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Review

Sercarzian immunology – In memoriam Eli E. Sercarz, 1934–2009

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ABSTRACT

During his long career as a principal investigator and educator, Eli Sercarz trained over 100 scientists. He is best known for developing hen egg white lysozyme (HEL) as a model antigen for immunologic studies. Working in his model system Eli furthered our understanding of antigen processing and immunologic tolerance. His work established important concepts of how the immune system recognizes antigenic determinants processed from whole protein antigens; specifically he developed the concepts of immunodominance and crypticity. Later in his career he focused more on autoimmunity using a variety of established animal models to develop theories on how T cells can circumvent tolerance induction and how an autoreactive immune response can evolve over time. His theory of "determinant spreading" is one of the cornerstones of our modern understanding of autoimmunity. This review covers Eli's entire scientific career outlining his many seminal discoveries.

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1. Early childhood

Eli was born in New York to modest beginnings. His mother taught Yiddish and his father was a radiation technologist. As a young child Eli had a fascination with maps, which he used to keep track of German advancements during World War II, a path of destruction that would claim the lives of his family members in Poland.

2. Education

Although Eli loved New York, after two bouts of rheumatic fever a change was needed. He had a passion for travel, and it was in this spirit that he moved to Mexico. Initially accompanied by his mother, Eli eventually settled by himself in Mexico and commuted by motor scooter to the United States for high school. After graduating as valedictorian, he continued his education at San Diego State University where he majored in chemistry and met his first wife, Renan. In 1955, he left with his new family for Boston to attend graduate school at Harvard. He found his coursework to be much more challenging and even contemplated leaving after taking his first exam. Fortunately, he received an "A" on the test and soon thereafter began enjoying his graduate studies. He even took part in a specialized Medical Sciences Program that had him studying side-by-side with a select group of M.D. and Ph.D. students, many of whom would eventually develop into some of the most noteworthy scientists of their day.

3. Introduction to immunology, early studies in immune tolerance

The 1950s were an exciting time for bacterial genetics. Scientists were working feverishly to crack the genetic code and Eli was interested in joining the mix as he set out to find a laboratory for his doctoral studies. However, after meeting Albert Coons his research interests would change. Dr. Coons had just initiated a major revolution in immunology by developing the immunofluorescent technique for labeling specific antibodies with fluorescent molecules. Eli joined Coons' group and soon became interested in understanding why a state of "immunological paralysis" occurred following repeat administration of antigen. At the time, the idea of tolerance was just being formulated. A few years earlier Billingham, Brent,

Abbreviations: EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; NOD, non-obese diabetic; HEL, hen egg white lysozyme.

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and Medawar published their seminal discovery that the fetus could "actively acquire tolerance" to injected foreign cells, demonstrating that mice treated in utero could accept allogeneic skin grafts as adults [1]. Others demonstrated that injecting massive amounts of purified proteins could induce "immunologic unresponsiveness" [2], but the mechanism by which this occurred was debated. One view was that following administration of a large amount of purified protein, the persistent protein antigen could simply neutralize antibody as it was formed. The alternative view was that antibody inhibition was, as Eli put it, of a "more fundamental nature." It was in this setting that the young Sercarz entered the picture. Eli would adopt Coons's technique to synthesize fluorescently labeled antigens, a very novel and state-of-the-art approach for its time. He then tolerized mice using either low or high doses of soluble antigen. To determine if antigen-specific antibody containing cells were present in the lymphoid organs following tolerance induction, the spleen and lymph nodes were removed from the animals, snap frozen, sectioned, and then stained with the fluorescently labeled antigens. Using this technique, Eli was able to conclusively demonstrate that the loss of the antibody response was due to a loss of antibody producing cells [3]. He also demonstrated that the loss of antibody producing cells was antigen-specific, as immunizing the tolerized animals with a second antigen resulted in unaltered antibody production to the untolerized antigen (Fig. 1). These findings were published in *Nature* and the *Journal of Immunology* [3,4].

4. Theories on immunocyte maturation and exhaustion

Dr. Coons's laboratory was modest in size, but rich in talent and Hugh McDevitt was one of Eli's fellow lab mates. In addition to discussing his research within this talented group, Eli also enjoyed seeking out other members of the research community. Coons's laboratory was located on the top floor of what is now called the Goldenson 2 building, located in the landmark Longwood Quadrangle of Harvard Medical School. Interlaboratory discussions were facilitated by the existence of a common eating area located on the same floor as the laboratories, complete with a lunchtime cook. (Goldenson 2 no longer houses these collaborative nooks). It was in one such discussion with Bernard D. Davis that Eli coined the term "immunologic exhaustion" to describe a phenomenon in which immune cells die or become unresponsive following their activation and division [5–7]. Eli's theory of exhaustion, "the productive expenditure of a particular compartment of immunocytes" predated the concept of activation-induced cell death. His realization that the immune system can exhaust its ability to respond to an antigen fit well into his developing views of immuocyte maturation. Early data from other investigators such as Burnet, Leduc, and Nossal were instrumental in establishing the memory cell as a distinct entity, different from the naive immunocompetent cell [8–10]. However, there was still much debate on how immuocyte maturation occurred. It was in this setting that Eli proposed the *X–Y–Z* scheme of immunocyte maturation [7,11–15], which helped bring some order to the field. In Eli's view, the *X* cell started out as an immunocompetent but "virgin" cell. It expressed on its surface receptors (e.g. IgM) that could respond to "division triggers." Upon encounter with a division signal, the *X* cell had two possible fates. It could either produce IgM or become "paralyzed." He viewed paralyzed cells as "reversibly arrested" cells. The IgM producing cells would have the option of class switching to produce IgG, or remain as IgM cells. *X* cells stimulated to produce IgM would acquire "specific memory receptors" marking their transition into a *Y* cell (i.e. memory cell). One of the main principles of the theory was that all *Y* cells originated from IgM-producing cells. Eli viewed *Y* cells as a heterogeneous population with many subtypes. Further stimulation of a *Y* cell would trigger the cell to proliferate and differentiate into a *Z* cell. *Z* cells also occurred in different flavors with the *Zz* cell being the terminal plasma cell. By conducting adoptive transfer experiments, Eli demonstrated that the process could not occur in reverse. For example, *Z* cells could not dedifferentiate back into *Y* or *X* cells. It was therefore possible for a sufficient antigen exposure to force all antigen-specific *X* cells to differentiate into *Y* cells and so forth. Cells undergoing immunologic exhaustion would proliferate and then die, which could occur at any step. Although immunologists no longer discuss immunocyte development in terms of *X–Y–Z* maturation, Eli's theory was a major conceptual advancement for its time and its basic principles hold true today (Fig. 2). Importantly, his theory predated modern concepts of anergy, activation-induced cell death, and the identification of cell surface markers of memory.

5. UCLA, developing lysozyme as a model antigen

After leaving Dr. Coons's laboratory, Eli did two short postdoctoral fellowships, first with Luigi Gorini at Harvard [16] and then with Salvador Luria at MIT. He then accepted a faculty position at UCLA as an assistant professor step III in the Department of Bacteriology. Unfortunately, his new position paid him less than his postdoctoral fellowships. In this financially challenging time, Eli's research managed to make slow and steady progress. At UCLA, he continued to develop his *X–Y–Z* theory of immunocyte maturation but by the late 1960s, Eli's research interests would shift once again. After meeting Alex Miller, he decided to focus on lysozyme as a model antigen to study the immune system [17–19]. Lysozyme was chosen because it was easy to purify, its amino acid sequence was known, and its structure had been characterized. At a time when many groups were studying the immune response to whole cells or somewhat random polymers, Eli's team began working hard to develop their model system. This work would help elucidate the hierarchy of T cell determinant structures, e.g. the existence of immunodominant, subdominant, and cryptic determinants [20–23] (completely reviewed in [20]). Although site-directed mutagenesis was still years away, Sercarz and Miller were able to intricately map out determinants, even demonstrating the importance of single amino acid residues in antigen recognition. This was accomplished by purifying lysozyme from different species, identifying the unique lysozymes' amino acid sequence by Edman degradation, and then studying the immune response, including the cross-reactive response, between the different lysozymes and their chemical cleavage fragments (Fig. 3). By knowing how the different lysozyme sequences differed from one another Eli's group was not only able to demonstrated the importance of particular intra-determinant amino acids in antigen recognition, but they were also able to demonstrate that amino acids located at sites distant from a determinant could affect immune responsiveness [25] and that B and T cells reacted to different determinants [24]. Hen, bob white quail, ring-necked pheasant, guinea hen, Japanese quail, and turkey lysozymes were most commonly used and became the staple of Sercarzian Immunology. However, Eli's group prepared (or at least attempted to prepare) lysozyme from every species they could get a sufficient sample from including: man, gorilla, monkey, rabbit, and rare exotic birds. Some of these animals lived in, and sometimes escaped from, the Sercarz lab. For the rest of Eli's career, part of his research would be dedicated to understanding the mechanisms by which determinant display hierarchies occurred. Studies describing determinant capture, competitive capture, and hindertopy, as well as others would eventually evolve into Eli's "MHC-guided" model of antigen processing (Fig. 4) [25–36].

Prior to work by Eli and others, it was widely assumed that MHC class I and class II molecules had a common mechanism of binding,