



The American Association of Immunologists Oral History Project

Transcript

K. Frank Austen, M.D.
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Interview conducted by
Brien Williams, Ph.D.

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Transcript copy editors: Bryan D. Peery and Elizabeth R. Walsh
Final edit by: John S. Emrich

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Williams: This is an interview for The American Association of Immunologists Centennial Oral History Project with Dr. K. Frank Austen, professor of medicine at the Harvard [University] Medical School. We are the 99th annual [ed. 96th annual] meeting of the AAI at the Sheraton Boston Hotel in Boston, Massachusetts. Today is Friday, May 4, 2012, and I'm Brien Williams.

Dr. Austen, I'd like to ask you first a little bit about your family background.

Austen: I grew up in Akron, Ohio. My father was an engineer with Goodyear Aircraft. I attended public schools in Akron. When it came time to go to high school, I did move to a private school. Then, most importantly, after growing up and spending my life in Akron, it came time to choose a college. I enjoyed playing sports, so I decided I wanted to go to a small liberal arts college, and the school I was in recommended one of the small schools on the East Coast that turned out to be Amherst College, which is I came east to attend Amherst.

Importantly for me, I used to work every summer on Lake Erie as a lifeguard and as a swimming teacher, and I came down with polio in 1946 and missed my freshman year at Amherst, spent time in the Children's Hospital in Boston, which is when I decided sports were not very important anymore and that I really became very interested in medicine and sort of established my career goals.

I arrived at Amherst a year late, so to speak, but they allowed me to go to Akron University each summer and, in a sense, graduate with my class. That was a very meaningful college experience for me, and from Amherst I came to the Harvard Medical School. So, basically, when I left Akron to come east to school, I've been here ever since.

Williams: I'd like you to talk just a little bit about your parents.

Austen: All right. My father was actually a doctor of engineering and a very fine mathematician, was an expert on—I'm not an engineer, but was an expert on mathematical analysis of stress when you build something, so that he built towers in terms of buildings and built bridges that did not have—they were called span bridges, which did not have supports going down to the water and so on, and was chief engineer for Goodyear. He did many things. In the Second World War, he designed the flip-up wings on the Corsair aircraft so they could land and be stacked on the aircraft carriers, and did a variety of very imaginative things in the field of engineering with Goodyear.

My mother basically managed the household—there were four kids—but was very well educated, so there was a lot of music and art and other interests. Akron was close to Cleveland, so there was excellent symphony and a very fine art museum in Cleveland that we experienced regularly. My father and mother both enjoyed gardening, and so I sort of continued to have that as a hobby.

Williams: Were your parents born in this country?

Austen: No. My parents were born in Europe. My father really learned this special kind of engineering in Germany and played a major role in building the dirigibles in Friedrichshafen, where he met my mother, who grew up in the area near Friedrichshafen.

Williams: When did they come to this country?

Austen: After the First World War. So my two sisters were actually born in Germany. My brother and I were born in the United States.

In many ways, it was apparently similar to after the Second World War. My father was offered the opportunity to move either to France, England, or the United States, in terms of moving his engineering capabilities and all his colleagues from Friedrichshafen. It turned out that Goodyear, under the president at that time called Litchfield, decided they'd go into the aircraft area, and so that's why Dad came to Akron and actually did build the first American dirigibles, the Akron and the Macon.

Williams: Interesting. What career paths did your siblings have or had?

Austen: My oldest sister, Rene, died in an automobile accident while I was in college. My second sister went through Michigan University. My first sister went through Radcliffe, Oberlin College and then Radcliffe graduate school before her very untimely death. My second sister, Susie, went to the University of Michigan, worked in occupational therapy, actually was a quite good artist, but ended up marrying a young man who was a physician, and they're on the West Coast.

My brother and I, who were very close, just a year apart, ended up going to the same secondary school in Hudson, Ohio called Western Reserve Academy, and I then went to Amherst and he went to MIT [Massachusetts Institute of Technology], which was very much in line of my father's thinking. During my freshman year at the Harvard Medical School, my brother and I saw each other a lot, and he became very interested in what I was doing.

Amazingly enough, partway through my freshman year at the medical school during an anatomy lecture, the professor—and I still remember his name; Erikson announced that he wanted to see me after the lecture. So I came down from the amphitheater to talk with him, and he said, "I'd like to take a walk." So after a while, he said, "Frank, the Harvard Medical School Admissions Committee is very interested in admitting your brother. He has no premedical prerequisites but a strong background in engineering. He's indicated that he will take organic chemistry in the reverse order, second semester first, finish in the summer. But we just want to be sure that the two of you get along well and this won't have a negative effect on your performance." [laughs]

Amazing. I was dumbfounded, to tell you the truth, that anybody would worry about that, but the medical school did, and, obviously, as soon as my brother got there, we then lived together for the next three years in the dormitory at the medical school. We were very good friends always.

Toward the end, about halfway through my senior year and his junior year, and because we had a double room, we usually had martinis on Friday with a group of friends. We were sitting there relaxing on a Friday, and my brother Jerry said to me, "Frank, we're good friends, but we're a little competitive. We shouldn't do the same thing. You're the oldest. You choose either medicine or surgery, and I'll do the other one." This is amazing true.

So I said, "I'm on surgery now. I'll let you know when I finish this rotation."

So six weeks later we were again chatting, and he said, "What have you decided?"

I said, "I'm not going to do surgery. I want to do medicine."

He said, "Fine. I'll do surgery."

We ended up both at the Massachusetts General Hospital. I ended up there in medicine. Jerry ended up there training in surgery. We continued to progress together. We were both chief residents in the same year. Then he stayed at the Mass General, became chief of surgery, and I moved from the Mass General to the Brigham [and Women's Hospital] when the chair of medicine at the Mass General became dean at the Harvard Medical School, and he felt that I should move and really initiate a major teaching program in immunology at the medical school within the Department of Microbiology while maintaining my clinical life.

So we've been very good friends ever since. I don't know what else to tell you. We were both active in the various Harvard committees. We make a point of only once have we ever served in the same committee. And we both became full professors very young.

Williams: What did you major in at Amherst?

Austen: I wanted to major in biochemistry, and Amherst didn't have a biochemistry major at that time, and so they concocted a major that was both chemistry and biology, and they called it biochemistry, and worked out the distribution of time and the nature of the final examination and so on. But in the end, I was very attracted at that time to chemistry, so I actually in the end spent more time on chemistry, and so I graduated with honors in chemistry, and that turned out to be my major. But by then I was already admitted to the Harvard Medical School, which had been my real interest.

Williams: So you were at Harvard Medical School from '50 to '54?

Austen: That's correct.

Williams: So what words would you use to describe that experience?

Austen: Marvelous. I mean, again, my brother and I lived together in the dorm. We pooled our resources. Our parents used to give us the money for tuition at the beginning of the year, so we would buy a car in the fall, sell it in the winter to pay the second semester, so that meant that we offered a lot of rides to friends, usually the shuttle to Wellesley [College]. So it was a good experience socially.

Academically it was wonderful faculty, some of whom I'll always remember. The beauty of the Harvard Medical School is the fact that it's affiliated with a number of hospitals, all of which are equal, which means in a sense that the Department of Medicine, which was my interest, was very strong, whether I took something at the Mass General or the Peter Brigham or the Beth Israel or the Boston City, and it just meant you could learn about renal disease or pulmonary disease or heart disease in four different places with diversity of opinions.

So the education, I thought, was wonderful. In a sense, the high point of my medical school was being accepted into the Mass General house staff program, which was one of the two or three most competitive in the country. That was a time when there were twelve interns, not sixty-eight or seventy, as there are now. I had very much hoped that I would be selected for that program, and so I was very happy to be house officer there with eleven other people who I felt were extremely able and enjoyed being with.

Very importantly in terms of the evolution of my thinking what I would do with my life, I had clearly envisioned originally having an education at the Mass General, doing some science and having an academic career in medicine. Just at the beginning of my second year, my assistant residency, the last polio epidemic hit, which was 1956, and Walter Bauer, who was the chief of medicine, in July of that year asked me not to go on my holiday as planned, but to stay and start to take care of the excess polio patients.

To explain that, in Boston none of the Harvard teaching hospitals took polio patients in 1956. We diagnosed them in the emergency room and then sent them either to the Haynes Memorial Hospital, which was the infectious disease hospital, or to the Boston City Hospital. The epidemic in '56 was such that those two institutions became full, and to the great credit of the Mass General, it then volunteered to accept polio patients for the first time.

However, there was no faculty with experience in managing polio, so two of us who were assistant residents were assigned to admit the polio patients and obtain advice from a chap called Lou Weinstein, who was the head of the Haynes

Memorial Hospital, where they had a vast experience, and also from a neurologist at the MGH named Ray Adams. Very quickly it turned out to be a very severe epidemic, and so the two of us, rather than taking care of all the polio patients, ended up taking care only of those who required an iron lung or a tracheostomy; that is, they either had polio that affected their lung function or their swallowing function.

That population grew so that the MGH then assigned an entire floor of the White Building to the iron lung unit, which the two of us were responsible for. Within a week or two, the mandate went out that no physician could write order on the polio patients except for these two house officers. So that was a phenomenal experience, and it lasted from July to November.

But during that time, I was very distressed when patients in an iron lung who are basically my age group died, since I had had severe paralytic polio and had had such a good outcome. So we assembled a group of people to try to help us understand why they were dying.

One day I noticed when we took a patient who was in vascular collapse out of the iron lung to change the linen and breathe them by hand, that the color of the patient improved greatly. So I then measured an arterial oxygen and appreciated that the patient was actually without adequate oxygenation in the iron lung, but with positive pressure breathing with an anesthesia machine, oxygenated perfectly well and the blood pressure returned to normal.

That then resulted in a paper in the *New England Journal of Medicine* really describing the fact that this vascular collapse in polio was due to a ventilation perfusion failure and not due to the virus in the midbrain or some other reason, and it meant that we managed those patients differently.

The reason I spend time on that is at the end of the two years I had an obligated military service, and as it turned out, I was the only one of the twelve who had not applied to the NIH [National Institutes of Health], so I was headed to the military. When I completed my basic training in Fort Sam Houston in Texas and the nice sergeant who was doing our assignments looked and saw that I had three papers in the *New England Journal of Medicine*, the sergeant decided I might have potential as a scientist, and rather than assign me to overseas, I was assuming it would be South Korea, sent me to the Walter Reed Army Institute of Research, where, in turn, they assigned me to the one immunologist that the Army had at a time when the NIH did not have an immunology program.

So the reason I'm spending time on that, that immunologist was named Elmer Becker, and it was really Elmer Becker and working with him during those two years that made me appreciate that I wanted to specialize in immunology. I was headed back to the MGH to be what's called a senior resident after my two years in the military with Dr. Becker, but he, appreciating that, began to make

arrangements for me to have a second fellowship in England with a beginning immunology program at their National Institutes of Health when I completed my senior residency at the MGH. However, because of my work with Dr. Becker, I was actually able to get my first NIH grant in 1958 and have a lab and a technician during the time that I was a senior resident for that year.

Then I went to England for two years to work in the laboratory of John Humphrey at their National Institutes of Health. At that time, there were two other well-known immunologists in there rotating through there as well: Hugh McDevitt and Emil Unanue. Each of us ended up spending our lives working on the projects that we started during our time in John Humphrey's group during that three- or four-year span.

I then returned to the MGH to be a senior resident, which meant I had four clinical years, and that was a very serious clinical year because we were responsible at that time for the emergency room and for the overnight ward. So on completing that, I wanted to take a third fellowship, and so that's when I went to Johns Hopkins [University] to work with Manfred Mayer. But because I'd had three different postdoctoral experiences really over the years, my laboratory training took just as long as the clinical training, so I entered really the faculty probably eight or nine years out of medical school.

But my time with Manfred Mayer at Johns Hopkins was shortened because when Dr. Bauer, who was my chief of medicine at that time, went into pulmonary failure, because of my experience in the polio epidemic, he wanted me to come back. So the polio business is a remarkable thread in my life. It's what caused me to choose or to think seriously about medicine and become a quality student instead of a haphazard student. It allowed me to make the observations that ended up with my assignment to Walter Reed and the introduction to immunology, and it just profoundly influenced a lot of things in my life that turned out to be really good fortune.

Later on, there's a third to piece to that that I'd almost forgotten. When Dr. Bauer died, he was then replaced as chief of medicine by Robert Ebert. Robert Ebert came to the Mass General from Western Reserve University. He knew a good deal about inflammation, and he then looked at my interest in immunology, my experience in infectious disease, my experience in respiratory area, and he moved me from the infectious disease unit to be head of the lung unit at the Mass General.

Then when he became dean, he was the one who prompted me to move across town to the Brigham to really do two things, to teach immunology within the Microbiology Department but to develop really an immunology capability at the clinical and research level for the school. That then became a very important next step in my life after I completed my training.

Williams: So you left the study of polio after you left Boston and you moved to these other sites to look into other aspects?

Austen: Into immunology and to become a competent immunologist, and because I then knew that I wanted to build my academic medical career on immunology and on the role of immunology and both innate, which is called inflammation, and adaptive immunity in human disease, and at that time the knowledge of immunology was, in my view, very limited, and I didn't want to just study in one laboratory, that in order to have a laboratory that was different from any other, I thought that I would want to put together a range of technologies and experiences. So that's what I did. But the central theme was really inflammation, broadly, and an interest in the human disease asthma in particular.

Relevant to that, during the time I was in England with John Humphrey, I didn't actually do a lot of immunology with John Humphrey. I was attracted to somebody else in his unit by the name of Walter Brocklehurst who was working on an unknown substance called slow-reacting substance of anaphylaxis, or SRS-A. SRS-A had been discovered by an Australian group as a material that was generated in the lung of a guinea pig during an immunologic reaction that profoundly restricted guinea pig airways.

Brocklehurst, with others, had identified the same substance in human lung generated by adding allergen to the lung tissue from patients undergoing surgery for cancer but also had a particular allergy, and the mixture of the allergy and the antibodies on the cells in that lung caused the human lung to release this slow-reacting substance of anaphylaxis. He elegantly showed that the human airways attached to that lung were exquisitely sensitive and contracted to it with a potency that had never really been seen before, and that that contraction was resistant to all known antagonists. So it struck me that that might be a candidate molecule for the severe constriction one sees in bronchial asthma. So, actually, that's one of the things I've worked on ever since.

With John Humphrey I worked on a particular cell called a mast cell because there weren't a lot of cells in which one could study immunology at that time, and I wanted to do biochemistry. This was a cell that secreted histamine, and it seemed that studying that would be a biochemical approach to histamine release and also an approach that I could use to study how SRS-A was generated.

During my time there, another postdoctoral fellow came from Johns Hopkins, and he and I got to be friends, and he thought I should complete my training by having some immunochemistry experience at Johns Hopkins with Manfred Mayer. So it was really Walter Reed with Arthur Becker, Mill Hill with John Humphrey and Walter Brocklehurst, and then Johns Hopkins, but always with the clinical experience included, because I did not want to lose that clinical part of my life.

Williams: Has that remained true all along?

Austen: I made general medical rounds until I was seventy, which means general medicine, which I loved. But around that time, the American healthcare changed a lot with the gatekeepers and with the focus on discharging people as quickly as you possibly could. I really felt that it was important for the teaching to be very practical, very “can do,” and that basically a measure function on mechanism was really not what those kids were focused on anymore. They really were focused on controlling costs by getting patients in and out very rapidly. So I continued my ambulatory practice, but I didn’t anymore teach inpatient medicine.

Williams: In protest against the direction in which the industry was taking?

Austen: No, no. In fairness to the interns and residents. I did not think I was the best person to help them turn over the patients in the shortest possible time. I knew what to do, but I like to discuss more the pathobiology of the disease and some of the things that were more academic and less practical.

Williams: Things that would have improved their education but not their success in the world as it is?

Austen: Not in meeting their responsibilities at that moment in time. Again, the system has gotten better in terms of teaching and creating time for teaching and so on, and so I don’t wish that to be misunderstood. It was a difficult time for teaching when the focus was on diagnosis, management, and discharge. That has continued, but in modern times we’ve kind of separated education from the “can do” function, and we even have intensivists now who care for patients in the hospital whose total focus is to help with that, shorten the time in the hospital.

Williams: I just want to be clear on this. So for you this was a pedagogical issue or it was a practice-of-medicine issue?

Austen: Neither. It was in fairness to the house staff issue. I didn’t think I was the best person to be doing that. I mean, it’s very simple. I mean, it’s important to know what’s happening at the moment and how you can contribute the most.

Also I should say, by the time I was seventy my house staff had really become my postdoctoral fellows, and so my teaching program within my department and within my section and within my laboratory really replaced the teaching that I used to enjoy in a more generic way to house officers, because part of what I liked about teaching was really getting to know the house staff, and that worked well when the number of interns was less than twenty, but when that number multiplied, it was much more difficult to see them.

Early on when I was teaching, you would be teaching the same house officer in the second or even in the third year because you would run into them as their rotations changed. As the house staff grew, you didn’t do that anymore. So there

were many reasons why I thought it was best to change my role and change my emphasis, but not my interest in teaching or my love of teaching or my love really of being a physician.

Williams: So you're not critical of early release necessarily?

Austen: No, sir. In fact, if we look at what's happening today, it's simply astonishing what we're able to do in an ambulatory way. The practice of medicine has profoundly changed, and I think to the credit of the discipline we're doing things in an ambulatory way that we never dreamed we could do, including major surgical procedures, everything. Learning to control the costs, in fact, I think has a lot of benefits since the hospital is a dangerous place at times.

Williams: Just to go back for a minute, did you attribute your polio to your summer work in the water?

Austen: Yes. I mean, it happened at the time of year when one gets polio, and it was very much associated with being a lifeguard or being on the water. It was just something we were aware about.

Williams: What were the steps in your recovery?

Austen: Well, I went to the Children's Hospital, underwent a lumbar puncture, became very good friends with the resident who did that, a pediatrician. I was in the Children's Hospital probably ten weeks or maybe twelve weeks, but there was no treatment. So the only treatment at that time were hot packs, which were to alleviate the spasm feeling in your muscles, but there was nothing else to do.

So the resident, he used to come and visit with me for hours. My parents obviously did. There was no television. I can't even remember, to tell you the truth. I couldn't move my arms or my legs, so I don't remember being able to read very much, but somehow the time passed, and the beauty of being seventeen or eighteen, the idea that I wouldn't get well never occurred to me.

Williams: Were you in an iron lung?

Austen: No, sir. My diaphragm and intercostal muscles were not affected, and my tongue and larynx were not affected, so I had no swallowing problem and I had no respiratory problem.

Williams: So where was your problem?

Austen: In my arms and legs. I left the hospital, my physical therapy was really lifting my mother's cooking weights, which she had on the scale which she measured food. But, again, I don't think a lot about that. I just had the faith. I just believed I would get well and that the issue was only how fast. So that by the second

semester I was already able to drive a car and take a math course at Akron U. By the summer I took a math course, and by the fall I was back at Amherst. I was completely well. I ran some cross-country.

Williams: Was that an exceptional recovery or was that common?

Austen: No, I don't think so. I mean, I didn't think about it, to tell you the truth. It wasn't really until those many years later when I was faced with the patients who weren't recovering. But I was very stimulated by that, so in addition to the observations about vascular collapse, made some additional observations about how to manage the bacterial infections and other kinds of things. But it convinced me that I wanted to engage in serious research and that understanding was how I wanted to think about medicine and that in all likelihood I would try to concentrate on diseases that were not that popular.

Williams: Just one other question on polio. In '56 when there was this sudden epidemic, who was making the iron lungs, and was there an industrial issue there? Were they produced fast enough?

Austen: Yes. We did not run out of iron lungs, and I can't remember the name of the iron lung, but it was a classic. But we had to use positive pressure anesthesia machines. The kind of positive pressure that is now absolutely routine devices were not yet available.

Williams: But they replaced the iron lung?

Austen: Yes, but they actually ended up replacing the positive pressure devices which we were borrowing from the anesthesia people. Early on on that ninth floor where we had the iron lungs, we had a unit where people squeezed the bag to deliver positive pressure.

Williams: The patients squeeze?

Austen: No. Doctors volunteered.

Williams: To spend the night squeezing?

Austen: And to guide these, to regulate the degree to which this equipment was automated.

Williams: That was a dark period in medical history, wasn't it?

Austen: Well, no, it was no different than anything else. Remember, you're talking to a fairly senior citizen. We had very limited antibiotics. We had to treat staphylococcal infection without a single drug that was cytotoxic. All our drugs were static. So just clearing up a superimposed staph infection because you had

an open wound with a tracheostomy of somebody in an iron lung required a lot of ingenuity because these were penicillin-resistant staphylococci. At that time, the only cytotoxic drug we had was vancomycin, but it produced deafness, so we had to manage that with static drugs, chloromycetin and erythromycin. So anything you ask me about in medicine was very limited in 1956.

Williams: So pick up your own personal story here.

Austen: So, goodness. Well, Robert Ebert became dean. He moved me across town. I left the MGH partly because of the dean, but partly because I knew that I wanted to have an immunology program, and that I would not have the kind of program I wanted if I was the only faculty member. So I knew that I had to leave a conventional Department of Medicine and make an arrangement in which there would be at least three people with a comparable capability to educate young postdoctoral fellows.

So I told the dean that I would make the move across town to what was then called the Robert Brigham Hospital, which was an arthritis hospital which joined the Harvard Medical School and which the dean envisioned as turning into a 100 percent immunology enterprise. So I thought that would be great, providing that he would help me recruit two other young people. So we recruited two other young people, named John David and Peter Schur, with a different background. My training had been in mast cell biology, SRS-A, and in the complement system. John David had trained at NYU [New York University] along the way. I'd known him as an MGH house officer, and he was in a laboratory in which they developed the first test-tube method for studying a cell-based immune reaction. Since I was dealing with acute immunologic reactions, I wanted to have somebody dealing with the cell-based sort of reactions. Peter Schur had had my job in the Army, so I had known him. He had trained with Elmer Becker as well some years later, and he had then been at the Rockefeller Institute with Henry Kunkel, obviously an icon of the immunology society and knew an immense amount about a disease called systemic lupus erythematosus and knew how to do translational research.

So the three of us started this new unit. Amazingly enough, it was a separate Department of Medicine of the Harvard Medical School at this arthritis hospital. We then developed very quickly a strong immunology program with two training grants, one training people in the rheumatic diseases, the other training them in the allergic and asthmatic diseases. So we had a steady influx of very able young M.D.'s, well-trained clinically from the Harvard system as well as coast to coast. That enterprise with three people and starting out with one or two postdocs and then five or six is now a division of more than a hundred people of faculty and postdocs and so on and has evolved. That, again, is an important part of my life.

This immunology program was going extremely well. I was enjoying the clinical work, when the dean again decided that what the medical school needed was to

merge the hospitals on the other end of town, which were all together around the medical school, which was the Peter Brigham, the Robert Brigham, and two women's hospitals which had already merged, the Free Hospital for Women and the Boston Lying-In then became the Women's Hospital. So the task was to merge the Women's Hospital, the Robert and the Peter Brigham, and that was no small feat.

The first task was to get a Certificate of Need, and at that time it was turned down for a variety of important reasons, but mostly because the community felt that building a bigger institution in their midst would further damage the concept of a community, and they felt that even the Peter and the Robert and the Women's was not paying adequate attention to the community.

So in order to get a Certificate of Need, the dean hired a sociologist from Brandeis [University] by the name of Steve Miller and assigned two of us to work with Steve and with the community and to find out what it was that we could do to gain their support for building this new medical center. So that's something I did in the evenings, which was quite interesting, in churches, in homes, and the like.

One of the first things that Steve Miller taught us was that in order to interact with the community, the community had to organize. So we actually paid the salaries of people in the community to work against us so that they could define what it was we had to do to make our project acceptable, which we did. They took about three years. We got a unanimous approval of the certificate.

Williams: Who issues the certificate?

Austen: The state. Then once that was under way, the next job was to get the institutions actually to merge, and so I did chair the committee of physicians and hospital directors that worked toward that end. We subsequently completed the merger, built the hospital, and it has now become a very large medical center with primary interactions with the Dana-Farber [Cancer Institute]. For example, all the Dana-Farber patients that need to be hospitalized or hospitalized at the Brigham and Women's Hospital, which is the name that we came up with because it came from these three constituent institutions. So we kept the name Brigham and we kept the Women's, importantly. It interacts with direct passageways to the Children's Hospital, and it's really next door to the medical school, so it's a marvelous place to work and to interact with all these institutions.

Williams: So during this period of transition, what effect did that have on your growing little department?

Austen: It had no negative effect because through an odd—which I'm not going to go into in any great detail. I made the decision that I was immensely enjoying my research and that I didn't want a bigger job, and so I decided not to do a number of other things elsewhere in the United States.

The dean one day asked me why I had turned down these other activities without talking to him and asking for anything, and I said because it wasn't really relevant. I was either going to stay with my research or I was going to take a larger job with responsibilities for other departments of medicines and the like, and I discovered, to my surprise, that I really didn't want to make a change and that I didn't want to reduce my research time.

About two months later, to my surprise, he talked with the university president, and the two of them said that for the next twenty-five years I could report directly to the dean, and I didn't have to report to any other mechanism, which was their idea, not mine, which profoundly facilitated the building of this division, which was treated as a freestanding department of the medical school, with great freedom for appointments and really recruiting and building what then became incorporated into this new medical center. But it's a department that has its own endowment, that has its own sense of mission, and has just continued to flourish even after the merger because of the twenty-five years in which it was allowed to build itself both financially, structurally, and in terms of academic excellence. Does that make any sense?

Williams: Yes, it does. I'm curious about the balance between clinical work and research work within that department.

Austen: Oh, well, again, time changed. For me I always spent one month in the hospital doing nothing but internal medicine, and then I had an ambulatory practice one day every week, and that continued, as I said, until I was seventy. But slowly my practice became more and more diseases in which I was particularly interested, and so my general medicine was really limited to my time when I was teaching in the hospital, and my practice was almost entirely focused on diseases relevant to the immune system. So that, again, it reinforced my research. It didn't compete in any way, as far as I was concerned.

Williams: What were the foci of your research?

Austen: Well, again, there were three things. One was the complement system, and early on through my experience with Manfred Mayer I had learned to do assays for the components of the complement system. They were exquisitely sensitive. So as we began to work on the amplification part of the complement system, we were able to design exquisitely sensitive hemolytic assays which allowed us to purify the critical proteins, which were present in plasma in very small amounts. So with Doug Fearon in particular, but also with Shaun Ruddy and Irma Gigli, we were able to define this amplification loop which creates all the pathobiology as well as the host resistance part of the complement system. That, for me, is one of the major accomplishments.

One of the things that has happened twenty years later was that one of the proteins that we purified at that time turns out to encode the gene for age-related macular degeneration. Now, that's a fabulous example of how basic science can have tremendous implication for human disease that has absolutely nothing to do with why you did the basic science, and it's why I have some reservations about the current, in my view, overemphasis on applied, that you quickly run out of things to apply, and you often don't know what to apply. I think the major advances in medicine have mostly come from the knowledge that was created and then taking advantage of that knowledge using other technologies.

I think finding that factor beta 1H which regulated the amplification system was the gene that determined more than 50 percent of patients with age-related macular degeneration is a wonderful outcome, quite separate from the progress that's been made building on the real purpose of doing that research.

The SRS-A that I mentioned to you earlier, I became very preoccupied with that, and with Jeffrey Drazen, editor of the *New England Journal of Medicine* now, we worked out a great deal of the pharmacology of that molecule, began to make real progress in the purification with a young man from MIT who was in their analytical chemistry group by the name of Bob Murphy.

I knew that it was not a typical protein and I was not going to be able to do it as an immunologist, so I went to talk with Klaus Beimann at MIT, and he was busy analyzing the moon rocks, so he said to me, "I can't help you. I'm too busy with the moon rocks, but I've got this very excellent young postdoc who I think could help you work on this project," and that was Robert Murphy.

With Murphy working on it, then we obtained an excellent characterization, and Murphy then took a sabbatical in Sweden with Bengt Samuelsson and worked out the actual composition of slow-reacting substance. As soon as he had the composition, E. J. Corey in the Chemistry Department at Harvard made the molecule for all of us, because it had a lot of double bonds. So E.J. felt there would be more than a hundred stereo isomers, and he said, "The best thing is you guys do your best purification. I'll synthesize what I think are the candidates. When the molecule I synthesize is exactly as active as the one you purify, we'll have the right structures," and that's what we did.

So that I was disappointed that I wasn't there at the end when we got the composition, but at least there was somebody I trained, and so my lab, we then immediately moved to take advantage of that to purify the enzyme that made it and then to clone the human enzyme for the first time and then to go on and make mice with various deficiencies and really work out that pathway. So that's the second area. It's now called cysteinyl leukotrienes.

The third area that I continue to work on is the mast cell, and I would say to particularly focus on what the mast cell makes, both preformed and newly

generated, and what its role is in biology. So I'm still working on the same three projects I was working on as a postdoctoral fellow, it's just fifty years later and we can do a lot more.

Williams: The question I've been asking people is—you've just described to me what you'd say have been your major accomplishments. What about disappointments and dead ends?

Austen: I also mentioned the disappointment. I would have liked to have gotten the composition of SRS-A, but I take joy in the fact that Robert Murphy did it with Bengt Samuelsson and used the purification that he worked out with me and my colleagues in our own laboratory. But I would have liked to do that. So what we did is say, "Well, that's that."

Once I knew the structure, I knew that we could not have done it because there was no way that I was going to resolve a lipid link to a peptide by a sulfur bond, so it was much better that he went to a laboratory with the knowledge that he had and had the creativity to lead that analysis. So that's when we moved very sensibly, I think, to isolating the enzyme that made it and that continued to make it. Then we obviously found a variety of receptors that determined all the functions. So it was a blip, but I'm glad it was done, I'm glad somebody else did it, and so it was the disappointment that afforded us the opportunity to go on really and move to the next stage.

Williams: And to collaborate.

Austen: And to collaborate, sure.

Williams: So what impact has your science had on disease and general public?

Austen: Well, I mentioned the issue of age-related blindness. I hope it's going to lead to therapy there, which will be based on blocking, the original reason for which we studied it, which is that amplification loop of the complement system. There are members of industry who are addressing that possibility by making inhibitors or approaching ways of inhibiting it. In the leukotriene area, the cysteinyl leukotriene area, there is a drug out there which is the only small molecule for bronchial asthma that is targeted to the cause of the bronchospasm. All the other drugs that we use are ways that relax the muscle or reduce inflammation, but they don't deal with the pathobiology itself. So the inhibitors of the cysteinyl leukotriene receptor type 1 are targeted to the mechanism of the disease, and they are effective in children and they are effective in the numerous adults and are a major contribution to the management of bronchial asthma that is mechanism-based. So that, obviously, is very meaningful.

Williams: What percentage of sufferers are positively affected by that?

Austen: I can't really answer it for you. I can answer it in simpler terms. Merck, who makes it—it's in that billion-dollar drug category, multi-billion-dollar drug category. Obviously, I know of many people who benefited from it, and I think there is more to come because we've only now appreciated yet another receptor, and so I think the system is more complicated than we anticipated and that there are more therapeutic opportunities.

So that the mast cell of the three areas lags behind in having a major clinical impact, but I think industry is starting to think about its role in inflammation and to develop some appropriate inhibitors. But I think there's more for us to do on the research side to understand how that cell really contributes to the pathobiology. I think it's more than SRS-A and it's more than histamines. But that's why I'm not retired yet. It's just too interesting.

Williams: Let's talk for a minute about your association with AAI. You became a member in 1962. What was the organization like, and what drew you to it?

Austen: Well, obviously I was committed to immunology by that time. My mentors were all in it. Elmer Becker and Manfred Mayer were all very active members in the United States. John Humphrey was a Brit, but he sometimes came to these meetings. But the British also had a British Society of Immunology, which I belonged to at the time. So it was the only place to exchange ideas about immunology. But it was very different. I mean, the meetings were small. The questions were very serious and very challenging and fun to try to answer. But it was just a totally different organization in terms of size, as is true of many organizations.

We read the journal religiously. Most of us who were in the field knew the editors. The *Journal of Experimental Medicine* was competed at times. It had a real interest in immunology long term. Some of the other very high-profile immunology journals did not exist. The society was the dominant society for the discipline and the meeting was the dominant meeting for the discipline, and I attended every minute of it.

Williams: Then did you go on the council?

Austen: Yes.

Williams: Did you have much to do as a council member?

Austen: Not at that time. I mean, I became president, as you know. It was really more an honor, to be honest with you. I mean, it was a tremendous honor, but we were supporting research, we were involved in the Federated Society enterprise. Immunology was an important component along with all the others, and we engaged in it. But the NIH was not a problem at that time in the sense I had the strong feeling at that time that if you did competent work, you were funded, and

that there was enough money in the system to take care of the folks who were making meaningful contributions.

I don't remember all the politics and the . . . And we had good support from Congress at that particular time. I mean, I didn't think of it in that way, but there were people who strongly believed in biomedical science, who understood immunology. But the important thing is immunology didn't need necessarily its own person. What it needed was serious commitment to the biomedical sciences and the belief that it could make a difference. So I don't remember fretting, honestly, about NIH support at that time or about any other major political issues.

Williams: You were president in the heart of the [James E.] Carter administration. Did that have any bearing on—you weren't malaised? [laughs]

Austen: No. I remember Jimmy coming to the National Academy and astonishing me by making a speech on the fact that he was going to get rid of the Panama Canal. I mean, that's a memory I have from the NIS, and sort of my reaction was, "Why is that the first order of business?" But other than that, I have no other recollection.

Williams: Looking back over your career, do you think you made the right decisions, or are there things that you sometimes think, "Oh, if I'd gone this direction—"?

Austen: I honestly believe I made the right decisions for me. I didn't plan them, you know. I just responded to the things that happened. It made administration a lot easier for me because I kind of believe that there really isn't such a thing as a right decision. I think that you make a decision and then you make it work or you make it right, and that made it quite easy for me to chair that division or department or whatever. The important thing was to make the decision and get everybody on the same page and then make it work. So that helped me, I think.

I don't know what more to say. The administration did not take a lot of my time. I shared everything I could possibly share with people who were tremendously competent, and competent people like responsibility and they like sharing.

Williams: What thoughts do you have about the general state of science in the U.S. today? Where are we?

Austen: Well, I mean, I think it's fabulous. My only worry is that are the young people who come into the program—I'm particularly interested in M.D. physician scientists, because I do strongly believe that an understanding of integrated biology is immensely helpful and the urge to understand in an integrated way and to take your structural biology and your DNA information and your cell-based information but always to try to visualize what it means in a more whole organism.

So I think it's important to have physician scientists as investigators in the system who see patients and whose research is influenced by it, because you may embark in an area of research that may not occur to somebody who doesn't have a clinical life. I don't think anybody would have worked on SRS-A or cysteinyl leukotrienes with the passion that I did if they didn't think it had something to do with asthma. For twenty years I didn't know the nature of the product I was working with.

So what does matter to is to keep a cadre of knowledgeable physician scientists in the system, and that's getting harder and harder because as the NIH reduces its funding per se and if you are going to maintain a clinical life and be competent in both basic science and in clinical medicine and be reasonable, meet your responsibilities as a family person, it becomes very difficult. So I worry about whether or not we can sustain that group and whether I can keep these young people committed to this life. So far we have been able to do that, but they're immensely talented and they keep their eye on the human disease at the fundamental level, which I think is very helpful to asking the right questions.

Williams: So would you recommend the field of immunology to someone starting out on the path in medicine?

Austen: Very much so.

Williams: Why?

Austen: I should have responded I think immunology is finally getting to the right place, that inflammation which is now elegantly called innate immunity, which recognizes the phenomenal diversity within our genes that is fixed, not adaptive but fixed, germ line. Our germ line diversity vastly exceeds anything any of us thought, and immunology is now beginning to think about this germ line information and how the adaptive immune system is profoundly influenced by the tissue that it's in, by cells that were considered nothing but structural or having some other function. We're beginning to really think about immunology in an integrated way, and so I think we're just entering the most exciting period of immunology where we put innate and adaptive together in a meaningful way.

Williams: You mentioned family. What advice do you have in terms of balance between scientific responsibility and family?

Austen: Obviously, I think it's immensely important to keep in mind one's family, that with the ups and downs of research, especially in the current climate, family is more important than ever because it keeps you focused on what's really important, which is do you have a reasonable relationship with your wife and are you really paying attention to your kids. Do they know you exist? Are you really helping with their development? Are you supporting your spouse in her role? Now with two-career families it's even more important to make sure that your

partner's career is also developing, and sharing becomes even more a matter of sensitivity and paying attention and not making one's career, no matter how passionate you are about it, more important than your family. These are simply alternate responsibilities, and you have to pay a lot of attention to make both work, but I think one without the other is very sterile.

Williams: I'm curious. The AAI, when you first became involved in the sixties, there probably weren't very many women.

Austen: That's true.

Williams: And that's changed quite a bit, right?

Austen: Well, I mean, my training program has gone from all males to a few women, to dominantly women, which, in turn, has taught me an immense amount about the current climate, about the two-career family, about the fact that women really do have a greater share of the responsibility from morning to night, no matter how you—even when they've married a really good guy who is more than willing to share, they still end up with 60 percent at a minimum. It's my firm belief that we have to find ways to support the caregiver who wants to develop a serious scientific career during some critical years, and that we have to make sure that the women in the system keep up by having some extra support. Simply saying you can have longer time is someplace between insulting and inadequate.

So I have raised some funds and have a fund for our group for women physician scientists or whoever the caregiver is who's working in the laboratory, so that they can have technical support at a much earlier time in their career. Because if a woman, generally a woman, can have a technician early, they can plan their day with their husband so that somebody drops the kids off in the morning, somebody picks them up at night, but by having a technician they can get things started in their lab if they're the one who drops them off, or finished up if they're the one who picks them up. So I don't think it's going to happen just because we keep getting mandates to make it happen. We have to put the support in there to make it sensible.

Williams: Are we leaving something unsaid today? I know you came with some notes and whatnot.

Austen: I never used them. I could have come on time and just left these, because I forgot and had to go back and get them. No, I mean, I think we've discussed it.

Williams: Well, this is an opportunity for you to be provocative or—

Austen: I mean, I think I've talked about women in science, which I feel strongly about. I've talked about basic science as opposed to this excessive commitment to application, which I think is very shortsighted. So I think that's probably enough.

[End of interview]