The American Association of Immunologists
Oral History Project

Transcript

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Williams: This is an oral history interview for t

but people would still prefer not to be in the service if they could avoid it. So the talent in that era at NIH was stunning, and indeed it populated most of the medical schools in the next generation. The leadership had all in common that they had all had an NIH experience for two, three, four years. Some stayed much longer, but at least you can go around and look at that era and you'll discover in everyone's background was this common experience of two, three, or four years in Bethesda [Maryland] at that time. So that was a great experience, both got me into science.

I had already, though, decided I wanted to do that and was already looking for where I would go to do immunology, even before I arrived in Bethesda, but that

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Williams: Are either of them—

Paul: No. Neither of them took a scientific bent.

Williams: As I hear it, you sort of moved from possibly doing clinical work to the endocrinology and then to immunology. Was that the progression?

Paul: Well, that's correct in the sense that, I mean, I had been trained as—I have an M.D. I'd worked in labs in the summers while I was in medical school. I think I had always had the expectation that I would do science. I probably didn't really have a clear understanding of what that would be. So whether I had intended to do clinical science and then change to lab science, I'm not sure about that. I probably was all along thinking of finding a career in laboratory science, but, of course, that didn't necessarily have to be. There were a whole set of, I have to say, lucky breaks that made it possible. If I hadn't gotten to the NIH, for example, and I'd stayed, I might have been in the Service in a clinical realm. I might have not been able to find a slot in a really first-rate lab. There's all sorts of ways the world could have turned out very differently.

Williams: The way you describe the NIH as this sort of wonderful place to be, was that during your first tour there or during the second or both?

Paul: I came as a clinical associate. That was our title. That era was really special. Then I finished that in 1964, and then I went to Benacerraf's lab in New York University for four years, and we came back in '68. When we returned, of course, my position was very different. In '62 to '64 I was, you know, a young person. I didn't have any

So I came into immunology seriously in 1964. It seemed to me it was a revolutionary period. I'm still waiting for the consolidation to start. [laughs] Every era seems to bring new changes. The field is continuously fascinating. In fact, I've often thought a good title for either a book or a lecture about immunology would be *Endless Fascination*.

Williams: What was driving this? Was it personalities? Was it technology? What was behind all of this?

Paul: Well, firstly, immunology is a very interesting field, in contrast to, say, biochemistry. Biochemistry is a way of doing science. You use biochemical tools to study particular things. Immunology is a coherent body of knowledge that you bring distinct tools to, and everyone who calls themselves an immunologist, particularly in the era when I was growing up, would share certain core knowledge that we would all have to know.

So it was a community of people who I would say, both at NIH but in the greater world, had a very common world view of this science, and, as you said, things were changing. Both there were new technologies, there were also new ideas. So as you probably know, immunological science is a young science. As a concrete discipline, in contrast to as just accidental findings, most people would date it to the latter part of the nineteenth century, to Louis Pasteur and Robert Koch and most, importantly of all, to Paul Ehrlich, and it was still looking for, so to speak, a central idea, a central theory that guided it.

It struggled with that for a long time, and it was only in 1957 and '59 that the central theory was enunciated; that is, what is called the clonal selection theory of immunity. In 1957, two papers appeared, one that's given all the credit by [Frank] Macfarlane Burnet, but actually an earlier one, which was really first, by David Talmage. Talmage was then a young assistant professor at the University of Chicago, went on to spend his career in Denver at University of Colorado, is still alive. I don't know if David was a president of this organization. He may well have been. If he was, you should interview him. He's a wonderful man.

So Talmage and Burnet enunciated the clonal theory in '57, and then in '59 Burnet published a really magnum opus, which described the clonal selection theory in detail, and beautifully written, and in many respects earned him the great status he has in the field, because the two initial papers were rather sketchy, but this book was wonderful. So it was really only until '57 to '59 that we had a grounding of a theoretical construct to underlay immunology.

So I'm coming into the field in the early sixties,wy

on, but it wasn't only the technology that was driving it. It was just the ideas, people recognizing what you could do.

It is true that people were understanding the structure of immunoglobulin. That was being developed at this time. [Rodney R.] Porter and [Gerald M.] Edelman were doing their work. The specificity of reactions, there had been a great effort in the twenties and thirties by Landsteiner to understand the specificity of antibody. But in Benacerraf's lab and my research project, we were interested in understanding the specificity of what today we would call T cell responses. Of course, we didn't know there were T cells and B cells in that era.

But it's true also that shortly thereafter, people understood the function of the thymus. All these things were unknown. And while the technology was important, even with some very modest technology, a lot of exciting work could be done. But it is true, as time went on, new and newer technologies kept being available, and immunologists were very fast to take them on. In fact, it can be said that monoclonal antibody use as an analytical tool almost certainly was best developed in immunology. Cell sorting was developed by immunologists, and we were the first to use it very aggressively, not so much the gene knockout technology, although even there immunologists were very early. Sequencing, there were more sequences done on immunoglobulins than everything else combined.

So we adopted the technologies early. I think it's true that technologies were important, and there's no doubt that without them the field would have leveled off. Each few years brought a new technology available to allow you to go forward. I used to say you can do today experiments that we would have called science fiction five or six years ago. That's certainly true.

So, yes, it was partly that, but not that only. It was a very strong sense of excitement of what could be accomplished, and I can certainly tell you on the eleventh floor of the Building 10—our NIH buildings have very poetic names. [laughs] Building 10 is the largest brick building in the world. But on the eleventh floor we'd be up and down the corridor. Every day was a new day. So it was very exciting, I have to say. That's certainly true, now that you remind me and send me back in the years to that era.

But that wasn't the only era that was terrific. So I had very good fortune, if I may go on, in my postdocs. So I came to NIH in 1968 with Benacerraf. I had been his postdoc at New York University when he asked me to join him, which I was very grateful for. The arrangement we made was that I'd work on my own projects half-time and the other half-time as a partner with him, which was fine with me. In that era we had fewer postdocs, so there were one or two postdocs that worked on the projects that I did with Baruj, and then I had one who worked on the projects I did myself, and everything was fine.

academic setting, but there was one great thing at NIH. So he had discovered the phenomenon for which he eventually got a Nobel Prize, and that was that the ability to develop immune responses against simple antigens was controlled by individual genes, was unigenically controlled or monogenically controlled. It turned out eventually that the genes that controlled it, which we called immune response genes, eventually were proved to be major histocompatibility complex genes, and that was, in the end, a great finding.

He had this work in guinea pigs. The guinea pigs were not all inbred; they were outbred. It was very hard to do good genetics in them. There was only one place in the world where there were inbred guinea pigs available in any numbers, and that was NIH, and he desperately wanted these guinea pigs. Souia7(e)4(d)-10(g)/Homp9at(pi)-E

But Dick was in that era in London, and he had reported that he could take cells from rabbit lymph nodes and expose them to certain stimulants in vitro and then measure their response by their synthesis of DNA using the uptake of tritiated thymidine. I read this paper and I thought this is terrific. I immediately started doing it in our system so I could now study the things we had been limited to study before in animals. I could study them in not petri dishes, but little culture [unclear]. It was transformative. Today, of course, the teouTJ 0.002 Tct6[((.)294.2-2(e)4(d)]

and then something else about the antigen would stimulate the B cell, that the immunoglobulin was not a true receptor in the sense that when it was occupied by its antigen, it did not transmit biochemical signals into the cell that would activate the cell, but rather it acted as a glue to bring to the surface of the cell a molecule that was intrinsically stimulatory for entirely different reasons. So that was one view.

Don Mosier and I argued, no, this is a true receptor, and we had many reasons. I can recall we'd go to meetings, and those who thought differently were very eloquent, and they'd win every argument. But we were right in the end. [laughs] Not completely. There were some truth on their side. The notion that the membrane immunoglobulin was a true receptor is, of course, true. I think more than any other group, we were the ones who really pushed that idea.

Then what happened was at that time Don Mosier, who had been my postdoc, became independent. So I said to Don, "Well, you take the B cell project and I'll do something else."

I started going back to my interest in T cells, which I had worked with earlier, and I'd worked with several other people, a colleague named [Ronald] Ron Schwartz, and we developed—one of the big problems with T cell biology in that era is for reason that to this day I can really not truly understand, it was very difficult to culture mouse T cells. It was easy to work with human T cells. Guinea pig T cells, which we'd worked with, were no problem. But we couldn't find good ways, good conditions, for working with mouse T cells.

The reason that was so important is the genetics of the mouse are so well understood, and the chemistry of the mouse protein so well understood, that to work with the guinea pig was like working, you know, with a handcart when someone's got a steam locomotive running by you. It was crazy to stay with the guinea pig. So Ron, particularly, but as my postdoc, he cracked that problem, got it to work. We were then able to move very quickly through repeating all the guinea pig stuff and moving forward, and that was really important stuff.

But the next big deal was my interest, going back to my B cell era, in growing B cells in tissue culture. We had this very curious finding that if the cell density was high, we could stimulate the cells with their antigen, if you like, to divide. But if cell density was low, we couldn't. We said, "Well, there must be something we're diluting out, and let's look for it."

So Maureen Howard, who was a postdoc, and I started looking. What we found was one of the first of the cytokines was a molecule called ( )-10i-4('(r)3(l)-12'u(c)4(ki)-2(n)]TJ

the eighties. Yes, in the mid-eighties. I don't know. I used to say it's twenty-five years ago. I still work on it. So was it a blessing or a curse? [laughs]

So the discovery of interleukin-4 and then understanding all of its biology, understand it turns out to be the principal regulator of all allergic and inflammatory disorders. Without IL-4 you don't make IgE antibodies, the type of antibody that is responsible for allergic diseases. So this is the central player.

Then we also discovered how you differentiate cells in vitro to become from being naive cells to become TH-2 or TH-1 cells. Susie Swain's lab and my lab

So he came to the lab, and we worked on a couple of really interesting projects together. Everyone recognized him as a man of surpassing ability. So after, I think, about a year, we all of us—when I say "we," I mean I was the chief of the lab, but several other P.I.'s in the lab, very good people, and we all agreed this was something special and we should do something. Mark had the idea that it should be possible to identify the T cell receptor. In that era, it was known that T cells have a receptor for antigen, but it wasn't known what it was. It was regarded as the greatest problem in the field at the time, what the chemical nature of this receptor was. And Mark had an idea of how it could be done.

What we did, we established an instant group. We cleared out a lab for him. One of my postdocs and one of Ron Schwartz's postdocs was excited, went to work with him. We found him a technician. So he had a little group of four people, and in six-months he had cloned the T cell receptor. It was a great, great accomplishment.

We all looked on from a distance, but we all restrained the idea that our names shouldn't be on this paper. He had done this all. That was probably the wisest thing I ever did, because it made me a friend for life, because in other settings, in other labs, the lab chief might have insisted that his name go on this paper. It would have been wrong. Absolutely Mark did it. He was a wonderful scientist. He *is* a wonderful scientist. But the great advantage of doing it that way was, we, to this day, have the highest regard for one another. So that was a wonderful experience.

So could I have done it myself? The answer is I would have never, never succeeded. I guess it's a disappointment that I didn't do it, but not a realistic one. In other words, you should be disappointed when realistically you could have done the experiment you failed to do, but I don't think realistically I could have done that experiment, and Mark could. We provided him, so to speak, the setting in which it could be done, the resources to do it. It was a great experience.

There have been a few other examples through the lab where things like that have happened. You know, maybe I'm too good-natured to—I can't think of great disappointments in that respect. There are always things we could have done better. Maybe I should have—you know, catching new trends, be ahead of the game.

The whole idea of the innate immunity revolution that Charlie Janeway instituted, another postdoc, the idea that Charlie had, which got such prominence, was quite straightforward. He enunciated it in an exquisitely clear way that galvanized the world, but the idea itself that there had to be chemical structures that were held in common by pathogenic organisms that would tell the immune system it should respond, that was probably well accepted.

Indeed, just as an example, the laboratory I had, the Laboratory of Immunology, was created in 1957. The first chief of that laboratory was a man named Jules Freund. Now, you're not an immunologist or a scientist, but everyone knows his name because whenever you try to immunize an animal with an antigen, if you are going to be successful, you have to add something called an adjuvant. The most famous adjuvant was Freund's complete adjuvant. It's adding an oil and water mixture with dead mycobacterial tuberculosis. And why did you do that?

So the first day I got a call from CBS. I never got a call at home again, so that was great. It turned out it was just at a tipping point. The advocacy community had gone for the view that you were going to make progress against this disease not by yelling at people, but by getting behind what ought to be the way forward, and the way forward was science. They were going to get behind the best science to deal with HIV, not all of them, but the really most insightful ones. Then they became the greatest supports for the Office of AIDS Research. They were terrific, great allies and wonderful people, the ones I worked with, really outstanding.

So it was a great experience. I went into it with a lot of trepidation. We had to develop a coherent plan for HIV research for the country—well, for the NIH component, which was 90 percent of what the country spent. It wasn't that we gave out individual grants or determined individual experiments, but we said these are the big areas and we're going to devote this component of money to these areas, and we're going to ask the institutes to build proposals based on this plan. We would then, based on that, allocate resottTthanof on ofn.y t said -10hd bs1 toe (ha)4 W

What had happened was that we'd been invited to the White House on World AIDS Day, which is December first, and this was in, I think,1996, probably. I can't remember, but I think it was. It was just after the protease inhibitors had come on line, so for the first time a real prospect that you could have an impact on controlling disease. So there were several of us. There was Tony Fauci; Harold Varmus; a woman named Helene Gayle, who was from the CDC [Centers for Disease Control and Prevention]; and myself. We were told we were going to have not a long time with the President, maybe. The order was to be I was last, and they said, "Well, there's a good chance they will never get to you, because once the time is up, it's up."

Tony gave a beautiful discussion of the new drugs which were transforming everything, but they did get to me, and I decided I'd talk about the desperate need for vaccine. The President responded to that very powerfully, plus a lot of other people. I shouldn't take that much credit. The idea was that really we needed a big push, and we got very quickly permission to go forward an appropriation to help build a building.

It turned out that the Office of AIDS Research received certain monies from an agreement between the French and American government dealing with the patents for the HIV and the tests for the blood supply, so we got certain money that came in. In contrast to appropriated funds, which have to be spent in the year they're appropriated, these funds were what they often call no-year money, which meant you could save them, and I had saved them.

So we didn't get enough money from the Congress to build a building, but I had in my pocket seven or eight million dollars which I dumped into that, and that was enough to build this really quite wonderful building on the NIH campus, which is working. It's been really one of the leading players in HIV vaccine development. So that was great. I loved that.

But after the fourth year I said, "It's time." Moreover, it was a very political job, and I knew the day would come when they would probably say, "You know, Dr. Paul, you've done a wonderful job, but now it's time for someone else to do it," and I felt I'd rather decide myself when I would go back to the lab. In any case, I felt if I didn't go back now, I could never go back. The longer I stayed away, the less and less likely it would be that I could ever be a competitive scientist again. The world was moving on.

So I decided in '97 that was enough, and I went back to the lab, and I'm delighted I did it and I'm delighted I stopped doing it. But I loved it at the time. It was a great experience, wonderful.

Williams: Did you have to be approved by Congress, that position?

Paul: No, no, it was not—

Williams: It was not kind of position…

Paul: No. The secretary made the appointment.

Williams: Which institute was Fauci heading?

Paul: He's NIAID. So this was the irony, Dr. Fauci told me. I knew Tony when he was a postdoc, so I still call him. We used to have joint lab meetings in the early days when I was working on IL-4 and he was working on something comparable. His group and mine would meet together. We knew each other very well. One

was done, that we set up blocks, that we have symposia in the morning, and in the afternoon we have the poster sessions and more small sessions. That's a program we still use today, and that was very well received. As I say, it's gone on till this day. Then I was asked to run for the C

My feeling was the journal should be responsible for itself. That is to say, it should make enough money to build a reserve. Once the reserve was where you wanted it, any additional resources that came in should be used to reduce the subscription cost, reduce the page charges, etc. It should not be used as a cash cow for the Society, because it was really serving the whole world, and it was really wrong for us to be basically going to people outside the United States and use their resources fundamentally to run our Society. So the idea was the journal should stand on its own legs.

The annual meeting, well, that was more of a complex issue. We were forced to meet with FASEB in that era, and the reason was that there was a big equipment show, and because FASEB was very big, and you have a big equipment show, that brought in money. If you didn't want to meet with FASEB, if you wanted to meet on your own, not only didn't you get the income, you had to actually pay FASEB for the right to meet by yourself, and that was a big era issue we had to resolve. So maybe by today's standards those are small things, but resolving those issues was quite important in that era.

The other big thing, which, unfortunately, was not well handled, was clinical immunology. So at the time, the AAI had a Clinical Immunology Committee, and I have to say it was not very active. It was the era when immunology as a medical specialty was beginning to get going, and there were proponents of developing a separate clinical immunology society, and I felt that would be very unfortunate because it would be better for it to be imbedded in the AAI. We went through that for a long time. In the end, they formed a separate clinical immunology society, which to this day I think was an unfortunate thing, and it's just led to a reduplication of effort.

So those are some of the issues that we grappled with. I mean, fundamentally, immunology was in good shape, the field was growing, it was exciting, important things were being done, the annual meeting was very exciting, and the

president of that congress, and I agreed. Joe Saunders, who had been the executive director, was there, and he was going to do a lot of the—what's the word I'm looking for? You know, the work necessary to get the congress going, lining up supporters and things of that sort. I would work on the leadership, and Philippa Marrack was going to be the person in charge of the program, and that went great.

Then I was asked to take on the job at the Office of AIDS Research, and I really

immunologists, but also individuals who were, let's say, master's-level people, and to take on a whole new set of functions that, let's say, a gastroenterology society would think appropriate to do, but a biochemistry society would not think it appropriate to do.