The American Association of Immunologists Oral History Project

Transcript

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At the same time, though, I had become interested in the idea of biomedical research, even though I really didn't understand what was involved in it. There was no background in that in my family, certainly. My sisters had gone to college and my eldest sister had pursued graduate work, but I really had no idea of what it meant to be a researcher or that one could actually make a living doing that.

It happened for whatever reason that I had applied to medical schools, and there was an interviewer who came from Washington University in St. Louis who was really a terrific, terrific guy, a cardiologist, but a man with broad interests. I began talking with him about some work that I was thinking about in the physics department, which had to do with the way in which snowflakes formed. This is of some interest, because, as we know, every snowflake is different one from the other, and yet they're symmetrical, and how do you form these very different symmetrical structures. There is actually a mathematics behind it, which is sort of interesting.

He thought that was pretty interesting, too, and we hit it off right away. I suspect for one reason or another that that interview having gone as well as it did resulted in my being admitted to Washington University in St. Louis, another place that I had never visited and knew absolutely nothing about and had no sense of what the middle of the country was like, certainly what it was like to live in a southern state, no sense at all.

I went there with the idea in mind that I would get a medical degree, but almost immediately, within minutes of stepping into the door of the place, I realized that that actually wasn't what I had wanted. I mean, what I really had thought about was medical research, and I had done an undergraduate thesis. All Reed College students have to prepare an undergraduate thesis. I was nominally in the biology department Reed was then and is now a fairly structured and strict place. It is very liberal with respect to the environment for students, but it has a very strict curriculum with comparatively few electives.

I had decided, based on some reading, that phthalate plasticizers, which are used to make plastics flexible and are included in virtually all the plastic materials that we use, but in particular they're used, for example, in blood bags and things like that to give them their flexibility, that these were items of interest because of the risk that they would contaminate biological preparations, like blood. This was something that I had read about in *Nature* or something like this, and I thought, well, I can look at this problem, because I can synthesize these compounds, I can mark them radioactively, and I can follow their movement through an organism. And I thought that would be a great thesis, which would combine both synthetic chemistry and biology.

And the Reed faculty said, "No way. No way." And I still actually don't know why they said, "No way," because it was actually an interesting problem back then, and it's still a matter of great interest, because the phthalate plasticizers have

To that point, I think almost no one in the biology departmentRead College inn t]ow(om)-

subsequently held twenty-some years later. But Roy and I were friendly then and have remained friendly ever since, and he has been a driving force in thinking about the application of basic research to the discovery and developm(hi)-2a(a)4(e)4(v)-

became clear to me that this was going to be the way that we would understand the molecular basis of immune function.

I recall as a young graduate student saying to some faculty members that they should just stop everything they were doing and convert entirely to this, because this was clearly a revolutionary technology that was going to supply a lot of information and could be done much more readily than the protein biochemistry that everyone else was doing. That seems so obvious now, but it was not so obvious then. And I was not so persuasive, because not one of them changed, and they were completely blown away, completely, and their fields of inquiry just completely supplanted by the advent of molecular immunology, by molecular

significant Divisions of Medical Genetics. But Arno Motulsky, one of the great

And he would say, “No, I don’t think so. No, actually, I’m busy working.”

“Richard, would you be willing to review this?”

“No. When I can’t do these experiments anymore, then I’ll review stuff.” He wouldn’t serve on any study sections, wouldn’t do any of that kind of work, because he felt like, “This is what I can dö,and it’s hard to argue with him. He was incredibly s

whether that would be a good thing. I had a very close friend, still a close friend,

to wind it down, there are grants, there are graduate students, there's all this sort of thing.

Of course, I misperceived completely, misperceived completely what the environment was in an industrial research laboratory. For some reason, people had told me that it was pretty much like being in an academic center and sort of the same thing, and while it's true that the skills translate to some extent, it is actually a very different animal. It's a different animal because you have alignment, or should, you have common goals, you have incentives, and if there's one thing that you learn in a business environment, it is that incentives are powerful, and you drive behavior with incentives.

Now, in a university setting, each university faculty member views themself more or less as an artist in a garret and they are pursuing their own research ideas and chance favors the prepared mind, and that's an important aspect. That freedom is an important aspect of what they do.

Clark Kerr, the president of the University of California system, famously said that a university is a collection of two thousand entrepreneurs with a common grievance in parking, and that's right. I mean, it is famously like herding cats. It's very difficult to bring them together.

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But the goal was still how do you get everybody aligned and how, in particular, do you

but they want it so much, because that's why they got into it. And you can give

to do that right, though, that means that you have to bring together everyone with their different backgrounds, chemical engineers on the one hand, physiologists on

Perlmutter: No, I don't think that's fair. I think it's, if anything, more vigorous. So Amgen's story is this. I was present at the creation. It was really started with Lee Hood and the original identification of both the erythropoietin protein sequence from a small sample, taking advantage of the protein chemical expertise that existed in the Hood laboratory, and the linkage with phosphoramidite synthesis, which Marv Caruthers had developed in Boulder, made it possible for Fu Kuen Lin, who was one of the first scientists at Amgen, to clone the erythropoietin gene. And from the founding of the company, Amgen, in 1980 until the launch of the first drug, which was in 1989, I guess, that's a pretty quick time to go from, you know, an idea to actually having a drug.

Indeed, when the company was started, they had no idea what they were going to do. The business plan included all kinds of things. The company was started really by Bill Bowes, a venture capitalist, a wonderful man, and Bill started many companies, as he points out. His view was this sophisticated. This is Bill talking. It was this sophisticated. He said, "Back in 1980, I figured that the world probably had room for three biotechnology companies, and there were only two. So I decided I would start the third, because, you know, why not?" There was Genentech and there was Biogen, so he started the third, which was Amgen.

And Amgen became the most successful earliest. Both Biogen and Genentech suffered, and eventually Genentech had to sign a pact with Roche that ended up with them being acquired. Biogen struggled for a long time. But Amgen was immediately successful with erythropoietin, which was something the Fu Kuen Lin had been asked not to work on. It was completely outside the business plan. And not only were they successful with that, but two years later, they were able to launch GCSF. So two successful drugs, astonishing, and they just skyrocketed, and there was money pouring in over the transom to do all kinds of things. Then they didn't register another drug for ten years.

So when I joined the company, hadn't registered a drug in ten years. Not only that, in the prior year they hadn't even introduced a single new molecule into clinical trials, zero. That was the state. When I sat down and spoke to the heads of research, each one of them told me the same things, the same two things. They said, "Number one, I'm not qualified to do my job, and, number two, I don't want the damn job anyway."

Well, that was pretty easy. Now we had to start at the beginning. So it involved recruiting a whole new team across the board in research and ultimately in development as well. Over that period of time then, the company was enormously successful. Not everything worked, some things didn't work, but we were able to register a terrific series of drugs. And by the time I left the company, we had a giant pipeline, arguably—as always, everyone has the best pipeline in the industry. It certainly was something that was viewed as being enormously valuable.

When I left the company, Kevin Sharer and I, the CEO, had decided, unbeknownst to everyone else, that it was time for a generational change. We'd been there for a long time. He basically became CEO, and I came in as one of the first recruits, and it was time. And we'd both had the privilege of recruiting and grooming our successors. So we decided that we were going to do something that was extremely unusual in American business, which was to orchestrate an orderly transition in leadership. Almost never happens, right? But we were going to get that done.

So nobody else knew it, we for a long time knew it, and we would go and give our presentations to the company and to everybody else, winking at each other that we knew we weren't going to be there. Then we announced, together, that we were going to leave in December of 2011, and we were both gone.

So the company's moving along by itself. When I look at the company now, and, fair balance, t weannnd, (t)-10(l)-2(s)-1(a)-2(a)4(t(o t)-2(he)4(c)4(om)-12(pa4(n)-10(y)20

Similarly, when I look back on my experience—and Ed was a little bit older than I am now when he told me this story—but when I look back on my experience, the problem of understanding antibody diversity, which perplexed everybody for half a century or more, I mean, you can figure that one out now in a couple of weeks, less, for a few thousand dollars, because the sequencing machine can quickly show you the difference between germline DNA and DNA in lymphocyte population. True, there's some other background that had to come, but, frankly, we had that background for a long time.

So technology drives science to a very significant extent, and the pace of technology advancement is only increasing. The DNA sequencing is, of course, famously—the pace of improvement has exceeded Moore's Law with respect to semiconductors, but that's true also with respect to all aspects of measurement and purification. In general, when you can measure things, you can make progress. You don't get what you expect, you get what you inspect. And if you can look at it and measure it and understand exactly what you're seeing, it's c nd4(que)4(n)-1(ve)4(r)3e1

discoveries are made in academic centers. They're not made in biotechnology companies or pharmaceutical companies, for the most part. When I was at Merck, I used to say that we can be proud of—we've introduced more new molecular entities than any other company, and we'vTc 0.2(i)-2(l)-6(ecu)1.15 TDhnA(s)tecuA(s.15