

Thankful for being pushed into allergy/immunology field

By Henry N. Claman, MD, FAAAAI

Thank you for the invitation to write this scientific memoir. It will concentrate on my professional life. It may be interesting to find out how people happen to do what they do. In my case, I came from a very medical family and never considered another career. It looked like a satisfying life for my grandfather, father and mother – why not for me?

After medical school at New York University (NYU), I headed into internal medicine at Barnes Hospital (Washington University) and Massachusetts General. My plans were to practice general Internal Medicine. First, however, it was time to give two years to the United States Army, courtesy of The Berry Plan. I was requested (i.e. *ordered*) to start an allergy clinic after only ten half-days of “training.” (What I didn’t tell the commanding officer at Ft. Meade or you, either, was that my mother was a prominent practicing allergist in NYC, trained by Robert A. Cooke. She was pleased [and I wasn’t] at this unexpected turn in the road.)

So, for two years I took all the histories, did all the physicals, put on all the skin tests and gave all the shots. It turned out to be very interesting! The U.S. Army changed my life! To really learn about what I was doing, I first bought John Sheldon’s textbook. Then I volunteered in the Johns Hopkins Pediatric Allergy Clinic in nearby Baltimore, so I could learn from their patients and excellent faculty. I decided to try research after leaving the army and before entering private practice in St. Louis. I didn’t think research was right for me, but I wasn’t certain. I was advised to join **David W. Talmage, MD, FAAAAI’s**, NIH-sponsored allergy training program at the University of Colorado Medical School in Denver. It was good advice: I am still here!

Talmage was a great mentor – brilliant, stimulating, generous. He had a fine group of young faculty and fellows including **David S. Pearlman, MD, FAAAAI**, Edward P. Cohen, MD, Andor Szentivanyi, MD, Chuck Fischel and **Charles H. Kirkpatrick, MD, FAAAAI**. The first day I was there I was taught how to hold and inject a mouse. Then I went to the clinic. It was a good mix. Dave taught me the value of Darwinian thinking in biology. Some of his aphorisms still stick. “Absence of proof is not proof of absence.” “When you are secure you can afford to be generous.”

All my experiments failed at first, but I was having a wonderful time.

What was going on, immunologically speaking? Up until about 1957, immunology meant serology, i.e. antibody production. Between 1957 and 1961, things began to change. The major change was a conceptual revolution – the Clonal Selection Theory.

The Clonal Selection Theory was put forth in 1957 by Macfarlane Burnet in Australia and Talmage, then in Chicago. It was almost certainly Talmage’s idea, but Burnet never gave him credit. (Burnet did get the Nobel prize, but it was awarded for immunologic tolerance.) I had read Talmage’s 1959 article in *Science* and was fascinated.

IgA was discovered in 1959. Now there were three immunoglobulin isotypes. Radioimmunoassay was developed in 1960.

The effects of neonatal thymectomy were published in 1961 by J.F.A.P. Miller. While he was looking for something else (the role of the thymus in leukemogenesis in the AKR mouse) he found that neonatal thymectomy impaired both the cellular and humoral arms of the immune system. This was the first important experiment about the possible function of “the thymus gland,” as it was called. It controlled both arms of the immune response – the cellular and the humoral.

The polypeptide chain structure of immunoglobulins was shown by Porter and Edelman in 1961. The hemolytic plaque assay for single antibody-forming cells was published by Jerne in 1963. Idiotypes were defined and demonstrated by Kunkel and Oudin in 1963.

These were heady days for basic immunology! I was interested in the thymus. It was still a “mystery organ,” responsible for the development and maintenance of the immune system but unable to make antibodies itself. Why not?

I had been to **Robert A. Good, MD, PhD, FAAAAI’s**, 1962 Thymus Conference in Minneapolis, and J.F.A.P. Miller spent two summers in our lab thymectomizing newborn possums. I decided to investigate how the thymus worked. It was 1965.

Using some of the new techniques, I worked with Edward Chaperon (my first post-doctoral student), and **R.Faser Triplett, MD, FAAAAI**, then a fellow in allergy. We tried to get thymus cells to make antibodies to sheep red blood cell (SRBC) antigens by adoptively transferring thymus cells to irradiated syngeneic mice, which were then immunized. Spleen cells worked fine, but thymus cells did not. We thought that maybe they were too immature and needed more time and more antigen in the recipient. We tried this modification but that didn’t work because the mice died from their irradiation. So we added syngeneic bone marrow to save them from irradiation death and... antibody was made! We juggled the strain of mice and the irradiation dose so we could do the following basic experiment:

<u>Donor</u>		<u>Antibody in irradiated recipient</u>
Spleen cells	SRBC	+++
Thymus cells	SRBC	0
BM cells	SRBC	±
Thymus plus BM cells	SRBC	+++

This was the basic experiment. We did not know which cell made the antibody and made an educated guess that it was the BM cell. We were correct as J.F.A.P. Miller and Mitchell were later to prove. (Miller, in spite of our friendship, never adequately credited us with the discovery of T-B cell collaboration. I understand that at a meeting he tried to demolish our experimental results and conclusions.)

Our discovery, published in 1966, was not greeted with thunderous applause. One colleague said it was an artifact. Nobody, including ourselves, knew how important the experiment was and no one predicted that it would open the field of cellular immunology. After all, how did the cells, soon called T cells and B cells, cooperate? Furthermore, it soon became apparent that a *third cell*, a macrophage-type cell, was needed for antigen presentation. It was getting complicated.

A particularly striking conceptual advance came from an analysis of “the carrier effect.” This kind of experiment had demonstrated that optimal antibody production to a hapten required that the carrier protein also be immunogenic. Somebody brilliant recognized that the carrier effect was an example of T cell – B cell collaboration; the T cells respond to the carrier and the B cells to the hapten. Whether it was Dick Gershon or Av Mitchison who should be credited with this insight has never been clear to me. Then MHC restriction in the cellular immune response was the next great conceptual advance.

Cellular immunology was on its way.

My research career moved to other areas, such as immunologic tolerance, serological techniques, graft-vs-host disease, mast cells and fibrosis, immune regulation and the role of “suppressor T cells” (which is the proper term for regulatory cells which suppress). I also investigated the regulation of contact sensitivity and the possible role of breast implants in autoimmunity. I found research stimulating, often frustrating, but ultimately rewarding. Still I was very pleased to be able to continue my clinic and my teaching.

I should point out some characteristics of immunology as a discipline in the 1960’s and 1970’s. It was different from today. The academic immunology community was a small club. It was possible to know almost all the “players.” Talmage was generous in introducing me around. (I suspect that I was still being called “Dave Talmage’s fellow” in my mid-40s).

The discipline of immunology was also not large. One could understand the advances in antibody structure and function, complement, delayed hypersensitivity, immunodeficiency, autoimmunity, etc. without difficulty. Immunologic meetings were manageable. Reading a few journals covered the territory. There was no significant movement into molecular biology. NIH money was not difficult to get, and research budgets, including salaries, reagents and animals were not large. There were few patents, no venture capital and every immunologist did not have a company! Papers were short, references were few and statistics were simple or absent. (All these characteristics pertain to our T-B collaboration papers.)

Academic life was simpler than it is today. It was possible to do hands-on research, see both inpatients and outpatients, and also teach medical students and house-staff. But it was demanding. My family, particularly my children, Jenny, David and Ruth, should have seen more of me.

I never moved from the University of Colorado Medical School. (I never wanted to be a department chair or a dean.) Instead, I changed my research project every 5 or 10 years. I also have been fortunate to participate in our training program in Allergy and Clinical Immunology and have had the privilege of knowing and teaching a large number of excellent physicians and some basic scientists as well.

Right now, I am engaged in a new Medical Humanities Program, designed to bring art, literature, music (i.e. “the humanities”, broadly interpreted) to our “science-only” campus. It has been a challenge, but one with rewards. It has also brought me back into contact with our medical students.

Medicine has been good to me and I have had a satisfying career. The arts have been extremely important to me. I have had the time and opportunity to play and appreciate music and to visit most of the great museums. I even wrote a book on medieval art, called Jewish Images in the Christian Church.

I firmly believe that, compared with half a century ago, we now have better-prepared medical students and a better training curriculum. I think, therefore, that we are preparing better physicians and scientists. After all, is that not the goal of every educator – to make sure that our students will come to surpass us?

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