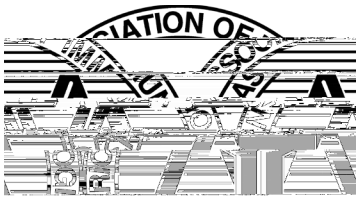

The American Association of Immunologists Oral History Project

Transcript

Ethan M. Shevach, M.D.
December 16, 2015
Bethesda, MD

Interview conducted by
Brien R. Williams, Ph.D.

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Williams: This is an interview with Dr. Ethan Shevach for the American Association of Immunologists (AAI) Oral History Project. Dr. Shevach is Chief of the Cellular Immunity Section of the Laboratory of Immunology at the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Shevach served as editor-in-chief at ( ) from 1987 to 1992, and he was awarded the AAI Distinguished Service Award in 1992. We are at the AAI headquarters in Bethesda, Maryland. Today is Wednesday, December 16th, 2015, and I am Brien Williams.

Thank you very much for doing this today, Dr. Shevach. Let's start with a little bit of your family background, where they came from and where you came from.

Shevach: Where I came from. So from what I know, my father was born in Poland and

undergraduate education with medical education. So one was accepted to medical school when one graduated high school, and if one maintained grades during college, during those two years of college, one was then allowed to enter medical school after two years of college ah d ge

Shevach: No. Terribly taught physics and chemistry mostly. Probably during medical school when I spent some time—I enjoyed medical school. I enjoyed certain aspects of medical school more than others, mostly biochemistry and pharmacology. I can't say I enjoyed gross anatomy or looking in a microscope every day. And a little bit of time in the lab really influenced me that this is something I'd like to pursue for my life's career. I like getting results. I actually liked doing experiments in those days, and I was willing to—one of the advantages of graduating medics of [illegible]

Shevach: I have one sibling, a younger brother who's a year and a half younger than I am. He had a different career at Boston Latin School in that he liked Ancient Greek, so he avoided science completely, took Latin, French, and Ancient Greek at the same time, went on to major in philosophy at Harvard and ultimately got a Ph.D. in philosophy, and taught philosophy at the college level. So, different things appeal to different people.

Williams: So what was the NIH campus like in 1969 when you arrived?

Shevach: It was a terrifically stimulating place. The quality of the postdoctoral trainees, particularly the M.D.'s—and there were many, many M.D.'s. A great majority of the fellows were M.D.'s in those days, relatively few Ph.D.'s were in the lab, and everyone was really very ambitious. Particularly when I joined the Laboratory of Immunology, my peers all turned out to be unbelievably devoted scientists. No matter how early I [illegible] evotl15.83J-29.79 -1.1t(e4 (o)-2 (n t)-

I think, or promote itself well, what a great place it is to do postdoctoral training in the basic sciences.

The other factor is a bit more subtle, in that fellows train in one of the big cities, say in Boston or New York or San Francisco, they're older, they're settled in their environment, and to take up and move and come to the NIH for training is tough. They may get equal—I mean, I can't say that the training at the Harvard Medical School area in Boston is any less good than coming to the NIH. So many have sort of stuck where they are and they don't come to the NIH anymore.

The NIH was a very unique place in the late sixties or in the early—really throughout the sixties and the early seventies, when one learned from people who'd been there what a great experience it was. When I was an intern, I had a resident a year or two ahead of me who had been at the NIH already, encouraged me to come. And many of my peers, my fellow interns and residents, also came to the NIH to do postdoctoral training, some in sw()-4 (a)n (a)nkmlo-6 (sos)-1 -0.00-0.00uno (e)

were multiple reasons for that. It was basically banned in 2005 and never happened again. So at the present time, we're not allowed even to consult for free for private industry. [laughs]

Williams: This is something that came from Capitol Hill or—

Shevach: It came from Capitol Hill. So there was a famous series of investigative articles by a reporter for the that claimed that NIH researchers were spending their time consulting for private industry, as you might imagine. But there were strict rules about what you could and couldn't do, and some of the rules were really quite reasonable. If you were away from your office consulting for a company, you

easier for us to hire foreign-born scientists than American scientists. So an American scientist required what was called an FTE [Full-time equivalent], a

out. So what I am interested in is in what accomplishments do you want to be, at

Everything seemed rather interesting, and the most important thing in that paper was the characterization of these cells involved the expression of a certain cell-surface antigen called CD25, which is the receptor for interleukin-2, this interleukin-2 alpha chain, and that was the key observation in the paper, that 10 percent of CE4 cells that expressed CD25 had this unique property of suppressing other cells.

So I looked at the data in the paper, and I said, "How did he identify this?" He used immunofluorescent staining, fluorescence sorting, and separation of cells, and he said 10 percent. That seemed like a very big number. So I said, "What antibody did he use?" And it turned out the antibody he used to identify CD25 positive cells was made some almost fifteen years earlier by Tom [Thomas] Maleck, who was a postdoctoral fellow with me in my laboratory, and published.

I went back and looked at my old paper, and we said 8 percent of the cells, normal cells, expressed CD25. Eight percent, 10 percent; pretty similar. We were actually not interested in what those cells did; we wanted to know why they had CD25. We took a different tack to the research. But the numbers seemed right.

So actually one of the few times in my career, I said, "Let's just repeat the experiments in this paper in and see if Sakaguchi is right." And a new postdoctoral fellow entered my laboratory at that time. I said to her, Angela Thornton, "Repeat these experiments. We have all the reagents." For other reasons, we were interested in the animal model Sakaguchi used. Everything repeated, and we went on to show that these cells had suppressor qualities. In vitro, we made a very simple in vitro assay rather than using in vivo experiments. Angela developed these technologies to do this, and we stuck with it.

So a lot of objection came up at the time because there

in tumor infiltrates, and clearly suppress the immune response, both in man and experimental animals to tumors.

Williams: So what do you want the layperson to know about your achievements? What is significant for —?

Shevach: For almost my entire career, I've worked in experimental animal models, ten

At the time, Joseph Feldman, who had been editor of for fifteen years, was retiring. The Council of the AAI was willing to take on—Joe Feldman was a permanent—that's all he did. He was a full-time editor. He had retired from his laboratory to Scripps, and I think really most of the fifteen years was the full-time editor of . I didn't want to abandon my labwork, and the Council of AAI proposed a different format, that the editor would not be a full-time editor, would still be involved heavily in running his own personal laboratory, and would have, perhaps, deputy editors who would assist him in editing the journal and would divide up the work, so to speak. And this was a concept that other journals had advocated over the years, particularly , which moved its editorial office and editors from one city to another every five years, and they actually move their entire editorial office, including the editors, all their staff, every five years, is the process they always had. That technically is probably tough these days, but that's the way they still do it.

Williams: Great for real estate agents. [laughs]

Shevach: Well, I don't know how—yeah, I guess so.

All the scientific editors were in one place. Obviously, being at the NIH, this was attractive to me because I felt I could recruit others. I didn't want to do this as a—I didn't realize how big a job it was when I took it on, needless to say. But there were other very competent people I knew I could persuade to help me at the NIH, and I, before applying for the job, said, "Would you be willing to form a committee of editors, so to speak, that will assist in this process?" So that was a carrot.

I convinced the Council of AAI that the NIH would be a model place to actually try this out, and I think changing editors every five years is a very good thing for a journal. There are some journals that have the same editors forever. That sort of breeds familiarity, it doesn't bring new life into a journal, so five years was a reasonable term that I was willing to put up with. I had been a—what did they call it—assistant editor [Ed. associate editor], I'd been a section editor of , I was interested in building up the procedure of . I felt I could do that and I felt that I could handle not only an adequate and a rapid but a fair review process. I knew the field.

The field was much simpler then, I have to say, 1987, probably think that one could have a broad knowledge of the entire field of immunology. I wouldn't say that today. Absolutely not. I could say in 1987 that I knew all the major workers in the field, so I could pick subeditors and deputy editors and section editors, whatever we called them. I knew who was doing good work. I'm not sure you can, again, make those statements today. The field is much, much broader than it was and much more difficult now.

Williams: So when you were a section editor, what section were you—

Shevach: [laughs] Curiously, for reasons that were never clear to me, when Joe [Joseph D.] Feldman asked me to do this, it was the section of Clinical Immunology, even though I was probably the least clinical immunologist there. I did a variety of things, but for about a four-year period, I handled clinically oriented papers.

Williams: So you came in as editor-in-chief with an agenda?

Shevach: Yes, I was asked to come in with an agenda. I mean, the Council of the AAI, the office of the Association, decided that they wanted and willing to have a new process for running the journal, which has been maintained since then and done slightly differently, I have to say. So I thought it was a terrific idea, and they thought it was a great idea that all the deputy editors come from the NIH. We had one deputy editor not from the NIH, and I learned that very early on—that was very important—that one of the deputy editors would handle all papers from the NIH. So that was a key thing that I learned very early. So approximately 10 percent of the papers published, at least in the ’80s, in
came from the NIH. I don’t know what it is today, but in the ’80s, right before I took over the journal, I actually looked, and 10 percent of the papers were coming from the NIH. So that’s a big number.

And I didn’t want to be stared down by people in the elevator coming up to my office saying, “What happened to my paper? How come my paper got rejected?” and things like that. So I completely removed all papers from the NIH from anything—I didn’t see them at all. They were all handled by an outside editor, Dr. Frank Fitch, who ultimately became editor himself at the University of Chicago at the time. Then I could breathe a sigh of relief, just say I had nothing to do with it, nothing to do with anybody I met in the cafeteria or in the halls of the NIH. But all the other editors were at the NIH, and that a (he)-6 .9 (w)-2 (er)-(our)-o-3.9 (i)-6

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tougher, but we weren't. I think the editors were very fair and pretty objective in what they did. I was happy with the process. Not everybody else was. I took a lot of flak, I have to say, at some point.

Williams: So you maintained that?

Shevach: I maintained that. It was tough enough establishing the system where five or six people handle the editorial process. One of the original suggestions was that the editors meet once a week to jointly discuss papers together. This is how some journals had worked. , I believe, works that way, that the editors would sit down together and go over things. I thought about that. There were just too many papers. There was no way. It would have taken a day a week or more for everybody to do that. It couldn't be done in two hours or something like that once a week. So all my deputy editors worked independently. I monitored what they did. I didn't want anybody accepting all papers and anybody rejecting all papers. That was part of my job, and to gently say—you know. I actually did very little of that. Most of them sort of subliminally had a 40 percent acceptance rate in the back of their heads, and we didn't manipulate that. That's the way it worked out over a period of five years, and the deputy editors all had significant expertise in their own subspecialty areas and they were picked for that purpose.

Williams: Are there changes that you brought to the journal?

Shevach: That was the major one and that was a big change, and I wanted to make other changes. So one of the problems with—I don't want to say "problems." was obviously regarded as a place where you can get things published, a good, solid publication, but it's not a high-impact journal, and still regarded that way. Certain people regard it as a high-impact, but there are more prestigious places to publish.

The chief competitor was in those days, and they had a very unique process of reviewing papers. You submitted a paper, and if your paper was not accepted, a month later you somehow got a form letter, without any critique, saying your paper was reviewed by the editors and didn't make the priority, was not enough interest, and you got it back with no outside critique. And they didn't send papers out, for the most part, papers from the outside for outside reviews.

That was a Rockefeller University journal; still is. Now they send papers out for outside reviews, but in those days they didn't. And the rumor had it—never validated, but I'll make it public [laughs]—that when the paper came in, someone looked at it, and if you weren't a member of the club, it was put in a drawer in someone's desk, and a month later it was taken out and sent back to you with a form letter.

So I didn't like that idea. I wanted things to be fair, and I felt we could be a bit tougher, maybe lower the acceptance rate. I learned quickly that probably was not a good idea. is unique and serves the whole membership of the AAI, and the AAI, although it's immunology, is a pretty diverse group of scientists, covering all kinds of things and all kinds of species, people were publishing important papers in areas that maybe were not so high impact, yet the service to the AAI that the journal was to provide was to provide a forum for publication for all good papers in all aspects of immunology, even those that weren't perhaps of gigantic general interest or importance, but they were quality science. And I learned pretty quickly that that's what I had to do, and I couldn't become a very selective journal and say I was going to avoid certain areas of immunology that aren't so hot. I learned my lesson very quickly that the journal was sort of a diverse group of scientists, and I had to do that as well. Quality was important, but I couldn't be selective in subareas of immunology to choose for publication.

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referees. I'll do my best to include a couple of your suggestions as referees."

And there's obviously people saying—you know, plagiarism comes up as an issue. Not many times. Sometimes people just inadvertently or accidently on purpose, whatever you may say, copied parts of the discussion of somebody else's paper verbatim. This is usually picked up by people rather quickly and we're notified. But nothing of a major fraud kind of episode. Over the years, I was lucky.

Williams: What about any major developments in the field that occurred and was published in during your tenure?

Shevach: Well, one of the most interesting—so certain areas were ignored by certain journals. Probably the one area that I remember where the most of the original publications came to was in the area of one of the cytokines, interleukin-12, which is a major cytokine influencing Th1 cell effector T cell development, and those papers on interleukin-12 were all published, many of them published in for the first time, and nowhere else. That was it. I mean, other papers perhaps went elsewhere. It's hard to say in the beginning that this is a major—it may take five years to become a major observation, so you don't know.

I was not the editor when Dr. Sakaguchi's paper was published in , and that has turned out to be a major development. But I haven't gone back and done—one does this by looking at citations, high-impact papers in , and trying to fit that in with developments in the field. I haven't gone back and done that in the period when I was editor.

Williams: While you were editor, the journal celebrated its seventy-fifth anniversary, and I wondered how that was celebrated.

Shevach: To be honest, I don't remember. [laughs]

Williams:

Shevach: My picture was on the cover, I remember that, along with the other editors at the time, but I'm not sure we had a big celebration.

Williams: That's interesting. [laughs]

It strikes me that there's been a proliferation of scientific journals and research notes and so on and so forth over the years. What effect has that had on the field and how do you handle it?

Shevach: Well, you can't handle it because it's all done by some of these online, completely online publications, so-called open-access publications, you know, which everybody can access for free, but they charge the author $3,000 to publish a paper, so the author is paying for the online publication. I don't think one can

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published more papers than another, but for some reason—and I don't know how and it wasn't my manipulation—it balanced out in the end.

Williams: While you were editor-in-chief—and obviously there were great demands on your time—how did that affect your scientific career?

Shevach: I didn't think it did, but it did. [laughs] So it's very hard to evaluate. I took the journal for one other reason that we didn't talk about, and that is I wanted—my position at the NIH allows me to manage a modest-sized research group of about ten to fifteen people, but really I had no other—I think, much to my benefit, no other administrative responsibilities. So one of the sort of minor to major reasons I took over as editor of the journal is I wanted the management experience of managing something else, and, in a sense, managing a modest-sized business. The budget of the journal even then was in the millions of dollars. And I also wanted to be involved in hiring people, journal staff, dealing with journal staff on a daily basis.

So I managed my time. I was very lucky over the years in terms of people who worked here in the office handling the fundamentals of paper processing and things like that, and that worked very well. I was very lucky. Joe Saunders helped me a great deal in hiring editorial office managers who really worked very hard and helped me out. The journal staff liked to see me every day, so I came over here for an hour every day. But the NIH is only ten minutes away, so I was here from two to three every day, for the most part, one hour in the office and a little bit of commuting. And they liked that, and I guess—and I'm not sure I really had to do it, but I did it every day, for the most part.

Then I sort of worked at night. Theoretically, I was forbidden, because I was being paid by the journal to be editor, forbidden from using any of my working hours at the NIH to handle journal business. I usually did it at night, probably another hour or two at night, sometimes more. But the journal never sleeps. That's one of the problems. And it usually doesn't sleep during periods when you'd want it to sleep. So the biggest input of papers to are two times of the year, right now. Between Thanksgiving and Christmas, more papers than ever come into the journal because people want to take a vacation at Christmastime.

The second period of time when the journal is busy, at least when I was editor, was July and August, summertime when everybody's on vacation. And if you think about it, it's only logical. People would finish their degrees. The academic year ends in June. One thing you want to do before you go on vacation is to finish your paper and submit it to the journal. So, actually, the journal was busiest at the times when I wanted to take a vacation as well, and I couldn't. I did, but it was tough.

So I suspect my science slumped some. It's very hard to know. I mean, your science always has its ups and downs. I've been in this for forty years. I've

So immunology itself has blossomed over the last twenty years, really. There were some disappointments. Initially, monoclonal antibodies were thought to be a tremendous advance; they were. But the clinical application, which was said to happen very quickly—remember, monoclonal antibodies were discovered in 1975. It wasn't until 1992 where people began to use monoclonal antibodies for the treatment of rheumatoid arthritis. So it's a long, long lag period between a tremendous basic advance in making a reagent, a drug, basically, or drugs or diagnostics, before it was applied to the clinic.

Now things are moving much faster, and major pharma is more interested in immunology and supporting immunology. Some pharmaceutical companies are only interested in small molecules. For many, many years now, biologics, the major research interest in almost every big pharma company. So immunology's had a big influence, will continue to have a big influence. And, unfortunately, we're producing very expensive drugs. That's the only other problem, who's going to pay for them. [laughs][ogi 0 -1.1-18bha[og4 0 -1.1/TT1DC Tf Tc -0.002 Tw 0 -1.15 TD

So I still advise people to go into medical school and to consider research careers, but that's very tough. The people in my lab—so life in the lab has also changed. So when I started out as a tenured scientist at the NIH, almost every fellow I trained had the goal of becoming an independent scientist and running their own laboratory. That is probably rare today or down to, I'd say, 25 percent. People are realistic as well. Do they want to go off to a university, apply for grants, run their own labs? That was the major goal in the seventies, eighties, maybe early nineties. Not true today. Everybody's thinking of different things. The last group of people who left my lab have all gone to industry, and they seem quite happy. They're doing research careers in big- to middle-sized to small-sized pharma, even, to startups. So Ph.D.s in immunology are quite willing to do that.

Williams: That movement, does that have effect on the hardcore academic scientific community?

Shevach: Not really. I don't think so. No, there are plenty of people. I mean, we need more funding for the hardcore scientific community, I think. The budget for the NIH hasn't grown in ten years now, so there's a restriction on people becoming members at —, but I think people are still interested in doing that, but it's a smaller percentage.

And the other issue is are we training too many people. We're still training lots and lots of people and probably training too many people. That's been argued. I'm not sure. The answer may be, yes, what are all these people going to do. Luckily, most of the people who've worked with me have stuck with it. A few of the M.D.s have gone into practice. I recently had a very good postdoctoral fellow 7[tc 0o.th c schee 15 Tdacencuniyecoy15 Td[a [(7[tcini)6tc(a)-1[(7[tc e i)-6c[(7[tc 0o.th 0o.th(al)-