

*This is an interview with Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases), in his office at the National Institutes of Health, in Bethesda, Maryland, on March 7, 1989. The interviewer is Dr. Victoria Harden, Director of the NIH Historical Office.*

Harden: Dr. Fauci, could you begin by describing the home in which you grew up, your parents, your grandparents and siblings; what you enjoyed doing as a boy, and your elementary and secondary education?

Fauci: I was born in Brooklyn, New York. My grandparents on both my mother's and father's side were born in Italy, except for my grandfather on my mother's side, who was born in Switzerland. They came to the United States at the end of the nineteenth century. Both my parents were born in New York City and went to public schools in New York City. My father, Stephen Fauci, graduated from the College of Pharmacy, Columbia University, as a pharmacist. My mother, Eugenia Fauci, went to Brooklyn College and Hunter College. They married very young, when they were eighteen years old, and went to college after they were married, while they were still growing up. I went to the neighborhood parochial schools in New York City. I was brought up in a Catholic grammar and high school environment. I went to Our Lady of Guadeloupe Grammar School in Brooklyn and to Regis High School, a Jesuit high school in Manhattan. I had the interesting experience of having to take a bus and three separate subway trains to get from my home in Brooklyn to high school in Manhattan. I believe that my childhood was a typical, very happy, and very active growing-up period in New York City during the early forties. I was born in December of 1940 in New York City and grew up as a child in the World War II and post World War II years.

My major interest was sports. I lived in a very sports-oriented neighborhood. We used to play basketball from the beginning of the basketball season to the end, baseball throughout the spring and the summer, and then basketball and football again in the winter. My sister, who is three years older than I, also went through the same sort of school system, same grammar school I went to, went to an all-girls' Catholic high school, and ultimately St. John's University in New York City. She was a teacher before she stopped to raise her family.

Harden: Who were your boyhood heroes?

Fauci: My boyhood heroes were predominantly sports figures like Joe Di Maggio, Mickey Mantle, and Duke Snyder. I was unusual in that I grew up in Brooklyn but was a New York Yankees fan. I was somewhat of a sports outcast among my friends who were all Brooklyn Dodgers fans. This was the time the Dodgers were actually located in Brooklyn as opposed to Los Angeles, where they are currently located.

Harden: How did a young man who was devoted to sports decide to become a physician?

Fauci: I don't think I can tell you the precise time when I knew that I wanted to be a physician. It was very early on. I know that in high school, when I was deciding the options I would have in college, there really was no question that I was going to be a physician. I went to Regis High School, a Jesuit high school, which had a major impact on my career even up to today. It was a highly academic, exclusive scholarship school. Students from every parochial grammar school in all the five boroughs of New York competed to receive admission, making it highly competitive, and the courses were extraordinary. They were very heavily weighted towards the classics. We took four years of Greek, four years of Latin, three years of French, ancient history, theology, etc. When I was at Regis, it seemed that the very bright people in school really had just a few options. If you wanted to go into medicine, that was fine. The other choices were law, science, engineering, or careers like that. My interest in medicine stems from my keen interest in people, in asking questions and solving problems.

Also, I think there was subliminal stimulation from my mother, who, right from the very beginning when I was born, wanted me to be a physician. She never really pressured me in any way, but I think I subtly picked up the vibrations that she wanted very much for me to be a physician. When the time came to go to college, I went to Holy Cross College, which has an extraordinarily fine reputation for premedical work. They do it in a very interesting way, at least it seemed so back in the fifties. I went to Holy Cross in 1958 and graduated in 1962. At that time, it was not unusual for premedical students to take a very strong classics course in premed. The title of my premed course was "A.B. Greek Premed," which was a classics course very heavily weighted with philosophy—32 credits of philosophy, plus French, Greek and Latin. At the same time we took the minimal scientific courses to get us into medical school. The students did very well, getting into the best medical schools in the country but with a very strong liberal arts background. The liberal arts background is something that was very much a part of my family because virtually all of my relatives on my mother's side—her father, her brother, and her sister's children—are all artists. They are successful people who made their living through the arts, usually painting. I was always and still am very interested in art, but I am somewhat of a frustrated artist because I certainly don't have the time, and probably not the talent either, to pursue it. I still am very interested in the classics. They were a very important part of my education.

Harden: Would you evaluate the broad, liberal arts, humanistic training and your Catholic upbringing in terms of how they have influenced your performance as a physician and as a researcher? I'm thinking of things like your world view, your interaction

with patients, and your approach to ethical questions.

Fauci: You can't separate very well natural abilities in a vacuum from your training, or from the combination of factors that have an influence on how you perform. But certainly, the humanistic education that I had has had a very positive influence on my ability to deal with sensitive situations with people. I credit very much the Jesuit training in precision of thought and economy of expression in solving and expressing a problem and in the presentation of a solution in a very succinct, accurate way. This has had a major, positive influence on the fact that I enjoy very much and am fairly good at being able to communicate scientific principles or principles of basic and clinical research without getting very profuse and off on tangents. This is something that was drilled into us from the very early days in high school.

Harden: Did you continue your interest in sports in college?

Fauci: My interest in it continued, but not my active participation. In high school, I played competitive sports—I played basketball at a time when you could play basketball without being 6'9" at the shortest. I don't think I would have any chance of playing basketball if I were in high school now. I enjoyed basketball, was the captain of the team and had a very successful time in high school. Alongside it, I played baseball. These were my two major sports. When I went to college, I continued to play a modest amount of intramural sports, but due to the nature of the premedical curriculum at Holy Cross, it was very difficult to be very active in sports. I did not play competitive basketball or even baseball at the college level, since they had very good teams. I could not play as much as I wanted to because the demands of the curriculum were such that you really had to put a lot of time into your studies.

Harden: Could you talk about your experiences at Cornell University Medical College and comment on how actually becoming a doctor compared to your earlier conceptions of the profession?

Fauci: This might be interpreted by some as being paradoxical, but I absolutely loved medical school. It certainly was demanding, but it was one of the most exciting experiences of my life. The exponential curve of knowledge accrual in medical school was so great that it completely overshadowed the fatigue and the stress factors and the other problems that are so commonly seen in medical school. Certainly, medical school training was very stressful, but unquestionably it ranked as one of the happiest periods of my life, because I was learning so much. The later years in medical school and in health care training and what had been my previous idealistic views about medicine did fit together. There really was the opportunity to apply a very basic scientific framework of knowledge to something

that is very human, very personal, with all of the sensitivities associated with dealing with human beings. Here I had the advantage of the humanistic training that I had received earlier on in high school and in college. This is a nice dichotomy of medical school, and that's why I think that there is no question that I was meant to be a physician and a physician-scientist. I can't imagine in my wildest dreams doing anything else that would make me as happy as this makes me. I enjoy the polarity. There are strict scientific principles that have to be adhered to in medicine. At the same time a humanistic touch is needed in dealing with people. They have to be combined. You have to combine social aspects, ethical aspects, personal aspects with cold, clean science. It is the art of the physician to put them together in the care of a patient, in the development of a protocol for a disease, the diagnosis or treatment of a problem. This combination exists in every aspect of patient-involvement.

Harden: Who influenced you the most during medical school, especially in your decision to go into immunology?

Fauci: The people who influenced me most in medical school are different from those who influenced my decision to go into immunology. Taking medical school first: My heroes were the strict clinicians of the New York Hospital/Cornell Medical Center. They were and still are in so many respects the real heroes. My teachers, whom I saw on the wards as a student and during my internship and residency, were people whose entire lives were devoted to clinical medicine. They reached such levels of expertise in patient care, diagnosis, and the delivery of patient care that they were really super stars. I tried to emulate them and make myself as good a clinician as I possibly could be. They provided a great inspiration. I think that it is very important for a young medical student to have a role model. There were several of them around at the time.

The reasons I went into immunology and research in general were due to an unusual situation. I left Cornell and went into my internship and residency in 1966. That was at the exponential phase of the Vietnam War, and every single physician went into military service. I can remember very clearly when we were gathered in the auditorium at Cornell early in our fourth year of medical school. Unlike today, we had only two women in the class and seventy-nine men. The recruiter from the Armed Forces came there and said, "Believe it or not, when you graduate from medical school at the end of the year, except for the two women, everyone in this room is going to be either in the Army, the Air Force, the Navy or the Public Health Service. So, you're going to have to take your choice. Sign up and give your preferences." I had heard about the NIH and the opportunity there. At the time, the NIH was just blossoming, and everyone who had any role in academic medicine spent some time at the NIH. So I put down Public Health Service as my first choice, and then the Navy. Essentially, I came down to the

NIH because I didn't have any choice. I was very lucky because I knew that it was a phenomenal scientific opportunity.

When I was trying to decide what laboratory to go to, some of my advisers at Cornell suggested very strongly that I pursue the field of immunology, since I had developed an interest in immunology in medical school. I had done some projects during the summer and had worked for a period with Dr. Marvin Schlesinger, who was the chief of gastroenterology division of the Department of Medicine. I also had worked with [Dr.] Graham Jeffries and [Dr.] Walter Rubin. The project I did as a student turned out to be a successful project. I was lucky, since that doesn't usually happen when you have a student project. Because of this research, I applied for the National Institute of Allergy and Infectious Diseases. It so happened that Dr. Schlesinger knew Dr. Sheldon Wolff at the NIH, and I came down to the NIH for an interview. I was interviewed by Dr. Wolff, and I immediately fell in love with the man. He was just my kind of person—intellectually and personally. I was accepted by Dr. Wolff right off. At the end of my residency, I came down to the NIH to work in the National Institute of Allergy and Infectious Diseases with Dr. Wolff. Over the years, even after he left the NIH, he emerged as the major mentor—personal and scientific—in my life. There have been a number of other individuals whom I have come into contact with who have had a major influence on me, but I think that Dr. Wolff clearly stands out as the person who made the greatest impact on my career.

Harden: Could you talk about the research you did with Dr. Wolff in his laboratory in this period?

Fauci: When I came down to what was the Laboratory of Clinical Investigation, of which Dr. Wolff was the laboratory chief as well as being the clinical director of the National Institute of Allergy and Infectious Diseases, I wanted to work on cellular immunology. But, interestingly enough, as popular as cellular immunology is now, there really were not very many cellular immunologists at the time, and certainly not in the Laboratory of Clinical Investigation. I went to work with Dr. John Johnson, who now practices rheumatology in Nashville, Tennessee. John was an immunochemist at the time, but he allowed me to work on problems in cellular immunology. I had to go around to different groups in different laboratories to learn the fundamentals of cellular immunology under the auspices of the Laboratory of Clinical Investigation. It was a great experience and a testimony to the flexibility of people like Dr. Wolff and Dr. Johnson, who allowed me to work in that field even though it wasn't their field of expertise. Dr. Wolff was mainly working on the pathogenesis of fever. I told him I didn't want to work on that, although it was a very interesting topic. I wanted to learn some basic cellular immunology with the ultimate aim of going into what has been my theme for the past twenty-one years—human immunobiology and the regulation of the

human immune system. I was then, and still am, extremely interested in clinical medicine, and I have been successful in being able to mix and meld together the very fundamental, basic concepts of immunology with clinical medicine. It was Dr. Wolff who encouraged me. I worked on some projects looking at the regulation of the immune system in animals, with rabbit and guinea pig models. I learned from Dr. Baruj Benacerraf, who was down the hall in the Laboratory of Immunology; from [Dr.] David Katz, who worked with him; and from [Dr.] Carl Pierce and a few others. There were in the laboratory working with Dr. Johnson two people who have gone on to be very successful and prominent immunologists—[Dr.] Alexander Lawton, who is now at Vanderbilt [University] and chairman of pediatrics, and [Dr.] Herbert Reynolds, who is now chief of medicine at the Hershey Medical Center of the Pennsylvania State University. They were just Fellows with me at the time, and we taught each other immunology. However, though I liked it very much, my main desire was to get back to the New York Hospital/Cornell Medical Center and to be a clinician. That's what I really wanted to do. I liked the scientific environment, but my real love was taking care of patients.

Harden: Why did you go back to Cornell for another year, and what made you decide to come back to the NIH and pursue your career here rather than going on into a private practice or into academic medicine?

Fauci: I was at that very critical period in my second year as a Fellow in a three-year program having to make up my mind about what I was going to do "for the rest of my life." Just about at that time things started to click in the laboratory. I was making some interesting observations, writing some papers that were turning out to be good papers. Virtually simultaneously, [Dr.] Alexander Bearn, who was the chairman of the Department of Medicine at Cornell at the time, asked me if I wanted to come back at the end of my third year to be chief resident in medicine. At the same time, Dr. Wolff offered me a job, which was one of those offers that you can't refuse. It was the position of senior investigator in the Laboratory of Clinical Investigation. I told him I wanted to go back and have another year in clinical medicine and make myself as excellent a clinician as I possibly could. His response was, "Fine, go back to New York; take a year as chief resident, and then come back; the laboratory will be waiting for you when you get back." I made the decision, but when you make decisions like that, you're not really sure why you made them. I think it was a combination of the personality of Dr. Wolff, with whom I was developing a very strong friendship, and the fact that as the months were going by, my immunology research was becoming more successful. I didn't feel that I was giving up anything because I was going back to New York to cement my clinical training. I decided that I would do it. I would go back to New York and come back to NIH after a year to my own laboratory, in which I would have total independence. I think it is important to emphasize that quality of

Dr. Wolff that has been responsible for the development of so many successful investigators over the years. It is important to recognize what he did with me as with many others. He could recognize early on in someone's career a person who had potential, who would succeed. Before that person did anything to make any kind of reputation, Dr. Wolff would give that person unqualified support. That was exactly what he did for me. Nobody knew who I was; nobody cared to know who I was. But Dr. Wolff said, "Here's your laboratory. You can have a technician. You can have a Fellow if you can attract a Fellow. So go ahead." I said, "Fine, that's great." I went to New York, came back to the NIH and started my own human immunobiology group. I was one of the few people at the time anywhere who was devoted exclusively to human immunobiology. There was [Dr.] Max Cooper in Alabama and Tom [Dr. Thomas] Waldmann at the NIH. Bob [Dr. Robert] Good and a few others were exclusively human. There were many excellent and great immunologists around who did either totally animal work or a combination of animal and human, but there were very few who were doing exclusively human immunobiology. That's when I started my work on immunoregulation of the human immune response, which I have continued throughout the past couple of decades. I am still working on it right now in 1989.

Harden: Your medical student years and just after marked the period of time when cellular immunology began to flower. Would you comment on what factors made immunology such a fruitful field?

Fauci: It was a combination of the emergence of technologies and the awareness of the extraordinary implications, if not tentacles, that the immune system had in controlling so many aspects of the human organism. For example, technology provided the ability to identify different types of cells and their subsets. There was the realization of the almost infinite possibilities of a repertoire of B-cells to recognize different antigens. The development of monoclonal antibodies and the ability to clone cells led to a virtual explosion in the delineation of the immune system, its structure and its function.

At the same time, scientists became aware that there were many immunologically mediated diseases. Diseases that were total mysteries years ago became understood as immune-mediated: lupus, rheumatoid arthritis, the connective tissue diseases, the organ-specific autoimmune diseases, and transplantation rejection are a few examples. This was also occurring during the emergence of molecular biology within the field of immunology. If you look at immunology, it has from the very beginning been inextricably linked to infectious diseases. Teleologically, what is the immune system for? The immune system protects you against invaders from without—microorganisms—as well as, in some cases, the emergence of certain tumors from within.

What was not realized until that period of explosive interest is that the immune system is an organ system just like any other system. It is an organ system like the cardiovascular system, the neurological system and the endocrine system. Initially, it was understood to be a response that the body had, but now, the immune system is viewed as a true organ system. It has structural components: there are lymphocytes; there are organs, such as the spleen; the blood is a lymphoid organ. The reticuloendothelial system, the bone marrow, the thymus and the lymph nodes are all parts of the immune system. This organ system has a way of communicating by a variety of soluble factors which we call cytokines. Knowledge about this has just emerged over the past decade. There are a large number of different molecules that have very specific functions, such as one cell's ability to talk to another cell. All of this started to emerge as the technology was developed that allowed the precise identification of the components of the immune system and their function.

Harden: Cell sorters, for example, were essential to this.

Fauci: Absolutely.

Harden: Some of the basic research in other fields, the work on protein chemistry and protein structure, for example, also facilitated the advances in immunological knowledge, I believe. It appears to be one of those "payoffs."

Fauci: Absolutely. I think immunology, certainly is one of the major examples of something that we stress very often. Basic, fundamental undifferentiated research will inevitably, sooner or later, emerge into something that is very important; but very likely you would not have predicted that it would relate to this particular arena. You're working in one direction and then all of a sudden you find something else that you don't understand now, but ten years from now it solves problems in another direction. Immunology and basic research on the immune system really provide a classic example of this.

Harden: The 1956 research by [Bruce] Glick, [Timothy S.] Chang, and [R. George] Jaap on the bursa of fabricius and antibody production in poultry seemed so far outside the mainstream of human immunology, if I remember correctly, that it could only be published in the journal, *Poultry Science*. Later, it turned out to be very important. Could you talk about your own work on Wegener's granulomatosis and some of the other problems to which you applied your knowledge?

Fauci: My research career at the NIH emerged in two parallel tracks. One was the very fundamental dissection of how the human immune system is regulated. The other parallel track was an examination of immune-mediated diseases and how one can classify and treat them. The work on the regulation of human immune system is

what led me into AIDS research. What we performed in the late sixties and early seventies were probably "breakthrough" studies on the development of cures for formerly fatal diseases such as Wegener's granulomatosis and polyarteritis nodosa. Things emerged from those interesting quirks of science, things that you never would have predicted. Dr. Wolff, even before I came to the NIH, had been very interested in immunosuppression, such as some of the cytotoxic agents. His major interest was fever. This is really very interesting, a story that I tell the Fellows when they come. It is the classic example of how science is so beautiful because it is so unpredictable. Dr. Wolff had collected over the years—he had been at NIH for at least five or more years before I got there—a group of patients with prolonged fevers of unknown origin, not just five or six weeks, but a year long at least. He had a heterogeneous group of people which numbered literally in the hundreds. He had been collecting them for a few years because he wanted to study the pathogenesis of fever. Some of them had granulomatous hepatitis, a disease that had never before been described and that he described. Some of them had juvenile rheumatoid arthritis; some of them had connective tissue diseases; some of them had hematologic diseases; and others had immune-mediated vasculitic diseases. They were a very interesting group of patients—interesting because the diseases were interesting but also because most of them would die from their diseases—particularly those with Wegener's granulomatosis.

At that time, I came as a Fellow and I wanted to stay involved in some clinical work while I was doing basic research in the laboratory. This is essentially what I'm doing now—doing clinical work while I'm doing very fundamental cellular and molecular work in the laboratory. I asked him, "Could I start collecting these Wegener's and vasculitic patients and put them on a set protocol, and look at these cytotoxic agents, particularly cyclophosphamide"? I was interested in this because the agent had been used successfully in one or two patients in a manner that was not very well organized since it was given to a patient as a last resort. Dr. Wolff, as usual, was extremely accommodating, and said, "Fine. I'll support you on that. Let's do it. We'll do it together and I'll help you out."

To make a long story short, we started a protocol that gave cyclophosphamide in low doses. Previously it had been developed as an anticancer drug and was given predominantly to individuals with leukemia in very high doses that would wipe out the bone marrow. We figured from animal studies, particularly those performed by investigators such as Bob [Dr. Robert] Schwartz and others in Boston, that low doses of a cytotoxic agent could suppress the immune system without wiping out the bone marrow. We then did something that was very unorthodox. We gave low doses of this cytotoxic agent, equivalent to the amount that in animals suppressed immunological function but didn't cause very severe toxic side effects like neutropenia.

The disease that we targeted at first was Wegener's granulomatosis. The cytotoxic agent completely shut off the disease, so much so that we've now treated over the years hundreds of patients with Wegener's granulomatosis, and the disease is essentially curable. We now have a 93% remission rate, whereas when I came to the NIH in 1966, 100% of the patients died. We have fine-tuned the regimen now, writing and informing physicians that if the dose is maintained at a level that keeps the white count above a certain level, then there will be very little trouble with secondary infection. If the patient is simultaneously treated with alternate-day prednisone as opposed to daily prednisone, which has toxic side-effects, infection will be largely avoided. So, the combination of alternate-day prednisone with daily low-dose cyclophosphamide essentially was responsible for essentially curing Wegener's granulomatosis, or at least putting it into prolonged remission.

Once it became clear from the first several patients that it worked with Wegener's, we then tried it with similar diseases—polyarteritis nodosa, cerebral vasculitis, lymphomatoid granulomatosis and Takayasu's arteritis. We had a series of seven or eight diseases that formerly were completely fatal but now people were coming to the hospital, and four to six weeks later, they were walking out and going back to their jobs. It was a heady and exciting period of time—both clinically and in research. At the same time we were looking at regulation of the human immune system at the very basic level, which emerged in the 1970s from cellular phenomenological research to work at the molecular level.

Harden: It must have been very gratifying to achieve such results.

Fauci: It was gratifying not only because I could do some good but because I actually saved the lives of some people. That is the epitome of what you want to do in medicine. I've always wanted to be involved with diseases that were very, very serious. I would rather be involved with patients who have fatal diseases than those with diseases that are just an annoyance. That just happened to be my bent. I wanted to be where the action was. So there it was, we had a disease that was formerly fatal and we made a major impact on it. The other thing that was so gratifying about that experience was that we were able to do something that people said you can't do—you can't do clinical medicine at the same time that you do very basic research. That is absolutely incorrect, if you organize your time correctly. If you ask the right questions, get the right training, you can do work that is very, very basic in its approach and yet has important clinical consequences.

Harden: In our next interview I want to examine how you as a clinical immunologist responded to the first cases of AIDS that you saw. But, before we stop today, I want to pose a hypothetical question. If AIDS had struck in 1955, before we knew about T-cells and other aspects of the immune system, how do you think the

medical community would have responded to it?

Fauci: I think it would have been much more frightening than it is now, and it is frightening now. I think we would not have had a clue as to how to combat this disease from a basic scientific standpoint. I think we would have realized just on epidemiological grounds that it was an infectious agent of some sort that was sexually transmitted and transmitted by blood. But about pathogenic mechanisms, we wouldn't have had a clue. We wouldn't have known how even to go about thinking about the virus, much less clone it and develop drugs against it. So within the framework of the catastrophe of AIDS, we're lucky in the sense that it came at a time when retrovirology, molecular biology, molecular immunology, and immune system studies were at that stage where we could very quickly identify the agent, how it works, the pathogenic mechanisms, its effect on the immune system, etc. If it had happened in 1955, we would have been in very serious trouble.

Harden: Thank you, Dr. Fauci. I look forward to the next interview.

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