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the pope of TOXOPLASMOSIS

by Noreen Parks

"Somehow I've spent a lifetime and failed to have the ob-gyn medical community and health insurance industry appreciate what it means for a pregnant woman to deliver a destroyed or dead baby because of an infection that's preventable!" says Remington.

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JACK REMINGTON, MD, world-renowned as an infectious diseases expert, always wanted to be a neurosurgeon. From the day as an adolescent that he saw a polio-stricken child in leg braces, Remington vowed to be the kind of doctor who could repair the nervous system to prevent such tragedies. But this initial goal -- combined with serendipity -- instead set Remington on the path to becoming a clinician and researcher in immunology and infectious diseases as a professor of medicine at Stanford.

In 1952, within weeks of beginning studies at the **University of Illinois Medical School**, Remington applied for a fellowship to study nerve regeneration in squids. When his application was denied, he was crushed. Wandering down a hall in the medical school in this dejected state, he attracted the attention of immunologist Harry Dowling, MD, chief of medicine at the U of I hospital, who stopped to ask what was troubling Remington. When Remington explained, Dowling pointed out that the fellowship was for postdoctoral research, and Remington had only just begun his first year of training. "But if you're so interested in research," Dowling suggested, "why don't you come and work with us?" Remington accepted the challenge and began research related to the immune system.

A second turning point came in 1957, when Remington was honored with an invitation to join the **first group of research associates at the National Institute of Allergy and Infectious Diseases in Bethesda, Md**. As he waited for an interview in the office of the NIAID director, Remington perused an issue of *Science* that featured an article on diagnosing the infectious disease toxoplasmosis, co-authored by **NIAID researcher Leon Jacobs**, MD. At NIAID Remington had counted on continuing his medical school research on immune system responses to antimicrobial agents, so he was distraught to receive an assignment instead to the Laboratory of Tropical Medicine. "But when I got there," Remington recounts, "there was Leon Jacobs -- who had written that article -- as head of the lab. He was a wonderful and brilliant human being, and his enthusiasm and the description of his research program led me to decide that I would work on *Toxoplasma gondii*."

T. GONDII, ALSO KNOWN SIMPLY AS TOXOPLASMA, IS THE MICROSCOPIC PARASITE THAT CAUSES TOXOPLASMOSIS.

The single-celled organism occurs worldwide. Nearly one-third of adults in the United States and Europe carry antibodies to it, acquired by exposure, usually through the consumption or handling of raw or undercooked meat from infected animals. Though a latent infection is benign in healthy people, immune-deficient individuals can develop acute, life-threatening infections. And women who develop toxoplasmosis during pregnancy can pass it on to their fetuses, 95 percent of whom, if untreated, will suffer tragic cons equences later in life.

Remington's commitment more than four decades ago to unlock the secrets of a then poorly understood parasite has borne fruit on a scale neither he nor anyone else could have predicted. Working in his laboratory at the Palo Alto Medical Foundation (where he served until recently as chief of infectious diseases), Remington has virtually "written the book" on the pathogenesis, diagnosis and treatment of toxoplasmosis. He and his collaborators have extended the frontiers of understanding about the workings of the immune system in many opportunistic infections, developed serological screening tests and **tested drug therapies for infections in AIDS patients. At the same time he has served as an energetic mentor to a cadre of postdoctoral researchers who have come of age in his lab and moved on to leading roles at prestigious academic institutions around the world. He has left his mark on the study of the immune system, in the United States and abroad, as author or co-author of more than 600 articles, the recipient of more than a dozen of the most prestigious medical research awards, and a leader in dozens of professional societies.**

Remington credits the basic discipline and dedication that have supported him in his multi-faceted role to mentors such as **Jacobs and Maxwell Finland, the "father of infectious diseases," under whom Remington served as a postdoc at Harvard from 1960 until 1962, when he joined Stanford's medical faculty.**

Remington had begun his work on toxoplasmosis at NIH in the late 1950s in pursuit of answers to a controversy over whether pregnant women could transmit the infection to their babies. At that time, in the USSR and many other countries such infections were blamed for stillbirths, spontaneous abortions and congenital abnormalities, and doctors warned women whose blood tested positive for exposure to toxoplasma not to get pregnant. Remington

experimented with chronically infected mice and found that they could indeed pass on toxoplasma to their offspring *in utero*. He went on to isolate the parasite in cyst form from the uteruses of women who were chronically infected but free of symptoms. These findings did *not* prove that latent infections in pregnant women necessarily led to serious problems for the fetus -- but unfortunately many medical practitioners jumped to this conclusion and urged that women seropositive for the organism undergo drug treatment and avoid pregnancy until antibodies no longer showed up in their blood. As Remington and others would show, such treatment is futile, for, once exposed, even apparently healthy individuals carry the parasite as cysts in their organs and antibodies in their blood for life.

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He worked hard to overcome the misinterpretation of his results. "Over the years I've tried to change medical opinion in Germany, Mexico, South America, and elsewhere," he laments. "I've had women flying in to see me from all over the world to ask if they should attempt to have a child, and I've told them that there is no proof their infection is a danger to their unborn child."

Meanwhile other clues in the toxo mystery had emerged. At NIH Remington and Jacobs had analyzed varieties of meat commonly consumed by humans and found they contained toxoplasma cysts, strongly suggesting a meat-to-man transmission route for the organism. The less thoroughly the meat was cooked, the higher were the chances that viable cysts, which defy digestion, would cause infection. A researcher in France, Georges Desmonts, MD, later proved the hypothesis.

Desmonts and Remington collaborated closely over the years, and it was in France that Remington earned his title, "pope of toxoplasmosis," from television appear ances in which he counseled pregnant women to eat only well-cooked meat.

Despite these successes, Remington's early mentor Harry Dowling chided him for his tenacious interest in "an organism in search of a disease." Remington recalls, "That smarted a bit, but somehow I liked toxoplasma, and I stuck with it."

In 1962, when he joined the Palo Alto Medical Foundation's research institute at the invitation of director and School of Medicine alumnus Marcus Krupp, MD, Remington became the first full-time Stanford medical faculty member to hold a concurrent position outside the medical school. Remington's double appointment has strengthened ties between the medical school and the research institute, says Stanford professor of medicine **Gary Schoolnik, MD, former chief of the school's infectious diseases division.** "It certainly has been an advantage for the medical school to have one of the world's best infectious diseases researchers and clinicians on the faculty," Schoolnik notes. "In Remington's era, physicians were encouraged to do both clinical work and research if they were energetic and bright. But if you really look at how many have done both at his level of excellence, it was very, very few."

From the start, the major focus in Remington's lab was host resistance against nonviral opportunistic pathogens. His clinical subjects were patients in Stanford's pioneering organ-transplant program and cancer patients at Stanford and the Palo Alto clinic. These immunosuppressed patients -- or "compromised hosts," to use the term Remington coined -- developed all kinds of potentially lethal infections from bacteria, fungi and protozoans (including toxoplasmosis when an infected organ from a seropositive donor went to a seronegative recipient). According to Schoolnik, "Remington and his lab were at the forefront of defining the spectrum of diseases that could occur in these severely weakened patients and experimenting with drug therapies for managing them."

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Meanwhile, the unfinished business of the impact of toxoplasma on pregnant women and newborns continued to hold Remington's interest. "Always on the side we were interested in working on toxo," he says. Since the 1940s the sole means of

detecting toxoplasmosis had been the Sabin-Feldman dye test, which measures immunoglobulin-G (IgG) antibodies to toxoplasma in blood serum. Though highly accurate, the test doesn't reveal whether the fetus or newborn has acquired an infection, or if its antibodies to toxo came from the mother via the placenta. Remington knew that another type of antibody, immunoglobulin-M, is too large to pass through the placenta. So, he devised a test to detect IgM antibodies to toxo in the fetus or newborn that would provide a reliable means for diagnosis.

This led in the early 1970s to the development of a battery of tests for detecting IgM antibodies to several infectious agents. Dubbed "TORCH" (for toxoplasmosis; other, including rubella; cytomegalovirus; and herpes), it is now used routinely worldwide for diagnosis of these infections in newborns and adults. In Europe it is known as the "test of Remington." The research associated with the development of the TORCH screening tests and with treatment of organ-transplant recipients contributed to Remington's serological lab evolving into the major reference facility in the United States for toxoplasmosis. At the same time, his growing prominence in the field of congenital infections prompted him to co-edit (with **Jerome Klein, MD, a pediatrics professor at Boston University School** Of Medicine) a comprehensive textbook on infectious diseases in fetuses and newborns. First published in 1976, *Infectious Diseases in the Fetus and the Newborn Infant* is now in its fourth edition.

As beneficial as the TORCH screening proved for identifying toxoplasma in newborns, it represented an "after-the-fact" diagnosis, and Remington pressed on for a means of prenatal detection and treatment. He and his colleagues found that anti-microbial treatments for women who become infected during pregnancy dramatically decrease the risk of fetal infection. And, if amniocentesis is performed and toxoplasma is found in the amniotic fluid, the fetus can receive treatment directly, via treatment of the mother. But by far the most proactive measure, says Remington, would be a periodic blood test before and during pregnancy, for swift response as early as possible. In the United States approximately 4,100 of the 4.1 million infants born annually have congenital toxoplasma infections. Most of these, if not treated, will suffer epilepsy, mental and psychomotor retardation, serious vision and hearing problems, or even death. The estimated lifetime costs for special services for infected children born each year are at least $222 million.

Remington decries the fact that serological testing for toxoplasma is not yet routine in prenatal care, as it is in France and Austria. "Somehow I've spent a lifetime and failed to have the ob-gyn medical community and health insurance industry appreciate what it means for a pregnant woman to deliver a destroyed or dead baby because of an infection that's preventable!" he laments.

Over time, as Remington teased out the workings of toxo, he saw that he could use toxo to tease out the workings of the human immune system. Toxoplasma, as a relatively large and easy-to-see infectious agent, was useful for studies of how the human cellular immune system functions when challenged. "You could see toxoplasma inside a cell," he explains. "You could tell if the cell killed it, because you could see it disappear."

IN 1968 POSTDOCTORAL RESEARCHER JOEL RUSKIN, MD, AND REMINGTON MADE A KEY DISCOVERY: MICE INFECTED WITH TOXOPLASMA WERE RESISTANT TO LISTERIA AND SALMONELLA BACTERIAL INFECTIONS.

With additional studies, the list of organisms warded off by this protective effect grew to include a range of unrelated fungi, viruses and mycobacteria. Spurred on by these findings, the pace in the lab accelerated.

"I had an extraordinary experience," recalls John Hibbs Jr., MD, a postdoc under Remington from 1969 to 1971, and now professor of medicine and chief of infectious diseases at the University of Utah. "There was an undercurrent of excitement, as the **lab was on a true frontier in the rapidly developing field of immunology**." Hibbs and Remington went on to show that the ongoing stimulation of the immune system in mice caused by toxoplasma infection also enhanced their resistance to tumors. The driving question was what conferred this powerful resistance.

The answer turned out to be macro-phages, the non-specific "wandering cells" of the immune system that engulf and kill intracellular invaders. Hibbs and Remington showed that macrophages activated by infection were highly cytotoxic

to tumor cells. "This was remarkable," Hibbs explains, "because previously it was thought that all such anti-tumor resistance was highly specific and mediated by sensitized lymphocytes. Ours was the first description of non-specific cytotoxity by a mammalian cell for a tumor cell." This breakthrough set off a flurry of investigations around the country, leading to discoveries of other non-specific defense cells.

Neurosurgeon Frances Conley, MD, member of Stanford's medical faculty and chief of staff at the Veterans Affairs Palo Alto Health Care System, worked with Remington in the mid-1970s to investigate whether the anti-tumor resistance conferred by toxoplasma would work against brain tumors. It did. "As a mentor," she recalls, "he is demanding and extremely honest. I learned research science from one of the great research scientists that this country has produced."

Remington's high standards extend to the realm where the research discoveries ultimately count the most: the patient's bedside. "In making infectious disease rounds, he absolutely does not tolerate mediocrity," Hibbs remembers. **"He's an uncompromising and compassionate advocate for the patient, and if the best wasn't being done by everyone involved in the patient's care, he would stir up a ruckus and make sure the message got across in no uncertain terms. One of the most important things you learned from Jack is implicit in being a physician, but it has to be emphasized for every generation: that first and foremost you have to be an uncompromising patient's advocate. Jack is that *par excellence*."**

His toughness has made him a legend among Stanford interns, residents, and house staff, and rumor has it that in some circles he is known as "STAT Jack." Hibbs recalls being at a professional meeting where a group of young doctors from Stanford, sitting at a nearby table in a restaurant, were laughing and competing in telling "war stories" -- the subject of which Hibbs could just make out. It was Jack Remington. "You could tell that they'd all had uncomfortable experiences, but in retrospect found them very humorous -- and they had a very warm attitude toward him."

In the early 1980s, when the AIDS epidemic broke, toxoplasma took on a new significance, as the culprit that caused encephalitis in immune-deficient HIV-infected patients. In short, the organism "in search of a disease" had found one in a big way. Remington pushed hard for all HIV patients to get tested for toxoplasmosis (at least 30 percent will come down with toxoencephalitis without prophylactic drugs). **Virtually every new drug that is currently used for toxo treatment in HIV patients was first tested in the Palo Alto lab.**

During the last decade, his lab research has concentrated on the roles of monocytes, cytokines, and specialized T cells in resistance to infections, primarily those of the brain. Thus he has made, and continues to make, an immense contribution to scientific and medical knowledge of the central nervous system, the subject that fired his passion for medicine more than four decades ago.

And before he considers retiring, there's at least one more contribution he's determined to make. "It's been my lifelong ambition to derive a means of identifying acute toxoplasma infection in pregnant women testing a single serum sample, so they wouldn't have to abort or worry throughout their pregnancy about having an abnormal child," he says. Given Remington's lifetime of fierce focus on the microorganism that's caused such heartache, it won't be surprising when he does it. SM