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Anthony Cerami Award in Translational Medicine

A Journey in Science: The Privilege of Exploring the Brain and the Immune System

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Real innovations in medicine and science are historic and singular; the stories behind each occurrence are precious. At *Molecular Medicine* we have established the Anthony Cerami Award in Translational Medicine to document and preserve these histories. The monographs recount the seminal events as told in the voice of the original investigators who provided the crucial early insight. These essays capture the essence of discovery, chronicling the birth of ideas that created new fields of research; and launched trajectories that persisted and ultimately influenced how disease is prevented, diagnosed, and treated. In this volume, the Cerami Award Monograph is by Lawrence Steinman, MD, of Stanford University in California. A visionary in the field of neurology, this is the story of Dr. Steinman's scientific journey.
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It is claimed that the brain is an "immune privileged" site and there is a special environment that it inhabits, protected from immune attack. This doctrine is probably no more than a fable. The brain is not immune privileged, as I shall share with you.

My first encounter with the concept of the brain and its supposed state of immune privilege was hardly abstract. On August 15, 1951, at age 3, when returning home from a sweet vacation with my grandparents in the countryside, I found that my sister, Ruth, age 6, had been stricken with poliomyelitis while at summer camp. Ruth was hospitalized in the Contagious Disease Ward of the Los Angeles County Hospital, battling with all the might of her immune system against a polio infection in her brain and spinal cord. With this stark evidence, although I did not comprehend it at the time, there was no way that "immune privilege" might actually exist for the brain.

Perhaps there is a real irony behind how my career has evolved. Although the brain is not an immune-privileged site, it has been an honor and a privilege to study the interactions of the brain and the immune system over nearly half a century.

Three years after my sister, Ruth, contracted polio, when the Salk vaccine (1) first became available, I vividly remember standing in line to receive this miraculous gift from the field of immunology. Jonas Salk became a family hero, and a decade later, our paths intersected in my first experience with laboratory research.

My research career has taken me repeatedly to the matter of whether the brain is immune privileged or not. My colleagues and I discovered a potent therapy for the most common immune disease of the brain—multiple sclerosis (MS). However, the U.S. Food and Drug Administration (FDA)-approved therapy for MS has a real vulnerability. The therapeutic known as natalizumab (Tysabri), in protecting the brain from an immune attack in MS, allowed the brain to actually become immune privileged, thereby permitting a devastating viral infection to develop. Once again, from my research, I witnessed firsthand another big hole in that fable known as "immune privilege and the brain." Immune surveillance of the brain does exist, and impairing this immune function resulted in opportunistic infections.

Here I will share my experiences in developing therapies for immune diseases of the brain. The ultimate aim of this research is to try to successfully implement antigen-specific tolerance for autoimmune diseases in the brain and

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elsewhere, so that we can leave normal immune surveillance intact (2).

LIFE IN A PRIVILEGED TIME FOR SCIENCE EDUCATION

One of my favorite high school mathematics teachers, Patrick Perrone, known as p^2 (P squared), referred to me as "Lucky Larry." Indeed, I have been very lucky with timing. Born after World War II, the Great Depression, and the Holocaust, I grew up in the sunny sheltered environment of middle class America, in Culver City, California. My parents put a high value on both education and creativity. My mother, Anne, was remarkably creative. For example, her meals were so very creative, that the good news at dinner was that a bad experiment in the kitchen was rarely repeated, although the bad news was that a good experiment was also rarely repeated. But she loved me, as she did all three of my siblings. "Unconditional" and "constant" describe my mother's support and encouragement.

My mother truly valued what we now call "thinking outside the box," not only in the kitchen, but in her professional life. Anne Steinman was particularly interested in the field of early childhood development. She was a teacher and her specialty was early childhood education. She was one of the founding teachers in Head Start. She firmly believed that there were critical periods in development and that the nursery school years were of the utmost importance for educational development. A few years later, her interest in early development may have stimulated my interest in the work of Torsten Wiesel and David Hubel, who were studying critical periods in developing the visual system.

My father, Norman, an immigrant from Russia, grew up in New York City. He was on his way to a brilliant career in mathematics as an undergraduate at NYU. He was President of the Mathematics Club there, and he graduated in 1939. My father and mother (who was born and raised in New York City) were married while my father was studying at NYU and my mother was at Hunter College (Figure 1).

Mathematics fascinated me as a child. My father was one of my best teachers. Norm Steinman once shared with me a paper from his NYU mathematics professor, Morris Kline. Professor Kline encouraged my father to continue in mathematics and to aspire to become a math professor. Kline himself completed his PhD in 1936 and had a remarkable career as a mathematician and educator.

My father shared Kline's gift for teaching mathematics and for teaching in general. In World War II, my father, a combat rifleman, taught reading, writing and arithmetic to illiterate members of his platoon. It came to my father's attention that many soldiers could not write letters home from the front because they were illiterate. For these soldiers, their loved ones were never sure whether they were alive or not. So writing letters home was an essential line of communication for those on the front in combat. My father helped these soldiers to communicate with families back at home and likely helped some of them learn to read and write.

My father had a gift for humor. His mathematics professor, Morris Kline, also shared this propensity to teach with a touch of humor. Kline wrote, "I would urge every teacher to become an actor. His classroom technique must be enlivened by every device used in theatre. He can be and should be dramatic where appropriate. He must not only have facts but fire. He can utilize even eccentricities of behavior to stir up human interest. He should not be afraid of humor and should use it freely. Even an irrelevant joke or story perks up the class enormously" (3). One of my other favorite mathematics professors, the beloved Professor Raymond Redheffer, started his calculus class at UCLA in the fall of 1964, stating, "I'm Redheffer, and that's no bull!" (4). (I was able to take math classes at UCLA, along with other high school students who lived near the campus.)

I might have learned from these math professors the key lessons about incorporating humor into teaching. I try to inculcate a good joke and some irony into my lectures. For example, I was asked to give a keynote lecture at the Society of Neuro-Oncology in San Antonio, just a short walk from the Alamo. I based my talk on an article that I wrote for

Figure 1. My parents, Anne Steinman, right, and Norman Steinman, left, in 1939. From the Steinman family collection.

the *Journal of Clinical Investigation* entitled "No Quiet Surrender" (5), about the guardian molecules that protect the brain from various pathologic attacks. The brain does have a remarkable capacity to withstand various types of attacks (5).

In my lectures, my opening slide traditionally shows my beautiful campus at Stanford, juxtaposed with a landmark from the location where I am speaking. So as you can see in Figure 2, "No Quiet Surrender" is juxtaposed with the Alamo. I think the audience appreciated the connection. I often post my lecture on a webserver, and I advise individuals that they can access my talk there. This particular lecture had quite a few uploads.

My father's career in mathematics was sidetracked by service in World War II. My sister, Louise, wrote a remarkable memoir of my father's experience in World War II in her book *The Souvenir: A Daughter Discovers Her Father's War* (6). Louise's book was reviewed in the *New York Times*, and Diane Cole wrote, "For Pvt. Norman Steinman, assigned to the 27th Infantry Regiment (the 'Wolfhounds') of the 25th Infantry Division (the 'Tropical Lightning'), the war, at its core, was horror: 165 days of continuous combat fought to reclaim from the Japanese the beaches, plains, mountains and caves of the Philippines" (7).

After World War II, my father was interested in a career in medicine. With quotas for Jewish students in many of our medical schools, he entered pharmacy school and graduated in 1949. He owned a neighborhood pharmacy in Culver City. I worked there half a day on weekends as a teenager. Perhaps my small immersion in the neighborhood pharmacy taught me something about pharmaceuticals, and perhaps it inspired me to develop new pharmaceuticals in the setting of a small business. That idea—pharmaceutical entrepreneurship in a small business—became widespread as the biotechnology industry commenced a generation later. Figure 3 shows my

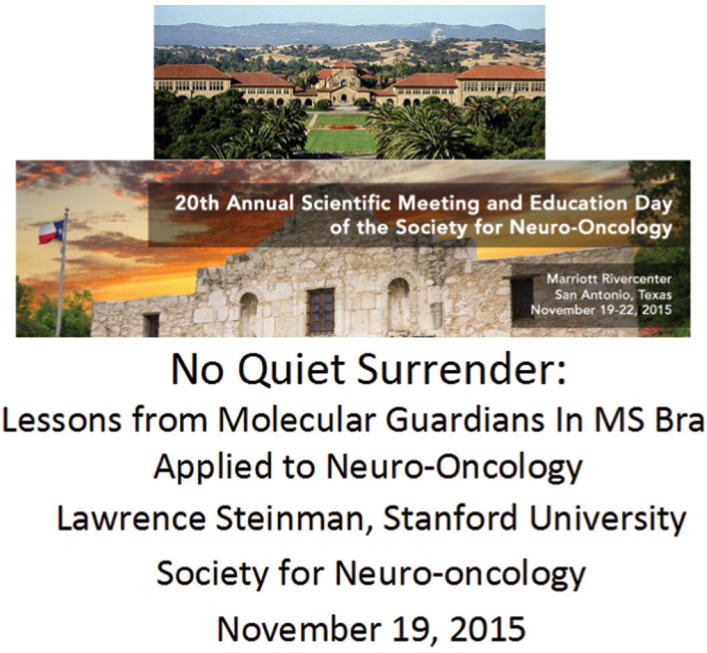

Figure 2. Poster for lecture at the Society of Neuro-Oncology, San Antonio, Texas, November 19, 2015. Humor is incorporated into teaching. A lecture on guardian molecules in the brain is entitled "No Quiet Surrender" and is juxtaposed next to a picture of the Alamo.

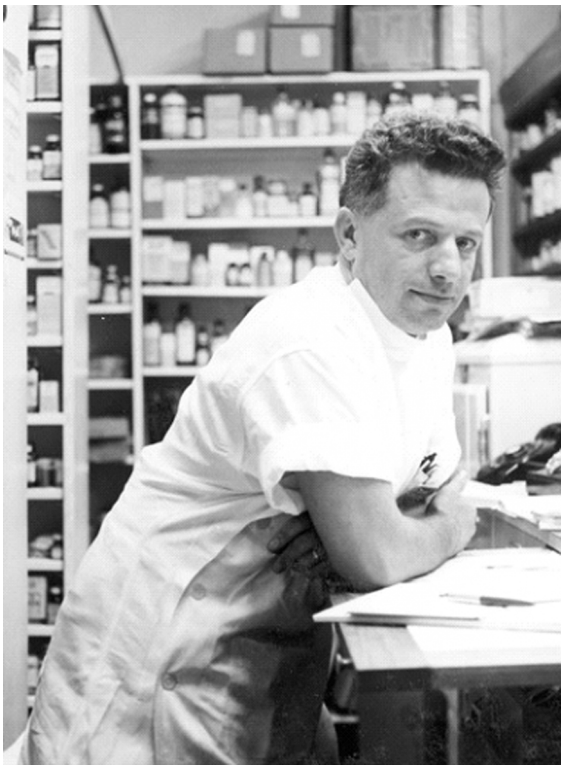

Figure 3. Norman Steinman at work in the neighborhood pharmacy, where I worked half a day each weekend. From the Steinman family collection.

father at the bench in his pharmacy on a typical day around 1955.

Like his professor, Morris Kline, my father valued humor and used humor in teaching all of us children some of the lessons in life. Humor, as I have learned, is an important asset when facing the brutality of science, where failure is common. In a life of science, hypotheses frequently crumble in the face of contrary data. Even after apparent success in a series of experiments, we still have to deal with peer review, which is harsh and often seemingly unfair.

In our home growing up, each of us four children developed various streaks of creativity, probably kindled by my mother. My sister, Ruth, despite braces and numerous corrective surgeries for her polio, was active in social organizations at school. Interestingly, her boyfriends and ultimately her husband were strong and very athletic males. My younger sister, Louise, was an artist and a dancer and remains a gifted writer (6–8). My younger brother was a musician. There were tight bonds between all of us sibs that have lasted.

INFLUENCE OF RUSSIA'S *SPUTNIK* ON MY EARLY SCIENTIFIC CAREER

During elementary school, a memorable event in the Cold War changed—for the better—the trajectory of my science education. The Russians orbited the first satellite, *Sputnik*, in 1957, and as a result, the United States, under President Eisenhower and then President Kennedy, supported a massive infusion of money to science education. Talk about timing and Lucky Larry! In 1962, I spent a summer at a National Science Foundation (NSF)-sponsored high school math institute in Corvallis, Oregon. I was able to track the NSF grant for $21,560 for funding the Summer Mathematics Institute at Oregon State under mathematics professor, Robert Gaskell (9).

Mathematics "geeks" from all across the United States were taught by the Oregon State math faculty. We learned Fortran programming, Boolean algebra, probability and statistics and number theory. There were high school students from all over the country. I remember students from Boulder, Colorado; New York's Bronx High School of Science; Meridian, Mississippi; and Snyder, Texas. The math institute was free and included tuition, room and board, and transportation. The program spawned numerous professors of engineering and mathematics, as well as lawyers, distinguished Air Force fighter pilots, and even at least one medical researcher from Culver City, California.

I attended Dartmouth College and majored in physics and minored in Russian. The legacy of the Cold War provided me with two more remarkable experiences. In 1966, I traveled to Russia under the auspices of a State Department program, sponsored under the National Defense Education Act of 1958. This act was another reaction to *Sputnik*, where the United States felt that it must "catch up" in science and foreign language competency. On my trip to Russia, we first spent an intensive month on the campus of the University of Indiana. We spoke only Russian in our month in Indiana. We then went on a trip to Russia, sponsored by the State Department. During that trip, I met many of my father's aunts and uncles in Moscow and Kiev. The next summer, in 1967, I had the good fortune to have my first experience in the laboratory at the Salk Institute, which had just opened. My stipend for living and transportation to the Salk Institute was covered again under the same National Defense Education Act of 1958.

I obtained the summer job at the Salk Institute in 1967 because of an encounter with Jacob Bronowski, who was visiting Dartmouth. Jonas Salk envisioned that the institute bearing his name would be a haven for not only science, but also for the arts and philosophy (1). Salk hired Jacob Bronowski as the first philosopher in residence at the Institute. I had served as host for Bronowski when he visited Dartmouth in the spring of 1966. I wrote to Bronowski and asked him if it were possible to work the next summer at Salk. Over Christmas vacation in 1966, when I returned home from New Hampshire to Southern California, Bronowski invited me to La Jolla to visit the Salk Institute. He took me on a half-day tour of the Institute, which had been just completed. He introduced me to many scientists. He assured me that he would arrange a job for me that ensuing summer. Then we had lunch in his backyard on the Torrey Pines Mesa, near the Institute.

I remain grateful to Jacob Bronowski. He was so very humble, charming, and caring about my summer plans. Although Bronowski was a celebrity—we remember him from the BBC series *The Ascent of Man*—he went out of his way to help me, a young college student. I have not forgotten this and have strived to make sure that students who ask me about research are given opportunities to work in my laboratories at Stanford. Over the past 35 years, my lab has hosted well over 200 high school and college students during the summers, including three Intel Science Prize finalists.

For the summer of 1967, I chose to work in the laboratory of Ed Lennox, who was a physicist turned biologist. Lennox was then working on a new topic in immunology, the genetic control of the immune response (10). Baruj Benacerraf had shown that the immune response to a hapten on a synthetic polypeptide poly-L-lysine was under genetic control and could be transmitted as a unigenic mendelian trait (11). Sela and McDevitt had just published their seminal paper in 1965 in the *Journal of Experimental Medicine* (7), showing that antibody responses to the branched, multichain synthetic polypeptide, poly (tyr,-glu)-poly DL-ala--poly lys, ((T,G)-A--L) and ((H,G)-A—L), a synthetic polypeptide in which histidine replaces tyrosine, were under strict genetic control (12,13). Both Michael Sela and

Hugh McDevitt were to play major roles in my career over the next 50 years. The subject of the genetic control of the immune response to a component of influenza became a major focus of my own latest research, nearly half a century later (14).

My summer at the Salk produced even more opportunities for Lucky Larry than "just" an introduction to a new field, the genetics of the immune response. At the neighboring bench, a colleague of Ed Lennox was visiting the Institute from Cal Tech. Seymour Benzer came to the Salk that summer, from Cal Tech with his collection of *Drosophila*. He was trying to grow synapses from dissociated *Drosophila* neurons. A problem arose for my own research, because my key measurement was a 12-h hemagglutination assay to detect antibody to influenza, not to clumped *Drosophila*. Often at the end of a 12-h incubation, all that appeared at the bottom of the titer plate was a dead fly. I confronted Professor Benzer after a month of exasperation and asked him to keep his bottles of flies capped. He jokingly grabbed me by my shirt collar and told me something like, "calm down, kid!" I was aware of Seymour's prowess from his phage work, from a genetics course in college. I had no idea that his work would branch far beyond phage, to help us understand the neurobiology of love, time and even memory. Jonathan Weiner's brilliant biography captures the aspects of Seymour Benzer that I met that summer of 1967 (15).

So Seymour Benzer capped his flasks of flies, and I measured antibody responses to influenza, observing different levels of antibodies in mice with different genetic backgrounds. Fifty years later, I returned to the same subject, this time in humans, who developed a neurologic disease after influenza immunization, but only when they had certain genetic backgrounds (14).

But that was not all that came from that remarkable summer. Remarkable visitors lectured all week. I recall Paul Berg's talks on SV40 and Roman Jakobsen's talks on the origins of language. In Renato Dulbecco's lab, Andre Lwoff was a visitor and David Baltimore was a postdoc. Jonas Salk himself was on the scene, and as you know, he had iconic status in my family. A phone call home mentioning that I had passed Jonas Salk in the hallway was likely to elicit a response from my mother about how fortunate Salk was to have me working in the Institute that summer.

In the Lennox lab that summer, Stephen Kuffler, who was Chair of the Department of Neurobiology at Harvard, and two of his colleagues, David Potter and Ed Furshpan, had joined Lennox and Benzer in attempts to grow synapses in culture. I was welcome to attend their long lunches and listen in on their discussions. It came to Stephen Kuffler's attention that I liked to play tennis. So every day at 6:00 PM, I was chosen to be his tennis opponent on the court behind the house he had rented that summer. Ted Geisel, Dr. Seuss, lived in the house neighboring the court. "And to think that I saw it at the Salk Institute," would have been a fully explicable extrapolation of Seuss' first book entitled, *And to Think That I Saw It on Mulberry Street* (16).

MEDICAL SCHOOL AND POSTDOCTORAL STUDIES

Following the theme of Lucky Larry, where one piece of good fortune leads to the next, perhaps because of positive recommendations from Lennox and Kuffler, I gained admission to Harvard Medical School in 1968. A good slice backhand in my tennis games against Stephen Kuffler may have outweighed some grades in statistical thermodynamics at Dartmouth.

With an interest in neurobiology, I decided to spend a research year under Professors Torsten Wiesel and David Hubel. In the Hubel and Wiesel laboratory, I was asked to perform some truly "bold" experiments. First, a young medical student named Jim Hudspeth and I were independently asked to operate on cats and then to identify with electrophysiological recordings the "simple," "complex" or "hypercomplex" cells in their visual cortex (17). After recording from these cells, we were supposed to inject them with a fluorescent tracer, so that we could then fix the brains and formally identify the cells and correlate their anatomy with the electrophysiology.

Whereas Jim Hudspeth was gifted in many ways, including wonderful manual dexterity, he could accomplish this formidable task; I found myself to be a laggard in comparison, without such gifts. Jim Hudspeth is a distinguished professor, now at the Rockefeller. When my son was interviewing for the MD, PhD, program at Rockefeller, he proclaimed that around the dinner table when he was growing up, his father (me!), would rarely discuss the name Einstein. Instead, the name he heard most often associated with the term "genius" was the name "Hudspeth!" (18).

I was then asked to do another experiment based on the finding by Grafstein (19), that radioactive tracers could be used to map the visual pathway. I was to repeat the classic Sperry experiment on the specificity of axonal connections (20) and to trace retino-tectal connections in the goldfish after optic nerve transection, followed by surgical inversion of the retina. I was then supposed to map the regenerating optic nerve fibers as they innervated the optic tectum. Although I had some success with these experiments, I could never provide convincing enough data to publish. Nine years later, Sperry, Hubel and Wiesel shared the Nobel Prize in Medicine (21). My mother of course was certain when she read of the Prize in 1981, that it was given to these distinguished scientists, because I had worked with two of them as a medical student. Perhaps much closer to what we call the "reason" that I chose to work with them, was my mother's interest in early childhood development.

I did have some good fortune during my research period with Torsten Wiesel. While studying the goldfish retina using radioautography, with a gifted postdoc Dominic Lam, we were looking at the uptake of gamma-aminobutyric acid (GABA) in the goldfish retina.

The uptake was regulated with activity. A radioautograph of the retina, done while investigating uptake of tritiated GABA, with a flashing light as the stimulus, revealed some stunning morphology. The uptake resembled a silver tracing of the horizontal elements in retina, first published by Ramón y Cajal in 1909 (22). The pattern of GABA uptake is shown in Figure 4, which is reproduced from the 1909 paper. The result was published in the *Proceedings of the National Academy of Sciences* as David Hubel's first contribution in 1971 (23). I was to return to the study of GABA, 38 years later (24). We showed that GABA suppressed the immune response in T cells and acted as an inhibitory signaling molecule in the immune system (24). I have remained a longtime friend of Dominic Lam, who is a polymath, a gifted artist and a biotech entrepreneur.

Before graduating from Harvard Medical School and heading to Stanford for internship and training, I decided to explore immunology. I always had the idea to combine my interests in neurobiology with immunology. In 1972, I traveled to Israel and met with Michael Sela, to discuss the possibility of doing a postdoctoral fellowship with him that combined neuroscience and immunology. Michael was extraordinarily responsive. On a steamy August day in Israel in 1972, we sat in his office at the Weizmann Institute for an hour, discussing all the impressive projects that were ongoing in chemical immunology, including a few that combined neurobiology and immunology. He did mention work on a peptide-based drug named Copolymer-1, which might someday become a therapeutic in MS. Copolymer-1 was 1-year-old at that time and ultimately became the best-selling prescription pharmaceutical for treatment of MS.

Thus, before leaving Harvard, I contacted Baruj Benacerraf to do a

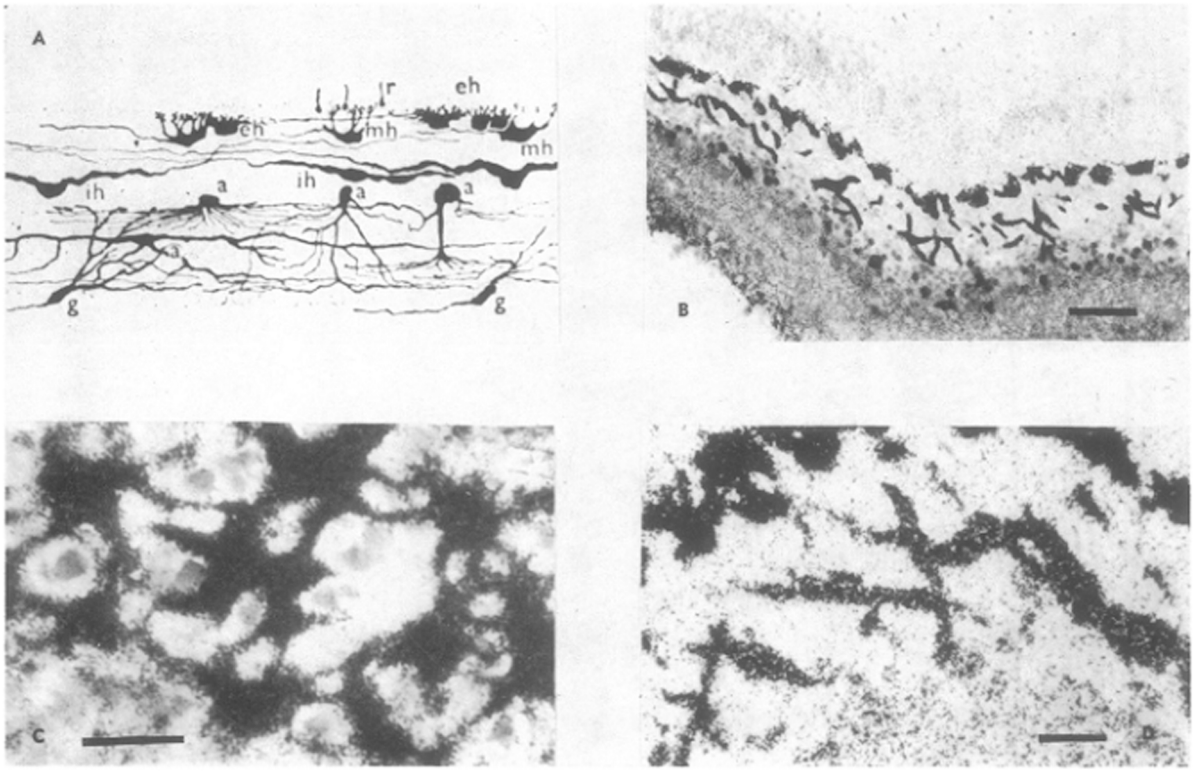

FIG. 4. (*A*) A vertical section of the teleost retina, stained by the Golgi method from Cajal (19). The section shows the horizontal connections in the retina. *r*, rods; *eh*, external horizontal cells; *mh*, intermediate horizontal cells; *ih*, internal horizontal cells; *a*, amacrine cells; *g*, ganglion cells.

B, *C*, and *D* are sections through retinas that have been incubated in [^{3}H]GABA under light stimulation for 1 hr. Scale 40 μm. (*B*) Oblique section showing external horizontal cells and their processes, which extend vertically toward receptors and laterally toward neighboring horizontal cells. The stellate geometry of the internal horizontal cells is also revealed. On the vitreous side of the inner nuclear layer, there is heavy labeling in what may be amacrine cells. Scale: 40 μm. (*C*) *En face* section through external horizontal cells, revealing extensive coupling between neighboring cells. Scale: 20 μm. (*D*) Oblique section through the internal horizontal cells, showing their stellate shape. Scale: 20 μm.

Figure 4. Radioautographs of the retinal uptake of GABA under illumination (23) reveal the horizontal cell networks in retina that Ramón y Cajal described in 1909 (22).

tutorial in immunology in my last year, 1973. Benacerraf was responsive and arranged for a weekly immunology tutorial for me with one of his impressive younger faculty members, Dr. Carl Pierce. With Carl, I learned about the new and dazzling world of helper cells, haptens and carriers. I left Harvard for Stanford in 1973 for my internship. I can remember the dean of students, Joe Gardella, mentioning that by going west, my decision would most likely mean that I would never get a job at Harvard. The dean at Harvard was correct in that I never applied for a job at my medical school alma mater. For me, it was "California, here I come, right back where I started from."

After finishing my internship in surgery and doing 6 months of pediatrics work, I headed to the Weizmann Institute in 1974. I was given a desk in the ground floor of the Wolfson Building in a laboratory shared with the late Dvora Teitelbaum, who along with Michael Sela and Ruth Arnon, held the original patent on the blockbuster, glatiramer: U.S. 3,849,550, "Therapeutic Copolymer" (25).

I spent three exciting years learning chemical immunology under Michael Sela and Ruth Arnon and cellular immunology with Irun Cohen. I had an exceptionally wonderful mentorship with Irun Cohen, who was a fellow clinician. Every day after work, we would have a long run through the orange groves, after which we would have a beer and discuss science, philosophy and Jewish history. All these faculty members at the Weizmann Institute taught me how to think about how experimental results might be translated in the clinic.

At the Weizmann, I also was introduced to the quintessential model of experimental neuroinflammation, experimental autoimmune encephalomyelitis (EAE), (26,27). I have written about how the EAE model could be used to test potential new therapies in MS. The EAE model, first introduced in 1932 at the Rockefeller Institute to study acute disseminated encephalomyelitis after rabies vaccination (28), was critical for the discovery of three therapeutics now approved and used widely in MS: glatiramer, natalizumab and fingolimod. Glatiramer came directly from the EAE model, where it was shown to prevent and reverse ongoing EAE (26,29). Natalizumab was discovered in my laboratory in the early 1990s from an experiment where we sought to analyze the molecules involved in homing from blood to brain (30,31). Fingolimod was saved from being shelved, after its disappointing effects in protecting from transplant rejection. It was shown to be effective in EAE, and Novartis decided to develop the drug for a new indication, relapsing remitting MS (32).

I returned to Stanford in 1977, with my Israeli wife, Chany, whom I met on the tennis courts at the Weizmann. I completed a residency in neurology over the next 3 years. In 1980, a faculty position was available, and I was appointed as Assistant Professor.

At Stanford, I aspired to try to be a "triple threat," describing an academic physician, who engaged in a clinical practice caring for patients, who taught medical students and graduate students, and who did laboratory research. As it turned out, the beginning of the era of biotechnology was upon us, and there was to be a "fourth threat": the merging of medical research with biotechnology companies.

EARLY YEARS ON THE STANFORD FACULTY

As a junior faculty member, I juggled clinical duties for about 4 months a year on the Child Neurology service as well as clinics in both child and adult neurology. Fortunately, in those days, it was easy to get federal funding, and no one spent much time even worrying about the thresholds for success on grant applications. The focus of my work was to try to understand the pathophysiology of MS and to develop therapeutics to treat MS.

To develop new therapeutics for treating MS, my research investigated how the elements of the tri-molecular complex involving major histocompatibility complex (MHC), myelin antigens and the T-cell receptor, which had just been identified by Mark Davis and Tak Mak, were involved in the pathogenesis of neuroinflammation (33). Mark Davis had just arrived at Stanford, and the immunology world was electrified with discoveries emanating from Davis' breakthrough. Hugh McDevitt and Len and Lee Herzenberg were remarkably open and interactive during this part of my career. Hugh McDevitt made available his entire toolkit of antibodies to components of the MHC. With Ram Sriram and Jim Rosenbaum, now professors at Vanderbilt and Oregon Health Sciences University, respectively, we published work on the suppression of paralysis in EAE with antibodies to MHC class II (34,35). We fully intended to develop this approach for clinical application and went as far as successful tests in nonhuman primates (36). Reports of toxicity when giving antibodies to HLA class II molecules in nonhuman primate studies made us reluctant to take this approach forward in the clinic.

We also developed an approach to treating MS with an anti-CD4 antibody. CD4 is the binding partner of MHC class II. In a series of preclinical and clinical experiments, initiated by my first graduate student, Matthew Waldor, who is now himself a professor at Harvard Medical School, we showed that an antibody to CD4 was potent and effective in reversing EAE (37,38). By the time these experiments were ready to be tested in the clinic, we were reluctant to lower CD4 counts much below 250/mm^3 because of our awareness of the consequences of low CD4 counts in HIV infections. Therefore, when taken into the clinic, anti-CD4 did not meet its primary endpoints in relapsing remitting MS, although a covariate analysis showed that relapse rate and disability favorably correlated with reduction in the CD4 count (39,40). Had we reduced the CD4 count in MS to levels comparable to what we routinely reduce the CD20 B-cell populations

with anti-CD20 antibodies such as Rituxan (41), perhaps clinical "success" would have been attained.

The chimeric CD4 antibody that we tried in the clinic was developed and manufactured by Centocor. I served as an advisor to Centocor from 1987 to 1989, when I was asked to join their board of directors. As a director of Centocor, I participated in many of the decisions in the successful development of anti–tumor necrosis factor (TNF) therapy with Remicade and in the development of anti-integrin therapy with Reopro. I had the opportunity to make lasting friendships with Marc Feldmann, Taini Maini and Jim Woody during these exciting times (42). My time with Centocor was the first of many fruitful experiences with the emerging biotechnology industry. Over my career, I have started or played a role as a director in six companies so far.

Our experiments exploring the pathophysiology of MS helped identify a key therapeutic target in MS. In the early 1980s, our group followed the elegant studies of Ben-Nun, Cohen and Wekerle, as we developed T-cell clones that recognized myelin basic protein (43). My second PhD student, Scott Zamvil, who is now a professor at University of California, San Francisco (UCSF), showed that these T-cell clones could provoke relapsing remitting paralysis with demyelination (44). With Jonathan Rothbard, we began a collaboration that has continued for over 30 years, to map the precise epitopes recognized by these T-cell clones (45). Our studies with these T-cell clones culminated in work looking at how these T cells traverse the endothelium and traverse from the circulation to the brain.

Our studies on T-cell migration to the brain involved a tight collaboration between Ted Yednock at a biotechnology startup, Athena Neurosciences, and my laboratory at Stanford. In experiments with Yednock and a gifted postdoctoral fellow, Nathan Karin, we showed that the key molecule involved in the homing of lymphocytes to the brain was α4 integrin. Karin later became Chief of Immunology at Israel's Technion. Yednock, Karin and our team were able to block paralysis and brain inflammation with an antibody targeting α4 integrin. After our 1992 publication in *Nature* (46), further preclinical studies led by Brocke and Veromaa confirmed the activity (47). Each stage of clinical trials continued to reveal a potent clinical effect with natalizumab blockade of α4 integrin. Clinical relapses in MS were reduced by over two-thirds, and inflammatory activity detected with brain imaging was reduced about 90 percent. An approved drug entered the market 12 years later (48–50).

I had worried about the consequences of blocking homing to the brain (51). My main concern was the development of opportunistic infections if immune surveillance of the brain was blocked. Within 3 months of approval, the first cases of progressive multifocal leukoencephalopathy occurred in patients who had been taking natalizumab for more than 2 years. There have now been over 500 cases of progressive multifocal leukoencephalopathy (PML) in patients taking natalizumab. The good news is that a test to mitigate risk was developed, so that we can reliably segregate individuals at risk from those who are virtually risk free (52). At present, natalizumab is the strongest therapeutic available for relapsing remitting MS, and its main risk can be mitigated by a predictive test (52).

While we were performing the experiments leading to natalizumab, we were also developing much more specific therapies. These approaches, we hoped, would be more specific than the concept in natalizumab that blocked the migration of large portions of the immune system, including T cells, B cells and macrophages, to the brain. Work from several laboratories, including ours, showed that T-cell receptor use was quite restricted when the immune system targeted a small portion of a protein, in the context of a given major histocompatibility complex. These experiments aimed at devising a therapy that would target the T-cell receptors involved in the pathogenesis of a disease. For EAE, induced by a small peptide, there is restricted T-cell receptor usage. We demonstrated that antibodies to the variable region of the T-cell receptor involved in the recognition and binding of the critical pathogenic autoantigen reversed ongoing autoimmune disease (53).

With an outstanding postdoc Jorge Oksenberg, now a professor at UCSF, and with a renowned collaborator Claude Bernard from Australia, we also showed that, even in lesions in MS brain, there was evidence of restricted T-cell receptor expression (54,55). Tomas Olsson and colleagues took these results forward into the clinic, targeting T cells with VB5.2 T-cell receptors. They substantially depleted T cells reactive to myelin basic protein that produced interferon (IFN)-γ (56).

FURTHER RESEARCH AT THE WEIZMANN INSTITUTE

From 1995 to 1999, I had a joint appointment in the Department of Immunology at the Weizmann Institute, along with my appointment at Stanford. In the Weizmann, I decided to do some high-risk "moonshot" type projects. With Ari Waisman, my laboratory in Israel began work on engineering a DNA vaccine encoding autoantigen, to tolerize the immune system for autoimmune diseases such as MS, type 1 diabetes and rheumatoid arthritis (57,58). We also began experiments on treating Huntington disease, where the protein, huntingtin, containing a polyglutamine repeat longer than 35 glutamines, causes a lethal disease. Our approach was to test a competitive inhibitor of the enzyme transglutaminase, which is activated in the brains of patients with Huntington disease (59,60).

TRANSLATIONAL RESEARCH AT STANFORD OVER THE PAST 20 YEARS

Returning to Stanford, my colleague, PhD student then postdoc, Marcela Karpuj, showed that cystamine had a beneficial effect in an animal model

of Huntington disease. In addition to inhibition of transglutaminase, treatment with cystamine induced various protective molecules including HSP40 (60). Five other independent groups showed benefit in animal models with cystamine and its simpler form cysteamine (61). Other protective molecules such as BDNF were induced with cystamine treatment (62). This work has been taken forward and is now in advanced clinical trials.

Most of the efforts of the laboratory at Stanford over the past 35 years have focused on understanding the pathogenesis of MS (63). We also initiated studies investigating the transcripts, proteins and lipid molecules that are present in MS lesions. These studies have culminated in five different clinical trials. I shall describe the efforts we have taken from the bench into the clinic in MS and in another autoimmune disease, type 1 diabetes.

Our efforts at understanding the pathogenesis of MS were directed at studying MS lesion material itself obtained from rapid autopsies. I did not want to participate in the large-scale team efforts in genome-wide association studies and decided instead to apply emerging technologies to investigate well-defined lesions from MS. We collaborated with Professor Cedric Raine at the Albert Einstein School of Medicine, who had some remarkable pathologic material obtained with rapid autopsies. These specimens were preserved in a manner that allowed us to perform large-scale sequencing of transcripts, as well as further analysis of the proteins and lipids in the same pathologic samples. These investigations allowed us to discover molecules that were quite unexpectedly present in lesions. We then used preclinical animal models, particularly various versions of EAE, to understand their potentialpathophysiologic roles.

In a wonderful collaboration with Dr. Renu Heller, then at Roche, we gained access to a robotic sequencer around the year 2000 for these studies. By using cDNA libraries, Sergio Baranzini (now a professor at UCSF), Dorothee Chabas (a remarkable neurologist from France), and Jorge Oksenberg (by then a professor at UCSF) were able to analyze the most prevalent transcripts in MS lesions. We found that aB crystallin was the most prevalent transcript in MS lesions. We did not study aB crystallin intensively for another 5 years, because we focused some of these initial studies on osteopontin (64–66). In a continued collaboration with Renu Heller, with the able collaboration of Chris Lock, now a Professor at Stanford, we also studied lesion material with gene chips (67). This same material was the subject of proteomic studies with my colleague, May Han (68,69). We also performed lipidomic studies on MS material with Peggy Ho, my research associate for more than a decade; my colleague, Bill Robinson, now a leading faculty member at Stanford; and our joint PhD student, Jennifer Kanter (70,71).

The role of osteopontin in MS was quite intriguing. Two of the proteins that bind osteopontin are VCAM and α4 integrin (63–66). In fact, the role of osteopontin and integrin in the migration of lymphocytes into the brain parallels the metastasis of tumors from the blood into solid organs. In a sense, the osteopontin-aided migration of lymphocytes into brain via α4 integrin is indicative of how the immune system gains access to brain. With my PhD student, Eun Mi Hur, now a researcher in industry, we showed that osteopontin can trigger clinical relapses in mice (65,66). Osteopontin levels are elevated around the time of relapse in MS (72,73).

Further studies on MS pathogenesis focused on the roles of lipids in MS. With Sawsan Youssef, now a researcher in the pharmaceutical industry, and Shannon Dunn, a professor at the University of Toronto, we studied the role of farnesylation and geranylation on the inflammatory response in MS. In a series of papers done in collaboration with Scott Zamvil, now a professor at UCSF, Youssef and Dunn showed that atorvastatin was effective in reversing paralysis in EAE (74). Moreover, we could modulate EAE with various isoprenoids in the sterol pathway. We demonstrated that the isoprenoid geranylgeranyl-pyrophosphate (GGPP) mediates proliferation, whereas both GGPP and its precursor, farnesyl-PP, regulate the Th1 differentiation of myelin-reactive T cells (75). We could reverse the beneficial effect of atorvastatin with the isoprenoid intermediate farnesol (75).

The role of statins in blocking the mevalonate pathway was taken forward into clinical trials first by Zamvil and colleagues (76). Recently, encouraging results with treatment with statins in individuals with secondary progressive MS were reported by Chataway and colleagues, where brain atrophy was slowed when statins were given compared with placebo (77).

Working with Jennifer Kanter, Bill Robinson, Peggy Ho and Shannon Dunn, we investigated the roles of lipids in MS further (71). Designing solid-phase arrays to detect the immune response to lipids followed naturally from work we had done with myelin protein arrays in association with my Stanford colleagues, Bill Robinson and PJ Utz (78). We discovered some fascinating short-chain fatty acids and phospholipids in the myelin sheath of patients with MS who had the remarkable feature of attenuating neuroinflammation. Remarkably, a component of the myelin sheath had evolved not only to serve as an insulator for the electrical response along axons, but may have coevolved to provide protection against inflammation in the brain (71). This result would exemplify how lipid components of the central nervous system have guardian properties to attenuate inflammation (5).

aB crystallin was the most prevalent transcript (64) in our study of prominent mRNAs in MS lesions. Van Noort (79) demonstrated that an immune response to aB crystallin was present in MS patients. He eluted antigens from myelin from an MS brain and asked which fraction most prominently

stimulated lymphocytes from MS patients. He found that aB crystallin was a stronger antigen and stimulated MS T cells to a greater degree than well-known myelin proteins (79). We tested whether injection of aB crystallin (cryab) would modulate EAE and, to our surprise, Shalina Ousman (now a professor at the University of Calgary) who led these studies showed that intravenous injection of cryab suppressed ongoing EAE. She also demonstrated that cryab suppressed the p38 MAP kinase pathway, a vital component of the inflammatory response. Surprising to us at the time cryab$^{-/-}$ mice had more severe paralysis and more extensive inflammation in the EAE model (80).

We noted that cryab was beneficial in other diseases including stroke (81), myocardial infarction (82) and ischemic optic neuropathy (83). The penumbra of stroke was greater in cryab$^{-/-}$ mice (81). Jonathan Rothbard, with whom I've collaborated for 30 years, informed us that David Eisenberg at UCLA had demonstrated that cryab is an amyloid structure and that it formed amyloid more slowly than other more notorious amyloid proteins such as tau, prion protein, amylin and β-amyloid. Moreover, Eisenberg and colleagues had shown that there was a minimal hexapeptide motif in these proteins that had sufficient energy to form β zipper structures and amyloid fibrils (84,85).

An entrepreneurial PhD student, Jacqueline Grant, had shown that injection of β-amyloid peptides 1–40 or 1–42, thought to be pathogenic in Alzheimer's disease, were capable of suppressing EAE (86). Moreover, amyloid precursor protein knockout mice (APP$^{-/-}$) had worse EAE (86). This result was therefore the second example of worsened EAE with a knockout of an amyloid-forming protein. We had shown in Ousman's work that cryab$^{-/-}$ had worse EAE (80) and larger strokes (81). Others had shown worse EAE in tau$^{-/-}$ mice (87) and in Prp$^{-/-}$ mice (88). Thus, with gain-of-function experiments injecting amyloid-forming proteins (either cryab or β-amyloid peptides 1–40 or 1–4), EAE improved, whereas in loss-of-function experiments, amyloid knockouts had worse EAE. These results were surprising, since most investigators had assumed that amyloid proteins worsened or provoked neuroinflammation.

Meanwhile, Rothbard and another outstanding postdoc, Mike Kurnellas, had done structure function experiments narrowing the domains of amyloid proteins that might exert their immune-suppressive activity (89,90). Finally, Rothbard and Kurnellas realized that Eisenberg's amyloid fibril hexapeptides might indeed have immune-suppressive properties. In a 2013 article, we showed that hexapeptides that formed amyloid fibrils would suppress ongoing EAE. We showed that hexapeptides derived from β-amyloid, tau, prion protein, amylin and cryab all suppressed EAE (91).

Three mechanisms are elicited when amyloid fibrils are injected. The amyloid structures bind inflammatory mediators in plasma (89–91). Amyloid hexapeptide structures elicit a type 1 interferon response (93). Most recently, we showed that these amyloid hexapeptides induce immune-suppressive B-1a regulatory cells, which secrete interleukin (IL)-10 (91).

Our proteomic studies elucidated other molecules of interest in MS lesions. As an example, we found evidence of angiotensin receptor in MS lesions in our proteomic studies (69,94). Peggy Ho, Tobias Lanz and Michael Platten, now a professor in Heidelberg, took this information and showed that we could reverse ongoing paralysis in the EAE model with standard dosing of lisinopril (94). Lisinopril inhibited inflammatory signaling through Stat1 and Stat4 and induced T regulatory cells (94). It was a challenge to find a pharmaceutical partner to sponsor clinical trials in MS with a drug used by millions for hypertension and that was generic. So in collaboration with entrepreneurs, transplant surgeon Tomasz Sablinski and Marc Foster, we established a company, Transparency Life Sciences, to disrupt traditional pharmaceutical development. Using crowd sourcing to help design the clinical trial, we obtained an investigational new drug (IND) designation from the FDA and have begun a clinical trial, sponsored by the National Institutes of Health, with Professor Fred Lublin at Mt. Sinai School of Medicine in New York (95).

One of the biggest challenges in the field of MS is our lack of understanding of why females are more susceptible than males to this disease. This female-to-male disparity is even more pronounced in other autoimmune diseases such as systemic lupus erythematosus and neuromyelitis optica. Shannon Dunn tackled this problem while a postdoc and has continued her brilliant work in a faculty position at the University of Toronto. We published a series of reports in the *Journal of Experimental Medicine and Nature Medicine* (96–98) describing the role of peroxisome proliferator–activated receptor (PPAR)-α and PPAR-δ in regulating the sexual dimorphism. PPAR-α is overexpressed on male T cells. Knockout of PPAR-α restored high susceptibility to EAE. Androgens drive PPAR-α, and they bias the immune response toward Th17. Female immune responses are tilted to Th1 with the dominance of IFN-γ, whereas male responses are pushed to Th17, dominated by IL-17 and IL-23. Dunn showed that this was true across species from mice to humans (97,98). Because PPAR-α is targeted by widely used drugs such as gemfibrozil, this dimorphism provides clues that can be translated to therapy with widely used approved drugs for other indications.

Perhaps the primary goal in my research over the past decade is to translate the concept of antigen-specific tolerance to the clinic. If you give any respectable immunologist the task of tolerizing an ongoing immune response to protein X in an experimental animal, most of us can achieve this goal with

a number of well-tested interventions including low-zone and high-zone tolerance, presentation of antigen in a different format (such as coupling the antigen to cells), and so forth. Remarkably, we do not have any approved antigen-specific tolerization therapies for any autoimmune disease in humans.

At the turn of the 20th century, Bill Robinson, PJ Utz, Hideki Garren and I earnestly began a program to try to tolerize to antigens in experimental autoimmune disease. We chose as our "platform" the DNA plasmid approach, since we could shuttle into the coding region of the plasmid the cDNA for the protein antigen of choice. We also engineered the backbone of the plasmid so that we would replace proinflammatory noncoding CpG (5′—C—-phosphate—G—3′, cytosine and guanine separated by only one phosphate) motifs with an alternative GpG (5′—G—-phosphate—G—3′, guanine and guanine separated by only one phosphate) motif. Paulo Fontoura, Peggy Ho and Hideki Garren were instrumental in devising the GpG motifs and engineering them into the plasmid backbone.

Our first efforts were in the EAE model of neuroinflammation and the NOD model of type 1 diabetes (78,99–102). In these models, we achieved success in both prevention and reversal of disease. We created large-scale arrays to follow the intramolecular and intermolecular epitope spreading (78). Reversal of paralysis in the EAE model indicated that we not only could deal with the issue of epitope spreading, but when we tolerized to key "drivers" of the immune response, we could observe "epitope contraction," the opposite of epitope spreading (78,101).

In an editorial that accompanied a 2003 paper in *Nature Biotechnology* (78), the "father of epitope spreading," the late Eli Sercarz wrote:

> One relevant principle that has emerged is that once a 'driver' T-cell clone (or clones) is established, it becomes the sensible choice to target in inducing tolerance. Such a driver clone usually would recruit other T_H1 clones, so controlling the driver may effectively close down the response. However, it is also likely that a dominant, small set of driver clones exists for each antigen in the target organ, so it would be an advantage to tolerize each of them. Maximum security from autoimmunity would be predicted when the crucial drivers, as well as their major recruits (to 'spread determinants'), are all tolerized. This is the tack pursued by Robinson *et al*., where the DNA encoding each of the antigens whose specific T cells are easily recruitable is used in a tolerance-inducing regimen to ask whether the number of disease relapses usually found in autoimmune animals can be reduced (103).

Garren, Robinson, Utz and I formed a biotechnology company, Bayhill Therapeutics, and licensed the technology we had developed from Stanford University. With Bayhill, we translated these experiments into two notable clinical trials: one in relapsing remitting MS (100,101) and a second in type 1 diabetes (102). In MS, we were asked by the FDA to try antigen-specific tolerance with one antigen. Our engineered plasmid encoded myelin basic protein. Phase 1 and phase 2 trials indicated that we were achieving antigen-specific tolerance. In phase 1, we showed with a carboxyfluorescein succinimidyl ester (CFSE) assay that we were able to reduce the number of IFN-γ–producing T cells that proliferate in response to myelin basic protein, by using a dye-dilution–based flow cytometric assay (100).

We next did a phase 2 trial in 267 patients with relapsing remitting MS (101). The primary end point in the phase 2 trial was the 4-wk rate of occurrence of new gadolinium-enhancing lesions on brain magnetic resonance imaging from wks 28 to 48. No major safety issues were seen. The primary endpoint was nearly attained with a reduction in gadolinium-enhancing lesions at 44 wks ($p < 0.07$) at the 0.5-mg dose, and several secondary endpoints were attained on reduction of gadolinium-enhancing lesions ($p < 0.05$). At the 0.5-mg dose, 23 anti-myelin antibodies including anti–myelin basic protein epitopes were reduced in the CSF, again demonstrating the contraction of epitope spreading of the antibody response, similar to what was seen in the phase 1 trial (101). One of the major issues in MS is whether immune responses to MBP are key drivers of disease. I think not, and in 2016, we are not really certain of the key targets of the adaptive immune response in any form of MS.

We made another effort in the field of type 1 diabetes. Thanks to the pioneering work of the late George Eisenbarth, we have a rather strong understanding of the islet antigens that the immune system attacks in individuals with type 1 diabetes (104,105). Proinsulin is at the top of the list of antigens that are targets of the autoimmune response in type 1 diabetes (104,105). In a detailed series of preclinical experiments, we identified proinsulin as the key antigen targeted in the NOD model of type 1 diabetes. At Bayhill Therapeutics, Nanette Solvason, Michael Leviten and Hideki Garren revised the tolerizing plasmid further with addition of a chimeric intron to increase expression and designed a non-secreted version of proinsulin, localizing proinsulin to intracellular sites (106).

In an 80-patient, placebo-controlled, clinical trial, aimed primarily at safety, we showed that the approach was safe. We demonstrated that there was actually increased production of C-peptide during dosing. There were indications of benefit in A1c hemoglobin and in insulin usage (102). I should remind readers that it was Tony Cerami who elegantly showed that A1c hemoglobin levels correlated with glucose control in diabetes (107). In this study, we collaborated with Professor Bart Roep in Leiden to demonstrate that antigen-specific tolerance to proinsulin was attained. The specificity was important because there was no diminution in CD8 reactivity to viral antigens such as EBV and CMV (102). Plans for the next trial with 52 wks

of dosing of the tolerizing plasmid are underway, including preliminary discussions with regulatory agencies. In the next trial, we plan to test the vaccine in children with type 1 diabetes, soon after diagnosis. Further optimization of the approach is possible in the future, including the use of plasmids encoding other islet antigens, including glutamic acid decarboxylase (108).

Another area of focus for our group was an attempt to use various proteomic and genomic technologies to predict what therapy might be used optimally in diseases such as MS, where we have 10 or more approved drugs. A set of biomarkers based on a measurement of blood is perhaps the most practical approach. This result has been achieved once before in predicting how to mitigate risk when using natalizumab (52). Investigations over the past 7 years, led by Robert Axtell (a postdoctoral fellow in my lab and then a faculty member at Oklahoma Medical Research Foundation), have stratified the different clinical types of the disease we lump together as relapsing-remitting MS. Axtell and colleagues use a combination of cytokine and chemokine profiles on serum and then advanced bioinformatics. We demonstrated that there is heterogeneity in the levels of a battery of cytokines and chemokines in individuals with relapsing-remitting MS, and the levels provide a signature that correlates with the therapeutic response to IFN-β (109).

One other area of intense interest in the past decade of my research ties together with the first experiment that I performed at the bench 50 years ago at Salk under Professor Lennox. There I looked at the genetic control of the immune response to influenza. In a wonderful collaboration with Dr. Sohail Ahmed, then at Novartis Vaccines in Siena, Italy, we studied how a particular influenza vaccine in 2009 triggered narcolepsy in individuals who were HLA-DQ 0602 (a gene locus in HLA). The research showed that there is a component of the influenza virus that is contained in some vaccines and mimics the receptor for orexin in the brain. The orexin receptor is intimately involved in sleep and feeding behavior (14). The intersection of the brain and the immune system, and the genetic control of the immune response apparently recurs in my life in research.

SUMMARY

I have tried to recount the history of what we have done in the laboratory over the past 50 years. The story is perhaps full of too much detail for the casual reader. Therefore, in this conclusion, I try to list some important lessons that I have learned in the past half-century in research.

Learn from "Apparent Failures"

Tony Cerami wrote a brilliant essay, "The value of failure: the discovery of TNF and its natural inhibitor erythropoietin" (110). What may appear as a "failed" experiment may actually be a piece of anomalous data, for which significance is even more important than the data one is seeking based on the hypothesis. Two obvious examples of turning "failures" (lemons) into successes (lemonade) are seen in my research. In 2000, we published that our attempts to use altered peptide ligands in MS to tolerize the immune response to myelin was fraught with problems. Our work showed that pushing a Th1 response toward Th2 created the risk of anaphylaxis. The clinical trial that we reported was discontinued because of this safety risk (111). A few years later, Rosetta Pedotti, Steve Galli and I showed that it was possible to induce anaphylaxis to self-antigens (112). Thus, Ehrlich's vision of Horror Autotoxicus (111) became reality. Another clear example of learning from a "failure" follows from our work showing that amyloid proteins do not worsen neuroinflammation. Instead, we showed that amyloid structures are strongly antiinflammatory, opening a whole new concept for amyloid in neurodegenerative disease.

I often think of the cliché about "searching for the lost key under the lamppost." On a recent hike to a promontory above the town where I grew up, Culver City, I found a remarkable place for "looking under the lamppost." In our city's yard for public works, there is a whole depot of lampposts (see Figure 5). Perhaps if one is looking for a lost key, one should go to a depot that is full of such lampposts. May I suggest that a trove of exciting data is under the lamppost, but you might want to explore where lampposts may be concentrated, not just under one such post. Exciting discoveries lurk in anomalous data, which might be considered a repository of "lampposts."

Compliment Your Colleagues

Complement has a major role in both the immune system and the nervous system (113). It may be time to remind ourselves that it is a good idea to send compliments. We spend a great deal of time as working scientists acting as "tough peer reviewers." I recommend sending a colleague a compliment on an exciting paper or a fine lecture, even if you may be jealous of their achievement. Sending a compliment once in a while might condition us to be more humane when we enter the role of "peer reviewer."

Teach

Teaching medical house staff, teaching graduate students and teaching colleagues is a wonderful way to learn. Questions raised by students are often effective challenges that give us new insights. One of my most pleasurable experiences at Stanford was to teach a course with a gifted colleague, Sara Brownell, on the brain and the immune system.

Write and Communicate

I think that the American public is in general rather ignorant about science, including the subjects of the brain and the immune system. Part of the problem has been our reluctance to write about what we do for the lay public. The main graded exercise in the course on the brain and the immune system that I taught

Figure 5. Lampposts in Culver City, California, Department of Municipal Works. The best place to find lost keys is under an entire depot full of lampposts.

with Sara Brownell (who is now on the faculty in science education at Arizona State) involved writing short pieces. We alternated between communication to scientists in other fields with an article similar to a "nature news and views" piece, with portions directed to the lay public, as we find in the science sections of our newspapers and general magazines. Brownell and I wrote, "incorporating formal communication training into undergraduate and graduate curricula for aspiring scientists will enhance the quality of discourse between scientists and the lay public" (114). We should work to improve our communication skills.

Take Discoveries Forward to the Clinic With a Team

My mother-in-law once scolded me for curing too many mice of experimental MS. Patients have poked fun at me, asking "could I be one of your experimental animals that was cured of EAE?" I really take these comments to heart. If and when possible, we really need to advance work to clinical trials. Translational research requires a diverse team, and one should realize that it is not possible to have real expertise across the wide swathe of fields necessary to go from the bench to the bedside. Therefore, teamwork and cooperation are essential for translational medicine. I should note that many members of my team either have MS themselves or have a family member that has been afflicted. Some of my colleagues, who have coauthored papers with me, are not formally trained in research, but because they have MS, they actually ask the toughest questions—questions that are worth trying to answer (115). These individuals are among my most eloquent teachers and scientific colleagues. To mix a metaphor about a disease of the brain with an allusion to another organ, these colleagues with MS have "skin in the game."

Keep Spirits High with Humor and Self-deprecation

As mentioned earlier, my father's teachers, such as math professor Kline, and my father himself, made it clear that we must keep a sense of humor as we approach life. This advice applies to even serious efforts in fields like math and translational medicine. Professional life is full of setbacks. So I recommend keeping spirits high with humor. One of my colleagues who employed perhaps the most charming, intelligent and insightful use of humor has been Robert Axtell (109).

Here I want to express my deep appreciation for my wife of the past 15 years, Lucy. She and I have known each other since childhood. She heard me speaking of endorphins and coined the term "endoLphins." This concept exemplifies an aspect of our brain's chemistry that may generate the joy that ensues from a career in translational medical science. Finally, as I started this article, I repeat here in conclusion, that it has been a privilege to work on the subjects of immunology and the brain, and that I have been one Lucky Larry.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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