

Dr. Alan Schechter

This is an interview with Dr. Alan Schechter (AS) on July 23, 2001. The interviewer is Sandeep Khot interviewing at the NIH in Bethesda, Maryland.

Khot: In your interview with Melissa Klein, you stated that you hadn't heard about the clinical associate training program at the NIH until your internship, and even then, it was quite by chance that you'd heard about it.

AS: Right.

Khot: How well known was the program during your medical school?

AS: I did not know about it. I think that early on, there were specific contacts between the people running the program here and Harvard, Johns Hopkins and perhaps Yale and a few other medical schools, and it may have been that Columbia was not part of it or the people that I interacted with at Columbia were not specifically part of it, but I never saw anything printed and learned about it almost by accident near the deadline for the applications.

Khot: Do you think it became better known in the late '60s and early '70s?

AS: Surely. As the Vietnam War heated up, it became common knowledge that this program existed as an alternative to being drafted and going to Vietnam. So I think that that was part of it. I did my internship and residency at Albert Einstein Medical College in New York, and few individuals from that group came to NIH at that point, whereas other schools had very large percentages of their internship class go. Initially, it was first the Northeast, but then over the next five years, it spread throughout the country. Individuals from California and other institutions from the South began to come as well. But it was hit and miss in the '50s early '60s.

Khot: What was the perception of medical school professors or classmates towards the program, like after you were accepted into the program?

AS: As the program became better known through the '60s, everybody became very positive about it and supportive and encouraging, and then it became very competitive. Many more people were applying than they had room for. Initially, the program was set up so there were something on the order of two research associates and a small number of clinical associates in each institute, and then there were other clinical associates being recruited to take care of the clinical responsibilities in the various clinical research protocols here. With time, as many people wanted to come, the size of the clinical associate program increased, but also another group of individuals, called staff associates, were created to work with the research staff, and that allowed the numbers to increase. But I think that at one time several hundred individuals were chosen for the program each year,

but it started on a much smaller scale, I think, in 1953 or so, and then slowly and gradually expanded during the '60s.

Khot: How important of a factor was the war or the doctor draft in your decision to apply to that associate training program?

AS: I'm not sure, in retrospect. On the one hand, I knew a little about the NIH. I had heard Anfinsen, with whom I eventually worked, give a lecture at Columbia during my last year as a medical student. I had heard of a few other NIH scientists; interestingly in particular somebody working completely on a non-medical topic, on firefly luminescence, and so my perception of this institution was not that it was particularly a medical research institution, but that it was a diverse institution. I was interested in medical research, and I might have opted to go to one of the Harvard hospitals or remain in one of the New York institutions if this opportunity had not come up. And so it was partially that I knew of specific scientists at NIH who were very good with whom I'd want to work with, but also one had the impetus of the draft. The two together made it a natural first choice rather than looking for a fellowship at a New York or Boston institution.

Khot: The draft, was it at that point, was it a considerable fear? I mean, did you have a lot of classmates who had gone to Vietnam?

AS: At that point I didn't even know about Vietnam. I think the war in Laos was already recognized, after all, this was the fall of 1963. There were no more than a few observers in Vietnam, but there was concern about the general doctor draft. For many individuals, there was something called the Berry Plan in which physicians could finish their training, get board certified or at least board eligible, and then go into the military in their specialty, and this was the path that many followed. But those that didn't might be drafted. The draft issue wasn't so much a question of Vietnam but a question of being diverted for two years from one's preferred path of study and specialization, and that the possibility of spending time doing something which was not one's cup of tea and which would not advance one's professional goals, not concern about going to Vietnam. In fact, that's why at that point the program was not that well known and was not that much of an imperative. It was a matter of choices rather than a major club hanging over one's head.

Khot: You also stated in a past interview that you had almost 40 interviews at numerous labs and institutes. How common was it for associates to be candidates for so many positions?

AS: Again, I don't know. I mean, I had done research in medical school in all of my electives and during the summers, and I had published several papers in *Science* and *PNAS*, first-rate places. Therefore, I obviously was considered among the most desirable candidates because of my research experience. Therefore, I suspect that everybody who saw my application checked off they would like to interview

me. As a result, I had the maximum number of interviews possible in the two days I was at NIH. I had interviews from eight in the morning till five or six at night, so much so that by the end of each day, I could hardly remember my own name and other information, just having repeated it to my interviewers at half-hour intervals, with 30 minutes off for lunch; first thing in the morning till well into the evening.

Khot: Considering the high level of competition, how important was it to have some sort of connection?

AS: I don't know at that point. I think that I'd always heard stories about telephone calls of people, of a mentor at one of the institutions calling an NIH scientist or an NIH director and arranging for jobs that way. As far as I know, I was not part of that mechanism. I applied and was, interviewed. I presumably asked for two or three letters of recommendation from people I'd worked with. But I don't know of any phone calls that occurred.

Khot: Can you describe the research-training environment at NIH when you arrived as a research associate in 1965?

AS: It was excellent in three different ways for me. One is that there was a set of formal courses through the Foundation for Advanced Education in Sciences, which offered courses each weekday evening Monday through Thursday evening from 5:30 to 9:30 or 10:00, generally one- or two-hour courses that met once a week for a semester at a time. And one could take courses from basic chemistry and mathematics and biochemistry to more specialized topics of medical research and genetics, medical genetics, for example. I took courses in introductory physics, in medical genetics, and I took a semester course in the history of medicine, which I'd always been interested in but never had any formal experience while I was in medical school. So these formal courses were a major asset. Having been in medical school, not on a university campus, we were, during medical school years, very far removed from a lot of such topics.

The second was that there was a program of informal seminars that had been started by Dr. Anfinsen in emulation of the Oxford University tutorial system. These were specifically for the research associates. There were two in each institute. But gradually they broadened, too, so the clinical associates and the staff associates were eligible. But it started out as a most specialized training program for the research associates. And, again, it probably started in the early '60s or the late '50s as a very general introduction to protein structure or nucleic acid chemistry or intermediary metabolism and topics like this, and then, with time, these evolved, too, so there were about 15 or 20 such seminar courses offered. Again, they would meet one evening a week, and I took several of these more informal courses, which were perhaps more intense and somewhat higher level than the formal courses in FAS. But they were specifically designed with the

physicians in mind and offered in a more active seminar fashion rather than formal lecture courses.

And the third was perhaps as important or more important than either of those two, was the fact that, in the better laboratories, such as the one I went to, which was Dr. Anfinsen's laboratory, there were many good, young people as postdoctoral fellows and young staff members, and there was a tremendous informal learning experience going on. I remember being surprised when I said something on the second or third day to Dr. Anfinsen., I asked a question and I addressed him as Dr. Anfinsen. He said, "Why not call me Chris?," and this was surprising because in four years of medical school and two years as intern and resident, we always had to call the attending physicians by their last name. And so this informality, which was characteristic of many laboratories, was a welcomed relief from the somewhat rigid formalism that existed in medical school and in the clinical training at that time.

Khot: Other associates have commented on how associates "taught each other" their respective fields. Can you describe any special collaboration in which you participated as a research associate in which other associates and you taught each other your fields?

AS: Sure. I mean, in two or three different ways. One were the seminar courses that I mentioned, which were almost entirely given by students who were the physician associates. They initially were research associates but then more of the clinical and the staff associates. And then the seminars were arranged so there would be 10 to 20 individuals, and each week one person or two people would present summary papers. They'd give handouts on background of a particular topic.

The one course that I was particularly interested in because it related most closely to my work was the protein structure one which Chris Anfinsen and David Davies had started probably about 1960 or 61. I took it perhaps the second or third time it was offered, in which we, for example, made molecular models of protein structures from coordinates as they were being deduced then. I think the first one was a myoglobin, then lysozyme, ribonuclease and finally staphylococcal nuclease. Eight or 10 of the associates worked together to build these molecular models and we learned a great deal about the principles of protein structure from building these models. These models are still on exhibit on the first floor near the Auditorium. But other projects like this characterized the interactions.

In addition, many research interactions and collaborations started with individuals from other labs whom one met at these associate activities. In fact, I met another associate, Robert Perlman, who left NIH four or five years later, We was just at a meeting in Chicago a week or so ago. I would not have met him except for the interaction in the NIH courses.

There was another set of courses which I neglected to mention. There were computer courses which the Division of Computer Research and Technology, DCRT, offered, and they, again, were a major resource. I doubt that there was any other place in the country that was offering such computer courses designed for young investigators, especially physicians, in '65 or '66.

Khot: Do you think that collaboration was unique at NIH, and do you believe it had to do with the caliber of associates?

AS: Yes. To this day, I think that the level of collaboration at NIH is unusual, compared with what I've noted for the last 30 years when I go give seminars in medical schools. I still see, for example, that if I'm invited by a basic science department, my friends in the clinical sciences rarely know about it unless I call them to tell them that I'm coming. Or, conversely, if I'm invited by a clinical department, my friends in the basic science departments don't know about it, and that in many institutions, there's either no calendar of events like we have here, where all the seminars in all of the departments-- not only seminars-- but a good number of them are listed weekly so you can know who is coming, and they're open to everybody. Or that in a university, the basic and the clinical sciences may be in different buildings, and so they just... word does not go out easily, and so I know even from how visitors are treated, that there's much more interaction here than in most places.

Also, it also works out in terms of actual research projects. There's been a tendency in universities and medical schools to regard the equipment that one bought with a research grant as one's own and not to let or certainly not to encourage, but frequently not even allow other investigators to use it because that was bought for this project, whereas at NIH, the nature of how equipment is acquired and other things has made sharing much more the norm rather than the exception. I think in part that was also because for a long time the NIH intramural program, being bigger than anyplace else, was a critical mass in almost any subject one wanted. So if one needed equipment in physical chemistry or immunology or electron microscopy or NMR or EPR, there was always somebody around. I think that now there are 10 or 20 major medical centers or academic research institutions which have such a critical mass and one can have that sharing going on, presumably. But in the '60s and '70s, the NIH intramural program was unusual in being especially large that critical mass was available in practically every subject.

Khot: Others have also remarked on the flexibilities of the principal investigators in allowing associates to learn and pursue their research interests in a way they wanted to. Can you elaborate on this? Was there a lot of flexibility in your area?

AS: There certainly was. I think the quintessential nature of Dr. Anfinsen was his flexibility and being an ideal mentor in supporting and encouraging all sorts of

interactions. That's all a mark of his science throughout his 60-year scientific career, which ended with his death at the age of 79, four or five years ago.

But I think that's not true of everybody. I mean, I frequently heard stories of mentors who were very authoritarian and rigid, but I think for each one of those, there were two or three that I knew about or heard about who were the opposite. I think there was some selective process in those who came to NIH and those who stayed that selected for individuals who were perhaps more open. The NIH bureaucracy, in dealing with the government bureaucracy, necessitated a certain amount of tolerance and easygoing approach that may not have been true in universities. Property rights did not factor in very much here, and so there were, both physically and intellectually, perhaps more openness for some of the reasons I gave you before about my mentor and the others in his laboratory, like Dr. Goldberger, Dr. Robert Goldberger, and Dr. Charlie Epstein and others in many laboratories that I knew about.

Khot: Do you recall if there was ever a specific research agenda for the associate training program scientists? And who decided what research you would do?

AS: Again, the way NIH has worked, and basically still works for now, is that each institute has a so-called scientific director. At times there was a scientific and clinical director that were equal, comparable, and that system is being revived in a few institutes now. But most of the time, the one, who's called the scientific director, was the leading figure, and he would work with the young trainees, especially the research associates, to get them into specific laboratories. And once they were in that laboratory, the decisions about the research were really between that person and his, or occasionally her, mentor, and so those decisions were made at the level of the mentors and there was very little input from the scientific director after that. But to the extent at which they helped steer individuals towards particular laboratories, they had input into that kind of decision.

Khot: In your opinion, was there any link at all between the ATP, the Associate Training Program, research and the war effort?

AS: No. virtually none that I was aware of.

Khot: What about the associate training program most appealed to you?

AS: That you have a large number of very good scientists, some superb nationally and internationally known scientists, a large number of physicians coming here, and it had the draft deferment possibility. It was also an interesting place to be, i.e., Washington, D.C., or at least a suburb thereof; so all four made it an attractive place to be.

Also, in the '50s, the salary was not bad. I mean, I think I was getting something like \$3600 or \$4800 salary as an intern and resident, and if I remember correctly, the salary here was about \$7500 per year, so it certainly was a major step up.

Khot: Can you elaborate on how the style of your laboratory chief and clinical director during your training program influenced your style as a scientific instructor?

AS: As a scientific...

Khot: Instructor, how you teach. How you were taught has influenced the way you teach.

AS: Okay. Well, I think the style that I observed and I've tried to emulate involves that each individual should have his or her own project, and that should be worked out by mutual agreement between the mentor and trainee. The individual should read for a while about the project and then start and then report to the mentor every few weeks about progress of the work. The person should not be arbitrarily assigned a specific project, should not be part of a team working on a project, should not be plugged into something in the middle of its going on, and should be able to see it as a complete project unto itself which has many advantages in training the individual for having his or her own research career.

But it has some disadvantages in that if a project is not finished when one leaves, it's difficult under the circumstances to start it up again and complete it. And also the likelihood of success of each project is probably less than 50 percent, so it requires being astute enough to know when to stop a project and move to something else and when to continue, i.e., to cut bait or not, and all those enter into the equation. With each project and individual, there are different boundary conditions, and so the decisions are never easy.

The other thing related is that, with time, it becomes clearer that projects which could be done in a year or two in 1965 now take three or four or five years 30 or 35 years later, so the factors involved in choosing projects and being a mentor change with time for diverse reasons.

Khot: How did the training to bridge clinical medicine and the lab bench work that you received in the program influence the way you train other scientists?

AS: Since I was a research associate, I did protein chemistry and protein folding with no relationship to clinical medicine. I did participate in a course on highlights of clinical advances, which were 14 or 15 lectures on important topics of progress in medical research or clinical research. I learned from those lectures, plus the medical genetics course that I mentioned, which Charlie Epstein gave, a lot about research medicine.

And then, at that time, my institute, which was then called NIAMD, Arthritis and Metabolic Diseases, had a Tuesday morning conference at 9:00 and a Friday morning conference at 9:00 in which as many people from the institute as possible were encouraged to go to. Tuesday morning was our basic science topic and Friday morning was the clinical topic. And the institute was small enough that a room that held 50 or 60 people could hold, sometimes via standing room, most of the staff. Most of the senior scientists and the post- doctoral fellows took both conferences, and so I went practically all the time that I could and heard about the clinical work on the Friday morning conferences as well as basic research on the Tuesday morning conferences. Thus I was able to keep up with the clinical work plus I read the *New England Journal of Medicine* and several other journals like *Science* since college. Even though I did not do clinical work, by reading and going to the conferences, and taking these courses, I tried to keep myself knowledgeable about the major research advances in medicine.

Khot: How did your experience in the associate training program modify your career decisions?

AS: In two or three major ways. One is that I opted not to go back to a clinical fellowship, which I actually had been offered at Albert Einstein to return to do a hematology fellowship. I decided to stay here and do basic science research for a while even though I eventually moved back into hematology research. I did not complete clinical hematology training, nor did I get my boards in hematology. And so that pathway probably would not have existed for me if I had gone back into a hospital or medical school training program in New York or Boston, as I'd originally expected to do; where almost certainly I would have done the clinical hematology training program and taken the boards. Actually, I would have finished a third year of the internal medicine residency and then the hematology training program. So by staying here and by having gotten the training here and then staying here, I opted for a more research-oriented approach to medicine than I would have if I'd done the usual training in the hospital-based programs.

Khot: Dr. Edward Rall has commented that the ATP has had a major influence on medical education with the addition of a serious research component to the training of M.D.s who were going to end up in universities was pioneered here. Would you elaborate on that?

AS: I think that it's true in several ways. One is that until the program started here in the '50s, it was very rare for an individual to leave a clinical setting and work in basic science laboratories with a goal of going back eventually to do something clinically related. I mean, individuals like Irving London, who had trained in medicine at Harvard and then did biochemical research at Columbia before he became chairman of the Department of Medicine at Albert Einstein in the late '50s, was very much an exception. Most physicians did their training in hospital-based programs, sat for the boards, and then had a research career in that context. But for an individual to actually go out of the department of medicine or

pediatrics or neurology or what have you, and work in basic science for a few years was very rare. There were a few M.D.-Ph.Ds.', but this was an extremely rare pathway as well.

The program at NIH showed that it could be done to advantage for many hundreds of individuals each year, and it had a mixed effect on universities in that they rarely, I think, followed the program here explicitly. It did, however, promote the idea of setting up M.D.-Ph.D. programs in medical schools, the vast majority of which I believe now have the M.D.-Ph.D. programs, perhaps half of them being funded with NIH grants, and so I think the M.D.-Ph.D. programs, which are an important component of most of the major medical schools, is an outgrowth of the NIH experience.

There have been attempts to set up an NIH-like program in a few medical schools; NIH-like in terms of the program we're talking about in the '50s, '60s, and '70s, with mixed success. I was once a consultant to the Board of Trustees of the Mayo Clinic, and the Mayo Clinic-- this was 15 or 20 years ago-- was having an internal debate about whether physicians, after they finished their clinical training, should next work in the basic science departments at Mayo or in the clinical departments. Each spoke strongly about the importance of their places as training for the physicians to do academic work. And I think even though I was invited there to be a spokesman for having physicians go into the basic science departments, the clinical departments basically won. They do not particularly encourage physicians to go into the basic science departments but rather encourage them to continue in the clinical departments and seek help from basic science departments if that is necessary.

I think that, except for the M.D.-Ph.D. programs, I don't know that there has been a program designed to emulate what goes on here. And now it's even largely extinct here. I mean, I hear very often complaints from very major basic scientists here, like Gary Felsenfeld and David Davies, that they haven't seen a physician investigator in five or 10 years, and now that it's very hard for the basic scientists to get such, especially American physicians. Sometimes medical graduates from abroad, who are not necessarily physicians but have a nominal M.D. degree, opt to go to any place where they can get a postdoctoral fellowship,. But for those who are really trained deeply in medicine and want to pursue an academic medical career, it's rare for them to now work in a basic science laboratory for a few years. It may be in part because there are more relatively basic laboratories in the clinical department, so they have options that weren't available 30 years ago or 40 years ago.

But I still think there's now an increasing dichotomy between those who are trained and opt to do clinical, that is work in a clinical department, and those who want to do basic research. Even physicians who have the M.D.-Ph.D. now, I think, unfortunately, when it comes to pursuing an academic career, opt to do it entirely in the basic science department, and not make use of their training to do

anything that's clinically related. The dichotomy that is occurring, is not necessarily dividing over whether or not one has an M.D., but whether or not one works in a basic science department or a clinical department. There's less going back and forth than there was at the height of the NIH program 30 years ago.

Khot: How do you think the ATP has changed, if at all, the reputation of NIH?

AS: Well, I think it had a tremendously beneficial effect on the intramural program being recognized, and for the period from 1975 to 1985 or '90, practically every leader in medical school programs had spent time training at NIH and so they knew about it. I think now that has been less true in the last 10 or 20 years, and so there's a new generation arising of leadership who've not themselves had experience at NIH. But I think the training program became widely known, caused more good people to come to NIH, had many beneficial effects on the program here.

Khot: In your opinion, what has been the long-term effect of the ATP alumni on the academic world and scientific research?

AS: As I just said, it's been very positive and has brought the message from here throughout the country. But I think that the times are changing rapidly now, and I think a lot of the lessons and trends that were started then are crumbling now for reasons of economics and various other constraints. I mean, the most important lesson is that you could weld basic and clinical sciences together, and I think that trend, which was very strong in the '70s and '80s, is crumbling now.

Khot: Do you think that is due to the fact that the technology required to do biomedical research has become so sophisticated, many existing clinical research training programs cannot accommodate this need?

AS: Yes. I think this is due to several things. One is that the equipment like NMR, EPR, and some of the other things I mentioned, is expensive. However, for better or worse, it's now believed that studying gene expression and doing knockout mouse studies is the end-all of clinical research, and that can only be done in major facilities. In addition,, for a whole variety of reasons, more explicit patient-oriented research is not valued as much. And so the dollars and emphasis are going towards things like working with genetically modified mice, which can only be done in a limited number of places, and so the places where research is being done is shrinking. Now it's almost all on the East Coast or West Coast and a few institutions in the central part of the country, in Michigan, Chicago, St. Louis, but it's getting harder and harder for this kind of research to be done in a great majority of institutions, institutions which were, I think, much more viable as contributors to research, the clinical research enterprise, 20 or 30 years ago.

Khot: In an article about the fate of the clinical investigator, Dr. Goldstein and Dr. Brown described a phenomenon in which scientists transition from patient-

oriented research to disease-oriented research over their careers. In many of my interviews with alumni, they have seen how the clinical training they received at NIH provided the inspiration for the basic research they pursued later in their career. Can you comment on that?

AS: Yes. That's a trend I'm concerned about, that one can learn about clinical problems and then pursue it in terms of disease or into research, but I think that only makes sense if you try to be cognizant of bringing it back to the patient at some point. Many threads of research are diversifying so much into such specialized areas that there are fewer and fewer people who are trying to move it back to the patient. The closing of the loop is what is being left hanging, and now the only ones who can and do close the loop are pharmaceutical companies, which do it in the form of drug studies. The role of the academics in patient-oriented research and human experimentation is getting less and less. And when clinical disasters occur, as occurred at the University of Pennsylvania three years ago, at Johns Hopkins University three months ago, what clinical research in the academic settings still exists gets under more stress, and I think the long-term effects are that there will be fewer and fewer places that do clinical research other than those explicitly organized, controlled, and paid for by the pharmaceutical industry, which has the financial resources to do it. In contrast, it's always been somewhat like baling wire and straw in the academic setting.

Khot: Did the collaboration with other alumni continue after you became a tenured intramural investigator? And, if so, for how long?

AS: Sure. As I mentioned, one interaction that I started my first few months here was advising the editorial board of the *Annual Reviews of Biochemistry* and a few other publications. I continue with other colleagues, being on committees and talking at meetings with others that I established contacts with first at NIH. That's also true of scientific collaborations. The nature of science, as spoken perhaps most eloquently by an English physicist who's written extensively on the sociology and history of science, John Ziman, is that science is a social enterprise, and it's this kind of informal college or interactions that determines directions and what gets done. And so the associate program here allowed one to plug into this informal college in which, fortunately, I still feel part of.

Khot: You feel that the program created a sort of an invisible college in which alumni from the program continue formal and informal...

AS: Yes, very strongly about that.

Khot: Can you discuss any unintended negative effects the program may have had in keeping minorities and women out of high-level research positions, that these groups were not represented in the program?

- AS: Probably it slowed down somewhat, women entering the research enterprise, since women, not being subject to the draft, were not generally accepted into the program. But I think that was also due to the fact that they neither were encouraged to apply, nor for whatever reason chose to apply. There were some, for example Dr. Bridget Leventhal, who did chose to come to NIH and made major contributions, in this case in pediatric oncology
- AS: Women who did apply, I think in many cases were spouses of physicians coming here, and so there were a small number of those here. I think in general, women who wanted to apply could and would get accepted. It's just that they were neither encouraged to do so nor necessarily felt a particular need to do so. And so probably there was a subtle disincentive. The numbers of physicians, black physicians, in the major medical schools were so few that I don't think that the NIH program had a noticeable effect. It was only when the schools like Harvard and Hopkins and Washington University started having a small number of blacks did it become relevant, whether or not the blacks would be accepted here.
- Khot: Dr. Sam Broder, is quoted as saying, "My fear is that the intramural program does not function at that same level in terms of the interplay between the lab and the bedside, and probably no place in the country now does. I think the NIH leadership clearly has not assigned full value to this function historically, in part because of the practical necessity and cost, and in part because of the lack of appreciation or respect for the process."
- AS: I agree with him. I mean, I don't think that there is much attempt to have a program here that bridges the lab versus the clinic, but that's true everywhere. Many other factors contribute other than the individual leadership decisions here, as I discussed above.
- Khot: Can you discuss the possibility today, in an atmosphere much more individualistic and less service-oriented, for the government to mobilize medical talent for specific objectives, let's say, dealing with the AIDS crisis.
- AS: The lessons from the NIH program for doing that?
- Khot: Do you think it's possible in today's atmosphere?
- AS: I think the one thing that they could do is the loan repayment program, and I think the Clinical Research Act does have a specific loan repayment program for AIDS research for the extramural community that's existed for the intramural community for the last five or 10 years. Skilled administration of something like a loan repayment program could do a great deal to train individuals for both basic and clinical research in AIDS or in other areas of emerging infections. If these programs are used correctly, they could have a very beneficial effect.

Khot: Over the past few years, there's been a movement in our society to honor those who served in the armed forces during World War II and Vietnam. On the other hand, while the legacy of the alumni has been enormous in altering American medicine, the recognition is somewhat lacking, and there's still a negative connotation associated with the term yellow beret. Are you aware of any resentment or sensitivity of associates to this?

AS: No. In fact, I think the yellow-beret term was a self-designation which was done in an ironic context, and it didn't necessarily have a sense of an external deprecation. I think people were very happy with the program and I'm not aware of tremendous resentment. In fact, it's a little bit self-selective because those who established themselves in medical schools came through this program. The others who didn't get in here very often did something very different, so they're not part of the same group.

Khot: In 1967, Representative Daniel Flood of the House Appropriations Subcommittee on Labor, Health and Education stated that "a quiet revolution in the practice of medicine is taking place as a direct result of research." Can you comment on this and on anything else that you think we should know about the program?

AS: I met him a few times.

Khot: Oh, really?

AS: He was a character. He had to resign because he got involved with some unsavory activities, but was very influential with the National Library of Medicine. He was a congressman from the area in southern Pennsylvania, near Harrisburg.

Khot: He stated it as "a quiet revolution."

AS: Probably true. But until everything broke out with the Genome Project and stem-cell research, you could say that all medical advances were a quiet revolution. I mean, there were a couple of big public things. For example, the first year or two I was here, heart transplantation got a lot of press, and then the assisted heart, Barney Frank and the Jarvik-7 or whatever it was called, in Utah. I mean, there were periods where what was going on in medical research got a lot of press, but for specific things like that, not for the slow, painstaking advances which were really a secret revolution. For example, bone-marrow transplantation, which has had a tremendous positive impact on health, was pioneered at the University of Washington by Don Thomas and his associates, but work was done here and in many other centers. That never got tremendous play at one point, and yet it took off and suddenly emerged as a full-blown therapy. The same with cancer chemotherapy, which was pioneered here, or cardiac valve surgery which was also pioneered here and then spread to many places. So, I mean, there were these revolutions that occurred over a decade or two decades, but the things that got a

lot of attention were the heart transplants or the assisted-heart devices or the cloning of an individual animal. It was really not until the Genome Project and stem-cell research and a few other things like that in the last five years, which have, for better or worse, been the subject of a great deal of media publicity.

Khot: In 1995, the NIH Directors' Panel on Clinical Research stated that there was low physician funding for clinical research due primarily to the fact that physicians do not apply in sufficient numbers. We already talked about this a little bit, but why do you think that is that physicians just aren't applying?

AS: I think that there are multiple reasons that, on the one hand, the time that it takes to do specialty training has gotten very long, and so after three to five years of training, individuals don't want to go for another three years of research training. Secondly, there's the loan repayment that many students are in debt from their medical school experience, and so they'll want to go to some pathway to pay off their debts more quickly. Third is that many are married and had families at an earlier time and had social pressures to go into practice. Fourth, there was a period in the late '80s and the early '90s where getting a grant was very difficult, especially in the clinical setting, and so the mentors were not encouraging and students did not perceive that for physicians to do research was necessarily a good thing. Fifth, that doing research, as we talked about earlier, involves the heavy technologies like NMR machines or like transgenic or knockout mice. There's not something that can easily be done by an individual after one or two years of training or is not the kind of research that's portable to take from the academic medical center where he or she has done it in New Haven or Boston or Philadelphia and go take that to Harrisburg or to Scranton or someplace that's not one of the 20 or 30 major centers. Many individuals don't see the relationship between where research is now and their clinical goals. As research becomes more and more specialized and more and more with animal or molecular models, relevance is more difficult to fathom, so physicians don't opt for this because of that issue. So there are many, many problems. I've mentioned just five or six that come to mind straight away. If pushed, I could probably think of another dozen that make that career less likely now. Another thing is that doing clinical research has gotten so difficult with the IRB and other barriers that people, unless they're really driven, don't opt for that.

Khot: Do you think the sense of excitement, opportunity and determination that used to permeate the field is compromised by financial and career anxieties?

AS: Yes, just as I said a while ago.

Khot: In recent years the concept of translational research-- we talked about this a little bit-- has come to reveal a directional bias in which basic discoveries are made in basic science labs and applied to clinics. Do you think in terms of your research, I know you, in a previous interview, mentioned how you initially were working more in protein chemistry, and later on in your career worked more in more

clinical work with sickle cell, that you, as you mentioned earlier, tried to close the loop a little bit more?

AS: Yeah. I have consciously in the last 10 years. Even my early sickle-cell research from 1975 to 1990 was largely in the laboratory. I worked with hemoglobin or red cells. But the last 10 years, I've tried to do more clinical research involving treatment of patients with hydroxyurea and now with inhaled nitric oxide, and so I have consciously tried to bring the work of the last 20 years to close the loop, bring it full circle. But very few people do, and I'm lucky to be at the NIH because I don't think I could do that in any other venue. And also, sickle-cell disease is an unusual situation that allows for that. We know enough that we can design therapeutic strategies on the basis of very rational arguments which have a high probability of working, unlike other diseases in which less is known. But also, in doing so, I've become aware the last decade about the tremendous difficulties there are in doing clinical research.

Khot: Another question I have also is that, in speaking with many others, there seems to be clinically driven paradigm shifts in their field of research. Can you describe any that you're aware of either in your own research or in other research in which research experience that you gained early on directly led to the clinically related research that you pursue?

AS: You're asking the question of whether clinical observations lead to new research?

Khot: Like, for example, when you were in the program, I know you weren't directly seeing patients, but you now... Has there been any clinically driven...

AS: Well, okay. I think that in the field of sickle-cell research, which I've been involved in now for more than 25 years, it's an example where over and over again what is done in sickle-cell research becomes applicable to many other diseases and, as well, even stimulates so-called basic research. For example, hemoglobin was the first molecules whose x-ray structure was known, myoglobin and hemoglobin, and then sickle hemoglobin. And so there was an imperative to work out the structure of the protein to understand sickle-cell disease. The cloning of the globin gene was the first to be cloned and sequenced, including the sickle globin, because of the interest in hemoglobin in general but also in the hemoglobin diseases. The working out of haplotype analysis and then prenatal diagnosis using restriction enzymes and DNA occurred with sickle-cell disease. The development of PCR techniques for amplifying and identifying the specific DNA sequences was first done, illustrated with hemoglobin and applied to prenatal diagnosis of hemoglobin and other hemoglobinopathies. So sickle cell and hemoglobin research has formed a substrate upon which new techniques and new concepts are worked out showing practical use and then applied more generally. Now, for example, I was reading over the weekend about trying to do haplotype analysis of polymorphisms in human DNA and look for, not individual polymorphic sites, but clusters of polymorphic sites which leads to these

haplotype analyses. I think these analyses again were used first in sickle-cell research 20 years ago, and now are being applied in the more general search of the human genome. And so I think that research in my particular field, in sickle-cell anemia, thalassemia, and the hemoglobin diseases, the genetic hemoglobin diseases, has allowed a back-and-forth between basic laboratory studies and clinically related studies, which has cross-fertilized and has advanced both sides very strongly. The things that I saw in the laboratory where we were constructing models of the proteins 35 years ago that I told you about, were directly applicable five or 10 years ago when we tried to find ways to inhibit the polymerization of sickle hemoglobin, which causes the pathophysiology of sickle-cell anemia. So there has been this strong to-and-fro in the hemoglobin diseases.

Khot: And now, the next generation not having this physician involvement in research will have a pretty drastic effect on the future?

AS: I think, one of the little understood aspects is that clinical research drives basic research as much as basic research drives clinical research. My friend, Elliot...what's his last name?

Khot: Gershon ?

AS: Elliot Gershon, thank you, who's now chairman of the Psychiatry Department in the University of Chicago, wrote a paper for *Perspectives in Biology and Medicine*, which I'm one of the editors of, arguing this and in showing that, for the DNA structure, for nucleotide triplets and for several other examples, the advances from clinical analyses led to whole fields of so-called basic research, and that it was the original clinical observations that led to the science not, as is commonly presupposed, the other way around, that basic research suddenly leads to clinical breakthroughs.

Khot: You commented on this earlier. Is there anything else you can think of that you believe you believe would revitalize the interest in clinical research?

AS: I think that we need the leadership of American medicine, starting with the NIH leadership but also the Institute of Medicine and the AAMC, deans of the medical schools, etc., jointly and in as many forums as possible, make this a major goal, and support such activities. Some of the things, for example, I suggest would be to have infrastructure for doing clinical research, paid IRBs staffs to help prepare clinical protocols. The medical schools bend over backwards to build animal houses and hire veterinarians to get ALAC accreditation, but they don't do as much, in my opinion, to get the infrastructure of clinical research well underway. I think there could be a lot more leadership than there has been.

Khot: That's all the questions I have.

End of Interview