacher!" Slowly I felt myself sinking into the woodwork, thinking, "How could Bob have been so callous as to transmit my harsh opinion of this guy?" when suddenly the young man in question perked up and added, "How perceptive of you, Dr. Rosen. I am a graduate of the Louisiana Baptist Seminary!"

Those of us who knew him will always remember him as a tireless scribe, always sitting in the front row on the center aisle, taking copious notes of everything that was said. His storehouse of immunologic knowledge was immense. He was the outstanding immunopathophysiologist of his time and he had no equal in that regard. I see him now, shuffling hundreds of slides, overflowing into yet another carousel, as he entranced many listeners with his experiments of nature, and those of us who were fortunate enough to have shared his cup of knowledge and were inspired by his tireless, inquiring mind will never forget him.

In the first act of Chekhov's *Uncle Vanya*, Dr. Astrov, who has just returned from a village where epidemic typhus was raging, asks the nursemaid, "Will those who live a hundred or two hundred years after us and for whom we have prepared the way, will they remember us with a kind word?" And the nursemaid answers, "No, people don't remember. That is why God remembers." In Bob Good's case, they will remember for generations and generations to come.

And you too, Fred Rosen, as well as all the other illuminating pathfinders, those medical scientists who have gone on before us, will be remembered by your colleagues, students, and friends for your contributions.

Editors

Nicholas P. Plotnikoff, Ph.D., is a professor of pharmacology at the College of Pharmacy, College of Medicine, and Graduate College at the University of Illinois in Chicago. His principal research interest is in the area of psychoneuroimmunology with special emphasis on stress hormones and cytokines (enkephalins and endorphins). His current research focuses on the clinical effects of methionine enkephalin in the treatment of cancer and AIDS patients. In 1999, together with Robert E. Faith, Anthony J. Murgo, and Robert A. Good, he helped organize an update of the state-of-the-art *Cytokines: Stress and Immunity* (CRC Press LLC).

Robert E. Faith, D.V.M., Ph.D., is the associate dean for veterinary medicine and director of the Biomedical Resource Center of the Medical College of Wisconsin. He earned a D.V.M. from Texas A&M University in 1968 and a Ph.D. in immunology from the University of Florida in 1979 and pursued residency training in laboratory animal medicine at the University of Florida from 1968 to 1971. From 1974 to 1978, Dr. Faith served as staff fellow and senior staff fellow at the National Institute of Environmental Health Sciences. He was director of the Biomedical Research Center at Oral Roberts University from 1978 to 1984, director of Animal Care Facilities at the University of Houston from 1984 to 1990, associate director of the Center for Comparative Medicine at Baylor College of Medicine from 1990 to 1997, and director of the Center for Comparative Medicine at Baylor from 1997 to 2002. He joined the Medical College of Wisconsin in 2002.

Anthony J. Murgo, M.D., M.S., FACP, is a medical oncologist and an adjunct professor of medicine at the Uniformed Services University of the Health Sciences F. Edward Hébert School of Medicine in Bethesda, Maryland. Dr. Murgo received his M.D. and M.S. in pathology and immunology in 1975 from the State University of New York Downstate Medical Center. He completed medical residency training at Maimonides Medical Center in Brooklyn and a fellowship in hematologic oncology at Memorial Sloan-Kettering Cancer Center in New York City. Dr. Murgo is board certified in internal medicine and medical oncology and is a fellow of the American College of Physicians. He was on the medical faculty at the Oral Roberts University School of Medicine from 1980 to 1983. He later joined the faculty of the West Virginia University School of Medicine where he was a professor of medicine in the Section of Hematology and Oncology until 1989. He subsequently was a medical officer at the U.S. Food and Drug Administration's Division of Oncologic Drug Products from 1989 to 1996 and then joined the National Cancer Institute specializing in investigational drug development and clinical trials.

Robert A. Good, Ph.D., M.D. D.Sc., FACP, earned graduate degrees from the University of Minnesota in the early 1950s. He was the physician-in-chief at All

Children's Hospital in St. Petersburg, Florida, and a distinguished research professor at the University of Florida College of Medicine. His remarkable career includes service as the president and director of the Sloan-Kettering Institute for Cancer Research in New York; professorships in pediatrics, pathology, and medicine at Cornell University; head of cancer research at the Oklahoma Medical Research Foundation; and head of research at Memorial Hospital in New York.

He distinguished himself with major contributions to both basic and clinical immunology. His research achievements include discovery of the function of the thymus and definition of the two distinct major components of the immune systems. Dr. Good was the recipient of 13 honorary doctorates and more than 100 major citations and awards. He wrote and edited more than 50 books and book chapters.

Dr. Good had been president of the American Association of Immunologists, Association of American Pathologists, Central Society for Clinical Research, American Society for Clinical Investigation, Reticuloendothelial Society, and Society for Experimental Biology and Medicine. In 1978, he was recognized by Citation Index as the most cited scientist in the world over a 10-year period.

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1 Behavioral Effects of Cytokines: A Psychiatrist's Perspective

Ziad Kronfol

CONTENTS

INTRODUCTION

The notion that cytokines play an important role as mediators between the immune and nervous systems is now well established. It is also well established that this interaction is bidirectional, with products of activated immune cells (cytokines) interacting with cells of the nervous system and products of nerve cells (neurotransmitters) interacting with various immune cells.[1] The resulting complex dialogue is meant to

help protect the organism and prolong survival of the species. However, as with every biological system, malfunctions can occur and resulting pathology follows.

In this chapter, we will first review some of the behavioral effects of cytokines commonly found in psychiatric patients. These effects include disturbances in sleep, appetite, mood, cognition, energy and fatigue levels, and sex drive. This will be followed by a critical review of the cytokine hypothesis of major depression. The roles of cytokines as mediators in depression and other major illnesses such as infection, cancer, cardiovascular disease, and AIDS will then be discussed. We will also address the issue of behavioral toxicity associated with cytokine treatment for conditions such as hepatitis C and malignant melanoma. Thus, we hope to briefly cover most of the issues associated with cytokines and cytokine treatment from the perspective of the clinical psychiatrist.

BEHAVIORAL EFFECTS OF CYTOKINES

The observation that cytokines are associated with specific behavioral symptoms dates back at least a decade or two. Animal studies revealed that rats and mice injected with phytohemagglutinin (PHA) or lipopolysaccharide (LPS), substances that stimulate the production of different cytokines, exhibited symptoms of lethargy, fatigue, anorexia with decreased preference for sweetened water, decreased grooming, and decreased sexual activity — a clinical picture that prompted certain investigators to label sickness behavior because of its resemblance to the behavior of animals that were sick with infections.[2] We will therefore start by providing an overview of the relationship between specific cytokines and specific behavioral symptoms, both in animals and in humans.

Sleep

Sleep is a complex physiological process that is important for the survival of a species. Mammals exhibit at least two stages of sleep: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. The administration of exogenous interleukin-1ß (IL-1ß) or tumor necrosis factor (TNF) to mice or rats enhanced NREM sleep.[3] Substances that enhance the production of IL-1ß or TNF (such as bacterial or viral products) enhance sleep, while substances that inhibit the production of IL-1ß or TNF inhibit sleep.[4] Furthermore, the inhibition of IL-1ß or TNF inhibits the sleep induced by muramyltripeptide, a bacterial cell wall product, implicating these cytokines in the sleep responses associated with bacterial infection.[5]

In addition, clinical conditions associated with excessive sleepiness or fatigue seem to involve TNF. This, for example, is true for HIV patients who have disrupted TNF rhythms,[6] sleep apnea patients,[7,8] and chronic fatigue patients[9] with excessive plasma TNF levels as well as cancer patients receiving TNF.[10] Patients with postdialysis fatigue also have elevated levels of TNF.[11,12] Treatment of rheumatoid arthritis patients with etanercept, a soluble TNF receptor, alleviated the fatigue.[13] In major depression, most reports point toward an association between severity of depression and levels of TNF.[14, 15] These cytokines, particularly TNF, seem to play a role in the

fatigue and sleep disturbances seen in psychiatric patients and in medical patients with psychiatric symptoms.

Appetite

Appetite changes and accompanying weight gain or loss are major symptoms of both medical (e.g., infection, cancer) and psychiatric (e.g., depression, anorexia, bulimia) illnesses. The physiology of appetite and feeding behavior is very complex and involves neuroanatomical, neurophysiological, and neurochemical pathways that have not been completely elucidated. Recent evidence suggests that pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, TNF, and interferon (IFN) suppress appetite.[16] Furthermore, conditions such as infection,[17] inflammation,[18] cancer,[19–24] and possibly advanced age[25–28] that are usually associated with increased cytokine production have also been associated with anorexia and weight loss.

This, however, has not always been the case. For instance, increases in circulating cytokine levels have not been found in all cancer patients[29,30] and may be associated with certain forms of cancers, (e.g., pancreatic cancer)[23] but not others.[30] Similarly, the cachexia or weight loss may correlate with one cytokine (e.g., IL-6) [23] but not another.[31] Similar reservations have been mentioned for the association of cytokines with appetite and weight changes in other medical and/or psychiatric conditions. In eating disorders such as anorexia and bulimia nervosa, cytokine measures have been made but the results appeared inconsistent[32–34] and, therefore, the clinical significance remains doubtful.

Mood

As mentioned earlier, cytokines are associated with sickness behavior, a series of well coordinated but non-specific symptoms generally associated with infection or inflammation.[35] These symptoms include sleep and appetite disturbance, lethargy, anhedonia, depression, and a state of amotivation, usually accompanied by fever and an increase in hypothalamic pituitary adrenal activity. The purpose of the increased adrenal activity is to mobilize the organism's energy to combat infection by enhancing heat production (which in turn stimulates the proliferation of immune cells and interferes with the growth of many pathogens) and changing behavior to maximize the ability to fight the invading organism.

The behavioral changes in experimental animals included decreased food and water intake,[36,37] conditioned taste aversion,[38,39] decreased social exploration,[40-42] decreased grooming behavior, decreased motivational activities, and decreased spatial learning.[35] While the mood and affect of an animal cannot be directly and accurately measured, the symptoms described above have been compared to the symptoms of depression in humans.[43] In fact, human volunteers who received endotoxin injections in a double-blind, placebo-controlled manner to stimulate cytokine production reported increases in depression and anxiety only in the endotoxin-stimulated group.[44]

The authors reported significant positive correlations between cytokine secretion and endotoxin-induced anxiety and depression. In addition, treatment with cytokines

(IL-2 for cancer, IFNα for hepatitis C or malignant melanoma, IFNβ for multiple sclerosis) was associated with a high incidence of depressive adverse effects varying from 5% to as high as 40% of patients treated.[45]

Memory and Cognition

Memory and cognitive disturbances are central to various neurological and psychiatric conditions. While the etiology of such cognitive impairment can differ and includes various structural and metabolic elements, the realization that cytokines can produce such an effect is new. The first hint that cytokines can influence memory in humans probably dates back to the cognitive effects of IL-2 in the treatment of certain forms of cancer.[46,47] Further observations revealed that cognitive disturbance was also a major adverse effect in the treatment of hepatitis C patients with IFN immunotherapy.[48]

There were also reports of cognitive disturbances associated with IFN in the treatment of multiple sclerosis. Experimental studies in human volunteers revealed that endotoxin injections that stimulated the release of various cytokines were associated with both verbal and non-verbal memory disturbances in treated patients compared to controls.[44] Animal studies support these findings and, in particular, point toward a significant role of the hippocampus in these interactions.[49,50] Furthermore, chronic dosing of IL-2 in aging mice produced memory deficits along with neuronal damage that seemed to affect the hippocampus selectively.[51]

Sex Drive

The relationship of neurocircuitry, neurohormones, gonadal hormones, and sex drive is very complex and not completely understood. Until recently, sexual behavior was thought to be driven almost exclusively by central neural pathways (e.g., serotonergic or dopaminergic systems)[52] and gonadal hormones such as androgens that modulate sexual behavior both in males and females. However, with the development of the sickness behavior model in association with different cytokines, the suspicion is growing that various cytokines may directly affect sex drive the same way they affect sleep, appetite, and other neurovegetative functions.

Avitsur and colleagues[53] investigated this possibility in female rats. They showed that IL-1 inhibits sexual activity, motivation, and attractivity in female but not in male rats following central or peripheral administration. They also showed that TNF may also have a synergetic effect on this activity.[54] They concluded that from an evolutionary and adaptive standpoint, females are less likely to conceive during an infection, thus reducing the chances for development of an abnormal fetus, while males are less affected by IL-1 because reproduction during an infection is less risky for them than for their female counterparts.[55]

Fatigue and Lethargy

Fatigue and lethargy are common symptoms of both psychiatric diseases and medical illnesses as well. Major depression and anxiety are frequently associated with fatigue. Schizophrenic patients are often lethargic. Fatigue and lethargy are also common

symptoms of cancer and cardiovascular disease.[56] The underlying pathophysiology in all of these conditions has not been adequately investigated. Different explanations range from purely psychological (e.g., being overwhelmed with a condition) to purely biological (e.g., changes in the levels of hormones or neurotransmitters).[57]

Several investigators have recently advanced the hypothesis that fatigue, at least in cancer patients, may be attributed to excessive secretion of pro-inflammatory cytokines brought about by immune activation.[58,59] The immune activation may be in response to a tumor or to the treatments for the disease. To test this hypothesis, Bower and colleagues compared specific cytokine markers in 20 fatigued and 20 non-fatigued breast cancer survivor controls. Their results showed significantly higher levels of markers of pro-inflammatory cytokines in the fatigued group, including IL-1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor type II (sTNF.r2), and neopterin.[60] They also noted lower levels of plasma cortisol in the fatigued group. They concluded that pro-inflammatory cytokines may play a role in the fatigue reported by some breast cancer survivors. Similar data have been reported for other types of cancers.

CYTOKINES AND MAJOR DEPRESSION

Psychobiological Features of Major Depression

Major depressive episode (MDE) is characterized by distinct clinical and biological features. Clinically, MDE is associated with persistent sadness or anhedonia (decrease in pleasurable activities). Other important clinical features are disturbed sleep (insomnia or hypersomnia), often with early morning awakening; disturbed appetite with increased or decreased weight; fatigue; psychomotor retardation or agitation; feelings of worthlessness, hopelessness, and guilt; difficulty concentrating; and suicidal ideation.

The biological features are more controversial. They include increased hypothalamic pituitary adrenal activity (manifested by increased ACTH and cortisol secretion, probably secondary to increased levels of CRH)[61] and defects in feedback mechanisms associated with cortisol.[62] Other biological markers include altered noradrenergic[63] and serotonergic[64] functions, the latter often associated with impulsivity and suicidal behavior. Sleep EEG findings are characterized by shortened REM latency and decreases in delta sleep.[65] Immunological characteristics of depression include neutrophilia and lymphocytopenia, decreased lymphocyte response to mitogen stimulation, decreased natural killer cell activity, and increased secretion of pro-inflammatory cytokines such as IL-1 and IL-6.[66] Other inflammatory markers that are increased in depression include C-reactive protein (CRP), neopterin, and haptoglobin.[67]

Cytokine Hypothesis of Major Depression

Because of the similarities between sickness behavior in animals and major depression in humans[43] and because both seem to be associated with stress, some investigators have proposed that depression may be the result of an exaggerated immune

response to stress.[68,69] The hypothesis states that in genetically predisposed individuals, stress (either past or present) will stimulate certain components of the immune system, resulting in excessive secretion of pro-inflammatory cytokines such as IL-1 and IL-6. These cytokines, directly or indirectly, will activate specific areas of the brain, leading to the appearance of sickness behavior along with other features of depression, such as neurochemical and neuroendocrine changes.[70]

What is the evidence in favor of this hypothesis? As mentioned earlier, one line of evidence is the similarity between cytokine-induced sickness behavior and the symptoms of major depression. The symptoms include disturbances in sleep, appetite, mood, cognition, level of energy, and sex drive and all of them have been reported in conjunction with the administration of cytokines in both humans and in animal models.[71]

The other line of evidence is concerned with the neurochemical and neuroendocrine changes associated with cytokines. Animal studies revealed that intraperitoneal injections of PHA or PLS are often accompanied by changes in neurotransmitter turnover in specific areas of the brain — areas associated with mood disorders. IL-1, for example, has been shown to increase the brain concentrations of norepinephrine and serotonin, but not dopamine. IL-2 increased the levels of serotonin only.[72] Similarly, animal studies revealed that intraperitoneal injections of cytokine (IL-1) activated the HPA axis, resulting in increased secretions of CRH, ACTH, and cortisol.[73] Increases in both neurotransmitter turnover and activation of the HPA axis have been described in depression.[61–64]

Perhaps the most direct line of evidence comes from immunological studies in depressed patients presented in a previous publication.[66] In summary, studies of cytokine in depression can be divided into two categories: (1) studies measuring plasma and CSF concentrations of cytokines and/or soluble cytokine receptors in patients with major depression compared to healthy controls and (2) studies measuring cytokine production in stimulated leukocyte cultures in these groups. The results of studies of serum and CSF concentrations revealed increases in IL-lβ,[74] IL-2R,[75] IL-6,[75–78] and SIL-6R[75] in serum and an increase in IL-1β but not IL-6 in CSF.[79] Unfortunately, the results are inconsistent and some results are contradictory.[80] Furthermore, many studies are plagued with methodological flaws, such as sensitivity, diurnal variations, heterogeneity of study populations, and medication status of subjects.

Cytokine production studies tend to be more informative, but they are fewer in number and vary in methodology (tissue used, nature of stimulus, duration of culture, type of control). Again, results vary. Maes and colleagues reported an increase in IL-1β production in response to PHA[81] while Weizman's group reported a decrease in IL-1β production in response to LPS.[82] Seidel and Kronfol did not find significant changes in IL-1β in response to PHA[83] or LPS.[84] The increase in IL-6 secretion, however, seemed to be a robust finding.[84] Similarly, the increase in IFN production seemed well replicated.[85,86]

Critique of Cytokine Hypothesis

The cytokine hypothesis of major depression, at first glance, can explain many of the behavioral, neurochemical, and neuroendocrine features of depression as described above. Furthermore, stressful life events that often trigger depressive

episodes can also activate the immune/inflammatory system, leading to excess secretion of cytokines.[69] There are also occasional reports of decreases in cytokine secretion in conjunction with the use of antidepressant medications.[87,88] While all these factors support the hypothesis, they provide only circumstantial evidence of a role for cytokines in the pathology of major depression. Direct evidence would ideally come from the assessment of cytokine activities in various areas of the brain in depressed patients and normal controls. However, since the technology to perform such testing is not yet available, testing of the hypothesis will have to rely on measurement of circulating cytokines or *ex vivo* cytokine production in serum or blood samples, knowing well that the results may not reflect actual values in key areas of the brain associated with clinical depression.

Another problem is the varying and often contradictory results reported in the literature for different cytokines in depressed and control subjects. This is particularly worrisome because the results come from a very small number of laboratories and are often not confirmed by other laboratories. However, even with more independent confirmations of the results, other challenges must be confronted before the cytokine hypothesis becomes universally accepted as a plausible and serious explanation for major depression. The challenges include discrepancies between common clinical features of depression such as insomnia and the clinical effects of cytokines, mostly fatigue and hypersomnia. Another controversy relates to the subtype of depression affected. The cytokine hypothesis predicts that many vegetative signs such as sleep and appetite disturbances and HPA hyperactivity are associated with severe or melancholic depression, while according to recent reports, cytokine abnormalities have been mostly associated with dysthymia,[89] a milder form of depression.

CYTOKINES AS MEDIATORS BETWEEN DEPRESSION AND MEDICAL ILLNESS

While immunological abnormalities in patients with major depression are now well documented,[66,71] the clinical role these reported immunological aberrations play in the physical and mental health of an individual is not clear. We have already addressed the relationship of cytokines and mental health, particularly depression. This section will address the relationship of immune dysregulation, cytokines, and specific medical illnesses such as infection, cancer, coronary artery disease, and AIDS.

Infection

Infection is usually the result of a complex interaction between invasive organisms (most commonly bacteria or viruses) and a host. Animal models have shown that stress increases susceptibility to viral infection by altering the immune response.[90] Human studies looking at the relationship of stress, infection, and immune function are rare. Cohen and colleagues, in a landmark study, experimentally inoculated healthy volunteers with five different strains of common cold viruses and conducted extensive psychosocial assessments of these individuals. Their results indicated a